Statistical Analysis Plan

for the Immunoglobulin Domain

for Patients with COVID-19 Pandemic Infection Suspected Or Proven (PISOP)

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1 COVID-19 IMMUNOGLOBULIN DOMAIN SAP VERSION

The version is in this document's header and on the cover page.

1.1 Version History

Version 1.1: Finalized on 23 Feb, 2021.

2 SAP AUTHORS

Scott Berry, Berry Consultants, Austin, TX, USA

Lindsay Berry, Berry Consultants, Austin, TX, USA

Elizabeth Lorenzi, Berry Consultants, Austin, TX, USA

Manu Shankar-Hari, London, UK

Lise Estcourt, Oxford, UK

David Menon, Cambridge, UK

David Roberts, Oxford, UK

Zoe McQuilten, Melbourne, Australia

Tom Hills, New Zealand

Alexis Turgeon-Fournier, Canada

Bryan McVerry, USA

Alastair Nicholls, Ireland

3 INTRODUCTION

This statistical plan for the first analysis of the immunoglobulin domain in the pandemic stratum of the REMAP-CAP trial is an appendix to the Pandemic Appendix to Core (PAtC) Statistical Analysis Plan (SAP). This document synthesizes that information and describes the details of the statistical analysis for the unblinding of the immunoglobulin domain, within the pandemic stratum of REMAP-CAP. This plan details the statistical analyses in the original REMAP-CAP core SAP and the pandemic stratum SAP applied to the analysis of immunoglobulin domain. The plan here is completely prespecified for the imminent unblinding of the results for immunoglobulin domain within the pandemic infection suspected or proven (PISOP) (COVID-19) stratum.

Enrollment in the COVID-19 Immunoglobulin Domain started on 5th May, 2020. The domain was halted in the PISOP stratum following a statistical trigger for futility met in the severe COVID-19 stratum. The REMAP-CAP ITSC decided on 7th January 2021 to stop the severe state of the Immunoglobulin domain of REMAP-CAP within the PISOP stratum and report the results for these interventions in the domain. Enrollment to the severe state of the Immunoglobulin domain was halted on 11th January 2021. Enrollment to the moderate state of the Immunoglobulin domain was halted on 18th January 2021 following the press release of results from the RECOVERY trial of no evidence of benefit (https://www.recoverytrial.net/news/statement-from-the-recovery-trial-chief-investigators-15-january-2021-recovery-trial-closes-recruitment-to-convalescent-plasma-treatment-for-patients-hospitalised-with-covid-19).

REMAP-CAP explores multiple treatment domains by randomizing patients within multiple domains. The adaptive platform trial was designed to have modular results for individual interventions or full domains announced upon reaching a platform conclusion. For this domain, there have been two interim analyses conducted and domain closure was based on both *internal and external results*; hence the results for the convalescent plasma intervention will be unblinded and made public. This document prespecifies the analysis plan for this unblinding.

The authors of this document are blinded to the data and results in the REMAP-CAP trial other than those already publicly disclosed or simultaneously unblinded for subsequent reporting.

4 DESIGN CONSIDERATIONS

REMAP-CAP is designed with Bayesian analyses as the primary analysis method for the trial. There is one overarching Bayesian model, prespecified in the SAP, driving all adaptations, platform conclusions, and result summaries. That primary statistical analysis model will be used to report the results for the immunoglobulin domain within the severe and moderate states of the PISOP stratum. At the time of concluding enrollment the Convalescent Plasma domain, there were less than 100 participants enrolled in the moderate state. Given this limited sample size, the primary focus of this

SAP is reporting results for the severe state of the Immunoglobulin domain. Descriptive and model summaries may be presented for the moderate state to facilitate future systematic reviews by others.

The decision to use a Bayesian analysis in REMAP-CAP was driven in part by the uncertainty of the extent of the pandemic. The sample size could be small, or large, and there may be unexpected external events, such as other trial results, that alter the design of REMAP-CAP. Given the expected evolution of the design, and uncertain sample size, the Bayesian approach is more appropriate. REMAP-CAP defines several statistical triggers within the trial, that at any analysis of the trial would result in public disclosure and a declaration of a platform conclusion. The following internal statistical triggers were defined for the severe state of the immunoglobulin domain:

1. **Domain Superiority**. If convalescent plasma is deemed to have at least a 99% posterior probability of being superior to no immunoglobulin against SARS-CoV-2, then superiority would be declared for convalescent plasma.
2. **Intervention Futility**. If convalescent plasma is deemed to have a less than 5% probability of at least a 20% odds ratio improvement compared to the control, then futility would be declared.

The 99% threshold for efficacy was selected to have good properties for potential outbreak sample sizes. For example, the type I error rate of any conclusion of efficacy for a single intervention 'A' vs. control is less than 2.5% for approximately less than 1000 patients on intervention 'A' with multiple interim analyses (see main and pandemic SAP).

5 UNBLINDING

REMAP-CAP has multiple domains to which patients can be randomized and multiple interventions within domains. At the unblinding of the COVID-19 Immunoglobulin domain, other domains to which the patients have been randomized will remain blinded for this analysis. In this analysis plan there are analyses conducted by the Statistical Analysis Committee (SAC) using additional randomizations and also unblinding of other randomizations. The SAC is unblinded to all interventions/domains in their function for REMAP-CAP. This SAP also includes analyses that are conducted with knowledge of only unblinded interventions and domains. At this time, that includes the COVID-19 antiviral domain, the COVID-19 corticosteroid domain, and the IL-6ra and control interventions in the Immune Modulation Therapy domain. Finally, the SAP includes other analyses that are conducted with only knowledge of the convalescent plasma/control allocation status for patients. These may be conducted by investigators who are blinded to other information about other interventions and domains. All of these analyses are identified below.

6 INTERVENTIONS

There are three assignments within the convalescent plasma domain. These are

P1. No immunoglobulin against COVID-19 (control or standard of care (SOC) arm)

P2. Convalescent plasma at randomization

P3. Delayed Convalescent plasma. This assignment has the following definitions: (a) Delayed convalescent plasma infusion for subjects who fail to demonstrate clinical improvement within 96 hours of admission; (b) Delayed convalescent plasma infusion as a rescue therapy for moderately ill hospitalized patients who require transfer initiation of ICU level organ support as defined by the Core Protocol care after 48 hours of hospitalization; (c) Severely ill patients requiring ICU-level organ support at the time of admission will be randomized to receive: Delayed convalescent plasma infusion for subjects who fail to demonstrate clinical improvement within 96 hours of admission.)

For the primary analysis completed by the SAC, all treatment arms will be modeled, but only analysis results for convalescent plasma relative to no immunoglobulin against SARS-CoV-2 (control) will be reported. For all secondary analyses completed by blinded investigators, convalescent plasma will be compared to the no immunoglobulin against SARS-CoV-2 intervention (control; P1). Delayed convalescent plasma (P3) will be treated as a separate arm in all analyses.

Some models in this SAP will estimate and report the interaction effects of convalescent plasma with the unblinded domains at the time of finalizing SAP. This includes the interactions between convalescent plasma and fixed-dose corticosteroids; convalescent plasma and pooled antiviral domain interventions (hydroxychloroquine (HCQ), lopinavir/ritonavir, and lopinavir/ritonavir + HCQ).

7 DISEASE STATES

There are two disease states in the PAtC, which are **moderate** and **severe**. The immunoglobulin domain has randomized patients in moderate and severe state(s). The majority of patients are in the severe state, with less than 10% of the randomizations occurring in the moderate state. The main focus of the reporting of the Immunoglobulin domain is the severe state, however summaries/results for the moderate state may be reported where appropriate.

8 ANALYSIS POPULATIONS

1. REMAP-CAP COVID-19 severe and moderate state intent-to-treat (ITT): This population consists of all PISOP patients randomized within at least one domain. This population includes patients in the severe and/or moderate states. This is the analysis population for the analyses performed by the unblinded SAC.
2. Unblinded ITT: This population consists of all PISOP patients in the severe state randomized within the immunoglobulin domain or any of the previously reported interventions and domains within the PISOP stratum (Corticosteroid domain, Antiviral domain, and IL-6ra/control

interventions within the Immune Modulation Therapy domain). This is the default population for secondary analyses.

3. Convalescent plasma specific severe state ITT: This population consists of only patients in the severe state randomized to convalescent plasma or control in the Immunoglobulin domain within the PISOP stratum.
4. Convalescent plasma specific per protocol: This consists of the patients in the Convalescent plasma specific severe state ITT population who have been treated as per protocol. In this domain that is defined as '*patients assigned to receive plasma will receive at least one and not more than two adult units of ABO compatible convalescent plasma (total volume 550ml ¬± 150ml) within 48 hours of randomization*' for the convalescent plasma intervention. In this domain, that is defined as '*patients assigned to receive no plasma will not receive convalescent plasma at any time after randomization*' for the control intervention.
5. Convalescent plasma specific moderate state ITT: This population consists of all patients within the PISOP stratum in the moderate state randomized to convalescent plasma or control in the Immunoglobulin domain within the PISOP stratum.

9 ENDPOINTS

The following endpoints will be analyzed, graphically displayed, and summarized through descriptive statistics.

1. **Organ-Support Free-Days** (OSFD)
   a. An ordinal endpoint with mortality as the worst outcome. The primary endpoint for the REMAP-CAP PISOP stratum. The organs considered are cardiovascular (vasopressor/inotrope support) and respiratory (ventilation support). See Appendix A for a detailed description.
2. **In-Hospital Mortality**
   a. A dichotomous endpoint of in-hospital death where the death component corresponds to a –1 on the OSFD endpoint.
3. **Mortality**
   a. This is a time-to-event endpoint through 90-days.
   b. Any patient currently in the hospital or transferred on organ support to an alternative care facility will be censored at their last known status alive.
   c. Any patient successfully discharged from hospital, alive, without organ support, will be imputed as a 90-day "no mortality" event if 90-day mortality data is not yet recorded.
4. **Progression to intubation and mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or death**

a. A dichotomous endpoint of whether a patient progresses to intubation and mechanical ventilation, ECMO or death in hospital.
b. This endpoint will only be analyzed for subjects that are not on intubation, mechanical ventilation, or ECMO at baseline.

5. **Cardiovascular Support-Free Days**
   a. An ordinal outcome of number of days free of cardiovascular support. This is the exact calculation of OSFD, with Vasopressor/Inotropes as the only organ support category. In-hospital death is considered a –1.
6. **Respiratory Support-Free Days**
   a. An ordinal outcome of number of days free of respiratory support. This is the exact calculation of OSFD, with respiratory support as the only organ support category. In-hospital death is considered a –1.
   b. Qualifying types of respiratory support include high-flow nasal cannula (HFNC), non-invasive respiratory support (NIV) and invasive mechanical ventilation (IMV).
7. **Length of ICU stay**
   a. A time-to-event endpoint of leaving the ICU alive. If a patient is known to leave the ICU and return to the ICU within 14-days that intervening time will be ignored.
   b. This variable will be truncated at 90-days: all deaths in ICU will be considered 90-days with no liberation of ICU.
   c. Patients still in the ICU at data snapshot will be considered censored.
8. **Length of hospital stay**
   a. A time-to-event endpoint of leaving the hospital alive. If a patient is known to leave and return to the hospital within 14-days that intervening time will be ignored.
   b. This variable will be truncated at 90-days and all deaths in-hospital will be considered 90-days with no events.
   c. Patients still in the hospital at data snapshot will be considered censored.
9. **At least one serious adverse event (SAE)**
   a. A dichotomous endpoint of SAE.
10. **The World Health Organization (WHO) 8-point ordinal scale measured at day 14.**
    a. A modified WHO ordinal scale will be used:

       0 + 1 + 2 = No longer hospitalized

       3 = Hospitalized, no oxygen therapy

       4 = Oxygen by mask or nasal prongs

       5 = Non-invasive ventilation or high-flow oxygen

6 = Intubation and mechanical ventilation

7 = Ventilation + additional organ support: vasopressors, renal replacement therapy (RRT), ECMO

8 = Death

11. **Domain Specific endpoints**

1. All-cause mortality at 28 days

a. This is a time-to-event endpoint through 28-days.

b. Any patient currently in the hospital or transferred on organ support to an alternative care facility will be censored at their last known status alive.

c. Any patient successfully discharged from hospital, alive, without organ support, will be imputed as a 28-day "no mortality" event if 28-day mortality data is not yet recorded.

2. Serious treatment-related adverse events

a. A dichotomous outcome endpoint of any treatment-related adverse event

b. This endpoint will be summarized descriptively. Treatment-related adverse events are defined according to each participating site's national or regional hemovigilance system definitions (such as SHOT/SABRE in the UK) summarized in Table-1 in section 10.1 of the Immunoglobulin COVID-19 DSA.

3. Venous thromboembolic events at 90 days

a. A dichotomous endpoint of any venous thromboembolic event through 90 days.

4. All thrombotic events at 90 days

a. A dichotomous outcome endpoint of any thrombotic event

Thrombotic events will consist of:

i. Confirmed deep vein thrombosis

ii. Confirmed pulmonary embolus

iii. Confirmed ischemic cerebrovascular event

iv. Confirmed acute myocardial infarction

v. Other confirmed thrombotic events

10 GRAPHICAL DATA SUMMARIES

1. All ordinal endpoints will be plotted using stacked cumulative bar plots and cumulative probability plots.

2. All time-to-event endpoints will be plotted using Kaplan-Meier plots. Positive clinical event outcomes will be plotted as the cumulative rate of event, and negative events will be plotted as the cumulative rate of event-free.

11 DESCRIPTIVE STATISTICS

1. Ordinal endpoints will be summarized by the cumulative frequency of each outcome. The 25th, 50th, and 75th percentiles will be summarized.
2. Dichotomous endpoints will be summarized by the number and proportion in each category.
3. Time-to-event outcomes will summarize the 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles from the Kaplan-Meier estimates, as available.
4. All thromboembolic and thrombotic endpoints will be summarized by the number and proportion in each category

12 BASELINE CHARACTERISTICS

The following demographics will be summarized across arms. More may be added as baseline summaries.

Age, sex, BMI, ethnicity, APACHE II score (measured from hospital admission to randomization), SARS CoV-2 PCR status reassessed at randomization, SARS CoV-2 antibody status reassessed at randomization, preexisting conditions, baseline use of high-frequency nasal oxygenation, non-invasive ventilation, invasive mechanical ventilation, ECMO, vasopressors/inotropes, renal replacement therapy, dose of convalescent plasma received (estimated as a function of donor plasma antibody titer and volume of plasma infused) and miscellaneous physiological values and inflammatory biomarker laboratory values.

13 COMPLIANCE

The compliance to convalescent plasma use will be summarized descriptively as the fraction of use, for each randomized arm.

14 ANALYTIC APPROACH

Each inferential analysis will be done using a Bayesian model. Some default frequentist methods are used for exploration and description. A summary of the analysis methods is provided below.

14.1 Primary Analysis of Primary Endpoint

The **primary analysis model** is a Bayesian cumulative logistic model for the ordinal primary endpoint. The model is described below.

The primary endpoint for the PISOP strata has 24 possible, ordered outcomes. Let the outcome for a patient by labeled as Y_i, with possible values, –1 (death), 0, 1, …, 21, 22. The outcome of 22 for the severe state (never received organ support) is not possible. Hence there are 23 possible outcomes

for the severe state. A cumulative logistic model is specified. The model is structured so that an odds-ratio >1 implies patient benefit. The full details of the model including both severe and moderate states are in the Current State of The Statistical Model, Version 3.0. The full details of the model including the severe state only are in the Current State of The Statistical Model, Version 2.3. The model has factors that are estimated within each state for:

- Each level of the ordinal endpoint
- Each Global site, nested within country
- Age; ≤39, 40-49, 50-59, 60-69, 70-79, 80+
- Sex
- Time; 2-week buckets of time working backwards from the last enrolled patient, with the most recent bucket being 4 weeks.
- For each domain an effect for being randomized to the domain
- For each domain an effect for being ineligible for the domain
- An effect for each intervention within each domain
- Pre-specified interactions in the model between domains, as stated within this SAP. Region-specific DSAs differed in whether an interaction between CP and antiviral as well as CP and corticosteroid would be included in the primary efficacy analysis, but these interactions are no longer planned.

The primary/secondary analyses for convalescent plasma use the following rules:

- The high-dose 7-day hydrocortisone arm will be combined with the 7-day hydrocortisone arm (fixed-duration). They were originally nested, which allows their pooling, and there were very few patients randomized to the high-dose 7-day hydrocortisone arm.
- All interactions between the shock-based steroid arm and other domains will be removed from the model (assumed to be zero).
- All sites within a country that have <5 patients randomized will have their results combined into a single site within that country.
- If there is an outcome in the ordinal scale that did not occur in the data, then that outcome will be combined to a single outcome with a neighboring outcome (the worse outcome). This is done for model stability. For example, if the outcome 11 never occurred a combined outcome of 10 & 11 will be modeled for the analysis.

In addition to the rules above, analyses run by the ITSC analysis committee will use the following conventions:

- The two IL-6 receptor agonists, Tocilizumab and Sarilumab, will be combined into a single pooled IL-6ra intervention and compared to control. This convention is used because the

investigator analysis team is unblinded to the efficacy of IL-6ra interventions compared to control but remains blinded to the comparative effectiveness of Tocilizumab compared to Sarilumab.

In addition to the rules above, sensitivity analyses run by the ITSC analysis committee that include additional interactions between convalescent plasma and the unblinded domains (antivirals/steroids/IL-6ra interventions) use the following conventions:

- The two IL-6 receptor agonists, Tocilizumab and Sarilumab, will be combined into a single pooled IL-6ra arm for intervention and interaction effects.
- All antivirals in the COVID-19 Antiviral Domain will be combined into a single pooled antiviral arm.
- A standard normal prior (N(0,1)) will be used on each interaction term for interactions involving convalescent plasma.

The analysis models will be referenced with certain model assumptions for sensitivity analyses. For example, the "time effects" in the model could be assumed to be 0.

14.1.1 Proportional odds assumption

The primary analysis model is based on an assumption of a proportional effect of treatment across the scale of the ordinal outcome. In order to assess the robustness of the results to this assumption, a dichotomous model is fit to every level of the ordinal outcome across the scale and the odds-ratio for each dichotomous break is presented. If the cumulative probabilities are less than 5% or greater than 95% for specific dichotomizations, these models may be ignored at the discretion of the statistician performing the analyses. No statistical test of proportional odds is conducted.

14.2 Analytic Approach for Secondary Dichotomous Endpoints

A Bayesian logistic regression model will be used for each dichotomous outcome. The model will always specify the "event" as the negative outcome, so that an odds-ratio >1 implies benefit to patients within each model. The model is the standard logistic link function model:

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha - [\text{factors}]$$

References will be made to the factors in the model and their prior distribution. Many of these factors will be the same as the primary analysis model, with the same priors, as the parameters have similar interpretation. For example, all in-hospital mortality models should use the Beta prior distribution implied by the Dirichlet prior in the OSFD model. If not otherwise specified, the prior distribution for the main effect is $\alpha \sim N(0, 1.82^2)$ (similar to a uniform prior on the probability scale).

14.3 Analytic Approach for Secondary Time-To-Event Endpoints

All inferential time-to-event analyses will be done using a Bayesian piecewise exponential model. The Bayesian time-to-event model is intended to mirror a Cox proportional hazards model, with the

underlying hazard rate modeled with a piecewise exponential model. The underlying hazard will be modeled with a hazard rate for each 10-day period in the model. The prior distribution for each hazard rate is a gamma distribution with 1 day of exposure and a mean equal to the total exposure divided by the total number of events. This prior will have very little weight but will provide numerical stability to the model. Each factor is incorporated as a proportional hazard ratio through an additive linear model of the log-hazard. The default prior for each factor is a the same as for the log-odds in the ordinal model. If other non-specified variables are added to the model, then a normal distribution with mean 0 and standard deviation 10 will be utilized.

14.4 Markov Chain Monte Carlo (MCMC) Model Stability

The Bayesian models have many parameters and there may be risk of poor model stability, including convergence of the MCMC and the mixing behavior. These instabilities may be based on sparse data on the outcome or covariates. The statisticians running the model may make changes that do not affect the overall outcome but provide reliable model diagnostics and scientific rigor. Any alterations will be noted.

14.5 Model Outputs

The standard model outputs for each treatment effect will be the mean, standard deviation, median, and 95% credible intervals (all credible intervals will range from equal-tailed percentiles, so 95% credible intervals will range from the 2.5^{th} percentile to the 97.5^{th} percentile). For the ordinal models, the odds-ratio will be summarized. For the dichotomous endpoints, the odds-ratio will be summarized. For the time-to-event models, the hazard ratio will be summarized.

For each inferential model, a posterior probability that convalescent plasma is superior to control will be provided. This posterior probability has been identified as the primary analysis metric between arms. A posterior probability greater than 99% of superiority has been identified as statistically significant in REMAP-CAP.

14.6 Exploratory Analyses

Exploratory analyses after unblinding will not be considered inferential and no p-values will be presented. Any post-hoc exploratory analyses will use the following methods:

1. Ordinal endpoints will be compared using a cumulative proportional odds model with summaries of the odds-ratio, with 95% confidence intervals and Wilcoxon test for robustness against a lack of proportional odds.
2. Time-to-Event analyses will utilize a Cox proportional hazards model, summarizing the hazard ratios and 95% confidence intervals.
3. Continuous endpoints will compare means with 95% confidence intervals based on two-sample t-test procedures.

4. Dichotomous proportions will be compared using logistic regressions summarizing the odds-ratio and 95% confidence intervals. Differences between proportions will be summarized using observed differences and normal approximations for the 95% credible intervals.

15 SPECIFIC PROSPECTIVE ANALYSES

There are 37* specific prospective analyses, summarized in the table and described in detail below.

The a priori patient subgroups of interest in this domain are:

- Receiving invasive mechanical ventilation at baseline
- Patients with undetectable virus at baseline (convalescent plasma intervention)
    - This will be considered as a dichotomous variable (baseline PCR positive versus negative), reassessed using samples collected at baseline by the trial team, post randomization.
- Patients with different levels of neutralizing antibodies at baseline (convalescent plasma intervention)
    - This will be considered as a dichotomous variable (baseline antibody positive versus negative), reassessed using samples collected at baseline by the trial team, post randomization.
- Dose of neutralizing antibodies received (convalescent plasma intervention, estimated as a function of donor plasma antibody titer and volume of plasma infused
    - This will be considered as a categorical variable with three pre-defined cut-off values (no units received with a Euroimmun ≥ 8, one unit received with a Euroimmun ≥ 8, two units received with a Euroimmun ≥ 8)
- Time from hospitalization to randomization into the trial (convalescent plasma intervention)
    - This will be considered as a categorical variable with three pre-defined cut-off values (up to 72 hours; 3 to 7 days; more than 7 days)
- Patients with known immunodeficiency (convalescent plasma intervention)
    - This will be considered as a dichotomous variable (patient has immunodeficiency (defined as on immunosuppressive drugs or underlying disease causing immune deficiency) versus those who do not)
- All potentially evaluable treatment-by-treatment interactions = all domains that have reached a conclusion (COVID-19 Antiviral Domain, Corticosteroid Domain, Anticoagulation Domain, IL-6ra/control).

The a priori patient sensitivity analyses of interest in this domain are:

- Per-protocol analysis of patients receiving the complete dose of convalescent plasma

Summary Table for COVID-19 Immunoglobulin Therapy Domain

#	Status	Population	Endpoint	Other
15.1	Primary	REMAP-CAP COVID-19 severe and moderate state ITT	OSFD	Includes all interventions and prespecified interactions
15.2	Primary	REMAP-CAP COVID-19 severe and moderate state ITT	In-Hospital Mortality	Includes all interventions and prespecified interactions
15.3	Sensitivity	REMAP-CAP COVID-19 severe and moderate state ITT	Dichotomized OSFD	A logistic regression will be run for each dichotomization of OSFDs as a robustness check.
15.4	Secondary	Unblinded ITT	OSFD	Includes all unblinded interventions and prespecified interactions
15.5	Secondary	Unblinded ITT	In-Hospital Mortality	Includes all unblinded interventions and prespecified interactions
15.6	Sensitivity	Unblinded ITT	OSFD	Remove site and time effects
15.7	Sensitivity	Unblinded ITT	In-Hospital Mortality	Remove site and time effects
15.8	Sensitivity	Unblinded ITT	OSFD	Includes additional interactions between unblinded domains/interventions
15.9	Sensitivity	Unblinded ITT	In-Hospital Mortality	Includes additional interactions between unblinded domains/interventions
15.10	Secondary	Convalescent plasma specific severe state ITT	OSFD	
15.11	Secondary	Convalescent plasma specific severe state ITT	In-Hospital Mortality	
15.12	Sensitivity	Convalescent plasma specific per protocol	OSFD	
15.13	Sensitivity	Convalescent plasma specific per protocol	In-Hospital Mortality	
15.14	Secondary	Unblinded ITT	90-day mortality	
15.15	Secondary	Unblinded ITT	28-day mortality	
15.16	Secondary	Unblinded ITT	Progression to intubation, ECMO, death	In patients not intubated at baseline
15.17	Secondary	Unblinded ITT	Cardiovascular support-free days	
15.18	Secondary	Unblinded ITT	Respiratory support-free days	
15.19	Secondary	Unblinded ITT	Length of ICU Stay	
15.20	Secondary	Unblinded ITT	Length of Hospital Stay	
15.21	Secondary	Unblinded ITT	WHO Scale at 14 days	
15.22	Primary Safety Analysis	Convalescent plasma specific severe state ITT	Serious adverse events per patient	Time effects are removed from the model
15.23	Secondary Safety Analysis	Convalescent plasma specific severe state ITT	Venous thromboembolic events at 90-days	Time effects are removed from the model
15.24	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by SARS CoV-2 PCR status reassessed at randomization
15.25	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by SARS CoV-2 PCR status reassessed at randomization

15.26	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by SARS CoV-2 antibody status reassessed at randomization
15.27	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by SARS CoV-2 antibody status reassessed at randomization
15.28	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by Convalescent plasma Dose administered
15.29	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by Convalescent plasma Dose administered
15.30	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by receiving invasive mechanical ventilation at baseline
15.31	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by receiving invasive mechanical ventilation at baseline
15.32	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by time from hospitalization to randomization
15.33	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by time from hospitalization to randomization
15.34	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by presence or absence of immunodeficiency
15.35	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by presence or absence of immunodeficiency
15.36	Graphical Summaries	Convalescent plasma specific severe state ITT	All endpoints	Including combinations across unblinded domains.
15.37	Graphical Summaries	Convalescent plasma specific moderate state ITT	All endpoints	Including combinations across unblinded domains.

* There is one additional subgroup defined in the DSA based on co-infection with bacterial pathogens that will not be persued, due to the small numbers.

15.1 The primary analysis for the convalescent plasma intervention of the COVID-19 Immunoglobulin Domain

- Population: REMAP-CAP COVID-19 severe and moderate state ITT
- Endpoint: Organ Support-Free Days
- Model: Primary analysis ordinal model
- Factors: All interventions and prespecified interactions, age, sex, site, time
- Analysis: Conducted by the unblinded SAC

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for superiority. A 95% probability of an OR < 1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported for each state:

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control (OR>1)	
Convalescent plasma is futile compared to control (OR<1.2)	

The following will be reported for each state:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.2 The primary in-hospital mortality analysis for the convalescent plasma intervention of the COVID-19 Immunoglobulin Domain

- Population: REMAP-CAP COVID-19 severe and moderate state ITT
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: All interventions and prespecified interactions, age, sex, site, time
- Analysis: Conducted by the unblinded SAC

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for superiority. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported for each state:

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported for each state:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.3 A sensitivity analysis of REMAP-CAP COVID-19 severe and moderate state ITT

- Population: REMAP-CAP COVID-19 severe and moderate state ITT
- Endpoint: Dichotomized Organ-Support Free-Days
- Model: A logistic regression will be run for each dichotomization of OSFDs as a robustness check
- Factors: All interventions and prespecified interactions, age, sex, site, time, convalescent plasma and control interventions
- Analysis: Conducted by the unblinded SAC

The following odds-ratios will be reported for convalescent plasma in the severe state:

OSFD Dichotomization	Mean	SD	Median	95% Credible Interval
-1 vs ≥0				
≤0 vs ≥1				
≤1 vs ≥2				
≤2 vs ≥3				
≤3 vs ≥4				
≤4 vs ≥5				
≤5 vs ≥6				
≤6 vs ≥7				
≤7 vs ≥8				
≤8 vs ≥9				
≤9 vs ≥10				
≤10 vs ≥11				
≤11 vs ≥12				
≤12 vs ≥13				
≤13 vs ≥14				
≤14 vs ≥15				
≤15 vs ≥16				
≤16 vs ≥17				
≤17 vs ≥18				
≤18 vs ≥19				
≤19 vs ≥20				
≤20 vs 21				

15.4 A secondary analysis of OSFD restricted to the Unblinded ITT

- Population: Unblinded Domain ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, pooled IL-6ra) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.5 A secondary analysis of in-hospital mortality restricted to the Unblinded ITT

- Population: Unblinded Domain ITT
- Endpoint: In-hospital mortality
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, pooled IL-6ra) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.6 A sensitivity analysis of OSFD restricted to the Unblinded ITT population with site and time factors removed

- Population: Unblinded Domain ITT
- Endpoint: Organ support free days
- Model: Primary analysis ordinal model
- Factors: Age, sex, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, pooled IL-6ra) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Convalescent plasma				

15.7 A sensitivity analysis of in-hospital mortality restricted to the Unblinded ITT population with site and time factors removed

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary analysis dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, pooled IL-6ra) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

c. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Convalescent plasma				

15.8 A sensitivity analysis of OSFD with interactions between unblinded interventions

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, pooled IL-6ra) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions, additional unblinded interactions in the severe state (interaction between convalescent plasma and pooled antiviral interventions, interaction between convalescent plasma and fixed dose corticosteroids)
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

b. Odds ratio effects and posterior probabilities for the interaction terms between convalescent plasma and the Antiviral Domain / Corticosteroid Domain / Pooled IL-6ra interventions will be reported relative to an additive effect. Odds ratios > 1 indicate a synergistic effect, odds ratios =1 indicate an additive effect, and odds ratios < 1 indicate a sub-additive effect.

c. The prior distributions will be set to N(0,1) for the following interactions: convalescent plasma with fixed dose corticosteroid, convalescent plasma with pooled antiviral interventions, convalescent plasma with pooled IL-6ra interventions.

The following posterior probabilities will be reported for the severe state

Quantity of Interest	Posterior Probability
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	
Convalescent plasma*Fixed dose corticosteroid OR>1	
Convalescent plasma*antivirals OR>1	

Convalescent plasma*Pooled IL-6ra OR>1	

The following will be reported for the severe state:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				
Convalescent plasma*Fixed dose corticosteroid interaction				
Convalescent plasma*antivirals interaction				
Convalescent plasma*Pooled IL-6ra interactions				

15.9 A sensitivity analysis of In-Hospital Mortality with interactions between unblinded interventions

- Population: REMAP-CAP COVID-19 severe and moderate state ITT
- Endpoint: In-hospital mortality
- Model: Primary analysis dichotomous model with weaker priors for the interaction effects
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, pooled IL-6ra) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions, additional unblinded interactions in the severe state (interaction between convalescent plasma and pooled antiviral interventions, interaction between convalescent plasma and fixed dose corticosteroids)
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

b. Odds ratio effects and posterior probabilities for the interaction terms between convalescent plasma and the Antiviral Domain / Corticosteroid Domain / Pooled IL-6ra interventions will be reported relative to an additive effect. Odds ratios > 1 indicate a synergistic effect, odds ratios =1 indicate an additive effect, and odds ratios < 1 indicate a sub-additive effect.

c. The prior distributions will be set to N(0,1) for the following interactions: convalescent plasma with fixed dose corticosteroid, convalescent plasma with pooled antiviral interventions, convalescent plasma with pooled IL-6ra interventions.

The following posterior probabilities will be reported for the severe state

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	
Convalescent plasma*Fixed dose corticosteroid OR>1	

Convalescent plasma*antivirals OR>1	
Convalescent plasma*Pooled IL-6ra OR>1	

The following will be reported for the severe state:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				
Convalescent plasma*Fixed dose corticosteroid interaction				
Convalescent plasma*antivirals interaction				
Convalescent plasma*Pooled IL-6ra interactions				

15.10 A secondary analysis of OSFD restricted to the Convalescent Plasma Specific Severe State ITT

- Population: Convalescent plasma specific severe state ITT
- Endpoint: In-hospital mortality
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.11 A secondary analysis of in-hospital mortality restricted to the Unblinded ITT

- Population: Unblinded Domain ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.12 A sensitivity analysis of OSFD restricted to per protocol patients

- Population: Convalescent plasma specific per protocol
- Endpoint: OSFD
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.13 A sensitivity analysis of in-hospital mortality in per protocol patients

- Population: Convalescent plasma specific per protocol
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.14 A secondary analysis of 90-day mortality

- Population: Unblinded ITT
- Endpoint: 90-day mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.15 A secondary analysis of 28-day mortality

- Population: Unblinded ITT
- Endpoint: 28-day mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.16 A secondary analysis of progression to intubation, ECMO or death

- Population: Unblinded ITT not on MV or ECMO at baseline.
- Endpoint: Progression to MV, ECMO, or death
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.17 A secondary analysis of REMAP-CAP COVID-19 severe state ITT cardiovascular support free days

- Population: Unblinded ITT
- Endpoint: Vasopressor/Inotropes free days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.18 A secondary analysis of REMAP-CAP COVID-19 severe state ITT respiratory support free days

- Population: Unblinded ITT
- Endpoint: Respiratory support free days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.19 A secondary analysis of length of ICU stay

- Population: Unblinded ITT
- Endpoint: Length of ICU stay
- Model: Primary TTE model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.20 A secondary analysis of length of hospital stay

- Population: Unblinded ITT
- Endpoint: Hospital length of stay
- Model: Primary TTE model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.21 A secondary analysis of WHO scale at 14-days

- Population: Unblinded ITT
- Endpoint: Modified WHO Ordinal scale at 14-days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.22 A primary safety analysis for convalescent plasma

- Population: Convalescent plasma specific ITT
- Endpoint: Serious Adverse Events (SAE)
- Model: Primary dichotomous model
- Factors: Age, sex, site, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	

The following will be reported:

Odds-Ratio Parameter	**Mean**	**SD**	**Median**	**95% Credible Interval**
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Convalescent plasma				

15.23 A secondary safety analysis of venous thromboembolic events

- Population: Convalescent plasma specific ITT
- Endpoint: Venous thromboembolic events at 90-days
- Model: Primary dichotomous model
- Factors: Age, sex, site, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Convalescent plasma is superior to control	

The following will be reported:

Odds-Ratio Parameter	**Mean**	**SD**	**Median**	**95% Credible Interval**
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Convalescent plasma				

15.24 A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by SARS CoV-2 PCR Status subgroup

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with PCR status (positive versus negative), immune modulation interventions (control, pooled IL-6ra), corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in PCR positive patients	
Convalescent plasma is superior compared to control in PCR negative patients	
Convalescent plasma is futile compared to control in PCR positive patients	
Convalescent plasma is futile compared to control in PCR negative patients	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				

Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in PCR positive				
Convalescent plasma in PCR negative				

15.25 A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by SARS CoV-2 PCR Status subgroup

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with PCR status (positive versus negative), immune modulation interventions (control, pooled IL-6ra), corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in PCR positive patients	
Convalescent plasma is superior compared to control in PCR negative patients	
Convalescent plasma is futile compared to control in PCR positive patients	
Convalescent plasma is futile compared to control in PCR negative patients	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				

Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in PCR positive				
Convalescent plasma in PCR negative				

15.26 A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by SARS CoV-2 antibody Status subgroup

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with antibody status (positive vs negative), corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in PCR positive patients	
Convalescent plasma is superior compared to control in PCR negative patients	
Convalescent plasma is futile compared to control in PCR positive patients	
Convalescent plasma is futile compared to control in PCR negative patients	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				

Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in PCR positive				
Convalescent plasma in PCR negative				

15.27 A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by SARS CoV-2 antibody Status subgroup

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with antibody status (positive vs negative), corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in PCR positive patients	
Convalescent plasma is superior compared to control in PCR negative patients	
Convalescent plasma is futile compared to control in PCR positive patients	
Convalescent plasma is futile compared to control in PCR negative patients	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				

Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in PCR positive				
Convalescent plasma in PCR negative				

15.28 A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by convalescent plasma Dose administered subgroup

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with dose subgroup (low vs mid vs high), corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in the 'low' dose subgroup	
Convalescent plasma is futile in the 'low' dose subgroup	
Convalescent plasma is superior to control in the 'mid' dose subgroup	
Convalescent plasma is futile compared to control in the 'mid' dose subgroup	
Convalescent plasma is superior to control in the 'high' dose subgroup	
Convalescent plasma is futile compared to control in the 'high' dose subgroup	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				

Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in the 'low' dose subgroup				
Convalescent plasma in the 'mid' dose subgroup				
Convalescent plasma in the 'high' dose subgroup				

15.29 A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by convalescent plasma Dose administered subgroup

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with dose subgroup (low vs mid vs high), corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in the 'low' dose subgroup	
Convalescent plasma is futile in the 'low' dose subgroup	
Convalescent plasma is superior to control in the 'mid' dose subgroup	
Convalescent plasma is futile compared to control in the 'mid' dose subgroup	
Convalescent plasma is superior to control in the 'high' dose subgroup	
Convalescent plasma is futile compared to control in the 'high' dose subgroup	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				

Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in the 'low' dose subgroup				
Convalescent plasma in the 'mid' dose subgroup				
Convalescent plasma in the 'high' dose subgroup				

15.30 A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by receipt of mechanical ventilation at baseline subgroup

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with baseline mechanical ventilation status, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in patients receiving mechanical ventilation at baseline	
Convalescent plasma is superior compared to control in patients not receiving mechanical ventilation at baseline	
Convalescent plasma is futile compared to control in patients receiving mechanical ventilation at baseline	
Convalescent plasma is futile compared to control in patients not receiving mechanical ventilation at baseline	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				

Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients receiving mechanical ventilation at baseline				
Convalescent plasma in patients not receiving mechanical ventilation at baseline				

15.31 A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by receipt of mechanical ventilation at baseline subgroup

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with baseline mechanical ventilation status, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in patients receiving mechanical ventilation at baseline	
Convalescent plasma is superior compared to control in patients not receiving mechanical ventilation at baseline	
Convalescent plasma is futile compared to control in patients receiving mechanical ventilation at baseline	
Convalescent plasma is futile compared to control in patients not receiving mechanical ventilation at baseline	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				

Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients receiving mechanical ventilation at baseline				
Convalescent plasma in patients not receiving mechanical ventilation at baseline				

15.32 A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by time from hospitalization to randomization

- Population: Unblinded ITT
- Endpoint: OSFD
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with time from hospitalization to randomization subgroups, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

b. Time from hospitalization to randomization into the trial (convalescent plasma intervention) will be considered as a categorical variable with three pre-defined cut-off values (up to 72 hours; 3 to 7 days; more than 7 days). The reference group is the subgroup randomized <72 hours from hospitalization.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in patients randomized within 72 hours after hospitalization	
Convalescent plasma is superior compared to control in patients randomized 3-7 days after hospitalization	
Convalescent plasma is superior compared to control in patients randomized >7 days from hospitalization	
Convalescent plasma is futile compared to control in patients randomized within 72 hours after hospitalization	
Convalescent plasma is futile compared to control in patients randomized 3-7 days after hospitalization	

Convalescent plasma is futile compared to control in patients randomized >7 days after hospitalization	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients randomized <72 hours after hospitalization				
Convalescent plasma in patients randomized 3-7 days after hospitalization				
Convalescent plasma in patients randomized >7 days after hospitalization				
Randomization 3-7 days after hospitalization (relative to <72 hours subgroup)				
Randomization >7 days after hospitalization (relative to <72 hours subgroup)				

15.33 A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by time from hospitalization to randomization

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with time from hospitalization to randomization subgroups, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.
b. Time from hospitalization to randomization into the trial (convalescent plasma intervention) will be considered as a categorical variable with three pre-defined cut-off values (up to 72 hours; 3 to 7 days; more than 7 days). The reference group is the subgroup randomized <72 hours from hospitalization.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in patients randomized within 72 hours after hospitalization	
Convalescent plasma is superior compared to control in patients randomized 3-7 days after hospitalization	
Convalescent plasma is superior compared to control in patients randomized >7 days from hospitalization	
Convalescent plasma is futile compared to control in patients randomized within 72 hours after hospitalization	

Convalescent plasma is futile compared to control in patients randomized 3-7 days after hospitalization	
Convalescent plasma is futile compared to control in patients randomized >7 days after hospitalization	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients randomized <72 hours after hospitalization				
Convalescent plasma in patients randomized 3-7 days after hospitalization				
Convalescent plasma in patients randomized >7 days after hospitalization				
Randomization 3-7 days after hospitalization (relative to <72 hours subgroup)				
Randomization >7 days after hospitalization (relative to <72 hours subgroup)				

15.34 A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by immunodeficiency status

- Population: Unblinded ITT
- Endpoint: OSFD
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with immunodeficiency status, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

b. There will be two subgroups based on the patients known immunodeficiency (convalescent plasma intervention): patient has immunodeficiency versus those who do not.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in patients with immunodeficiency	
Convalescent plasma is superior compared to control in patients without immunodeficiency	
Convalescent plasma is futile compared to control in patients with immunodeficiency	
Convalescent plasma is futile compared to control in patients without immunodeficiency	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				

Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients with immunodeficiency				
Convalescent plasma in patients without immunodeficiency				
Immunodeficiency (relative to no immunodeficiency subgroup)				

15.35 A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by immunodeficiency status

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with immunodeficiency status, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

b. There will be two subgroups based on the patients known immunodeficiency (convalescent plasma intervention): patient has immunodeficiency versus those who do not.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in patients with immunodeficiency	
Convalescent plasma is superior compared to control in patients without immunodeficiency	
Convalescent plasma is futile compared to control in patients with immunodeficiency	
Convalescent plasma is futile compared to control in patients without immunodeficiency	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval

Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients with immunodeficiency				
Convalescent plasma in patients without immunodeficiency				
Immunodeficiency (relative to no immunodeficiency subgroup)				

15.36 Graphical summaries

The following graphical summaries will be provided for all endpoints:

- Population: Convalescent plasma specific ITT
- Endpoint: all endpoints
- Factors: Convalescent plasma and no immunoglobulin interventions
- Analysis: Conducted by the ITSC Analysis Center

The following additional graphical summaries will be provided for OSFD and in-hospital mortality:

- Population: Convalescent plasma specific ITT
- Endpoint: OSFD, in-hospital mortality
- Factors:
    - Convalescent plasma and no immunoglobulin interventions interacted with pooled fixed-dose corticosteroid
    - Convalescent plasma and no immunoglobulin interventions interacted with pooled antiviral domain (no antiviral control, HCQ, Kaletra, HCQ + Kaletra)
    - Convalescent plasma and no immunoglobulin interventions interacted with pooled IL-6ra interventions (no immune modulation therapy, pooled IL-6ra)
- Analysis: Conducted by the ITSC Analysis Center

Appendix A: Definition of organ support-free days

This outcome is an ordinal scale of integers from –1 to 22 for each state (Moderate or Severe) derived from a composite of the patient's vital status at the end of acute hospital admission and days spent receiving organ failure support while admitted to an ICU (including a repurposed ICU) during the 21 days (504 hours) after randomisation.

A patient enrolled in the Severe State while still in an Emergency Department is regarded as 'admitted to an ICU' and the time of commencement of organ failure support is the time of randomisation, as it is for all other patients in the Severe State.

Patents who survive to hospital discharge and are enrolled in one or more domains in the Moderate State and are enrolled in one or more domains in the Severe State have a primary end point value for each state, which may be different.

If deceased between first enrolment and ultimate hospital discharge, code OutcomeDay21 as -1

If not deceased, ModerateOutcomeDay21 = 21 – (the sum of the length of time in days and part-days between time of first commencement of organ failure support while admitted to an ICU and the time of last cessation of organ failure support during that ICU admission plus time between first commencement and last cessation of organ failure support during any and all subsequent readmissions to ICU, censored at the 504 hours after enrolment in the Moderate State)

- A patient who is enrolled in the Moderate State who never receives organ failure support while admitted to an ICU has an ModerateOutcomeDay21 = 22.
- A patient who is enrolled in the Moderate State in a ward location who commences organ failure support on the ward and is transferred to an ICU while receiving organ failure support has a commencement time of organ failure support corresponding to the time of ICU admission.

If not deceased, SevereOutcomeDay21 = 21 – (the sum of the length of time in days and part- days between time of enrolment and the time of last cessation of organ failure support during that ICU admission plus the lengths of time between first commencement and last cessation of organ failure support during any and all subsequent readmissions to ICU, censored at 504 hours after the time of enrolment

Decimals are rounded up or down to nearest whole day.

If transferred between hospitals before the last study day 21 and known to be alive at ultimate hospital discharge use all available information to calculate Outcome Day21 with an assumption that no subsequent organ failure support in an ICU was provided.

If transferred between hospitals before the last study day 21 and vital status at ultimate hospital discharge is not known, code as follows:

- If last known to be on a ward use all available information to calculate Outcome Day 21 with an assumption that the patient has not died prior to ultimate hospital discharge and that there were no subsequent ICU admissions.
- If last known to be in an ICU, code OutcomeDay21 as missing (999)

If a patient is discharged alive from the ultimate hospital before 504 hours from each enrolment, assume all subsequent time is alive and without provision of organ failure support in an ICU.
If the patient is alive at the end of one or both censoring time points, the hours will be calculated as above. If the patient dies after the end of one or both of the censoring time points and before hospital discharge, the value will be updated to -1
A patient who remains admitted to an acute hospital and is still alive at the end of study day 90 no further changes to coding will be made.