



Statistical Analysis Plan for the secondary analysis of long-term survival and disability in relation to randomized treatments in patients with suspected or proven COVID-19 in the REMAP-CAP trial

COVID-19 Long-term outcomes SAP Version 1.1 dated 10 March 2022



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1. COVID-19 LONG-TERM OUTCOMES SAP VERSION

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

1.1. Version history

Version 1: Finalized on 17 February 2022.

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2. SAP AUTHORS

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3. INTRODUCTION

This statistical plan for the analysis of the Long-term outcomes in the pandemic stratum of the REMAP-CAP trial is an appendix to the Pandemic Appendix to Core (PATC) Statistical Analysis Plan (SAP). This plan details the statistical analyses in the original REMAP-CAP core SAP and the pandemic stratum SAP applied to the analysis of longer-term outcomes for participants in the immune modulation, corticosteroid, immunoglobulin, anticoagulation, antiviral, and antiplatelet domains.

REMAP-CAP explores multiple treatments by randomizing patients within multiple domains simultaneously. The adaptive platform trial was designed to produce modular results for individual interventions or full domains upon reaching platform conclusions. Each of the domains analysed in this SAP has been unblinded and results for the primary and key secondary outcomes made public. This document prespecifies the plan for analysis of long-term outcomes among these participants.

As outlined in the core protocol, day 90 all-cause mortality is collected in all regions. Additional outcomes beyond day 90 are collected, where feasible, may be mandated in a DSA or a RSA, and may be collected by central trial staff or site staff. The decision to participate in the collection of outcomes beyond day 90 was made regionally or locally reflecting funding, competent authority approval, and site resource availability. These outcomes include:

- **Survival** at 6 months after enrollment (where feasible, refer to relevant regional RSA)
- **Health-related quality of life (HRQoL)** at 6 months after enrollment using the EQ5D-5L (where feasible, refer to relevant regional RSA)
- **Disability status** measured at 6 months after enrollment using the WHODAS 2.0, 12-item instrument (where feasible, refer to relevant regional RSA)

This statistical analysis plan (SAP) outlines an analysis of these long-term measures in relation to investigational treatments received during the trial among participants in closed domains. In this SAP, we explore the hypothesis that the observed treatment effect persists over long-term follow-up, evidenced by favourable survival outcomes, freedom from major disability, and better quality of life. In a distinct but complementary SAP, we outline a second analysis which examine these long-term outcomes in greater detail, including the component parts, as well as evaluates predictors of long-term outcomes (see separate SAP for more details).

4. PLATFORM 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. REMAP-CAP defines several statistical triggers within the trial that, at any adaptive analysis of the trial, may result in a declaration of a platform conclusion. Participants in the platform are stratified into states for the purpose of analysis on the basis of illness severity at time of randomization (moderate: noncritically ill; severe: critically ill): In this analysis, data are only available in the severe state.

5. PLATFORM DOMAINS INCLUDED IN THIS SECONDARY ANALYSIS

The analysis of longer-term outcomes will be conducted on closed domains in the PISOP Stratum. These domains include:

1. Corticosteroid domain
2. Immune modulation domain
3. Antiviral domain
4. Immunoglobulin domain
5. Anticoagulation domain
6. Antiplatelet domain

6. INTERVENTIONS

Only interventions that have been closed will be included in the analysis of longer-term outcomes. Where a domain reached a platform conclusion and was closed, but has subsequently reopened, only patients enrolled prior to the initial closure of the domain will be included in the analysis.

The interventions which will be included in the analysis are:

Corticosteroid domain:

1. No corticosteroid/hydrocortisone (control)
2. Fixed duration hydrocortisone for 7 days (fixed-duration)
3. Shock-Dependent hydrocortisone (shock-dependent) or
4. High-Dose hydrocortisone for 7 days

For consistency with the original corticosteroid analysis (and due to the small number of patients recruited in the high dose hydrocortisone group), the fixed dose hydrocortisone and high-dose hydrocortisone groups will be report as a pooled fixed-dose hydrocortisone group.

Immune modulation domain:

1. No immune modulation for COVID-19 (control)
2. Anakinra (interleukin-1 receptor antagonist; IL1Ra)
3. Tocilizumab (IL-6 receptor antagonist; IL6Ra)
4. Sarilumab (IL-6 receptor antagonist; IL6Ra)

The interferon-beta-1a (IFN- β 1a) intervention within the domain will not be analyzed due to the low number of patients randomized (n=19 with consent in the severe state). As tocilizumab and sarilumab met the predefined trigger for equivalence, they will be primarily reported as a pooled IL-6 RA group (with individual interventions effects also reported).

Anticoagulation domain:

1. Usual care thromboprophylaxis
2. Therapeutic anticoagulation with heparin

Antiviral domain:

1. No antiviral for COVID-19 (control)
2. Lopinavir/ritonavir
3. Hydroxychloroquine
4. Hydroxychloroquine and lopinavir/ritonavir

Immunoglobulin domain:

1. No immunoglobulin against COVID-19 (control)
2. Convalescent plasma

The delayed convalescent plasma intervention within the domain will not be analyzed due to the low number of patients randomized (n=11 in the severe state).

Antiplatelet domain:

1. No antiplatelet (control)
2. Aspirin
3. P2Y12 inhibitor

As the aspirin and P2Y12 inhibitor groups met the predefined trigger for equivalence, they will be primarily reported as a pooled antiplatelet group (with individual interventions effects also reported).

Due to sufficient data support, the interaction effect will be estimated for interventions in the Antiplatelet Domain and interventions in the Anticoagulation Domain. Interaction effects of the interventions in other domains are not prespecified in this secondary analysis due to insufficient data support to estimate interactions. Any analysis of other interaction effects will be treated as exploratory.

7. DISEASE STATES

There are two disease states in the PAAtC, which are **moderate** and **severe**. Long term outcomes will be evaluated in patients enrolled in the severe state, as outcomes beyond day 90 are only collected in patients with a randomization in the severe state.

8. ANALYSIS POPULATIONS

1. Unblinded ITT. All patients randomized in the severe state to an intervention in the domains of interest (where the randomization occurred prior to the initial closure of the domain) that have been unblinded in which enrollment has been closed within the PISOP stratum.

Sensitivity analyses will be conducted in restricted populations to assess key assumptions of analyses of the Unblinded ITT. The Unblinded ITT analyses assume a constant treatment effect for all patients randomized with suspected or proven COVID-19. A sensitivity analysis removing patients with only negative COVID-19 tests will qualitatively assess whether the treatment effect is consistent for suspected and non-negative patients. The primary analysis in the Unblinded ITT population uses all patients to estimate covariate effects based on an assumption that covariate effects are proportional across domains. For each domain, we assess the sensitivity of the assumption of constant covariate effects by repeating the primary analysis in a population restricted to only patients randomized within that domain. The domain specific ITT populations also provide an isolated view of the effects of the domain-specific interventions without the adjustment of interventions from other domains. Sensitivity analyses will be conducted in the following populations:

2. Unblinded non-negative COVID-19. All patients in the Unblinded ITT population after removing those with ≥ 1 negative test for COVID-19 and no positive tests. This population comprises of

patients who were randomized as “suspected” COVID-19 but never proven to either have the disease or not, due to any reason.

3. Immune modulation specific ITT population. All patients randomized in the severe state to Tocilizumab, Sarilumab, Anakinra, or no immune modulation interventions in the Immune Modulation Therapy Domain within the PISOP stratum only.
4. Corticosteroid specific ITT population. All patients randomized to No corticosteroid/hydrocortisone (control), Fixed duration hydrocortisone for 7 days (fixed-duration), Shock-Dependent hydrocortisone (shock-dependent) or High-Dose hydrocortisone for 7 days in the Corticosteroid Domain within the PISOP stratum only. For all analyses and data summaries the high-dose 7-day hydrocortisone arm will be combined with the fixed-duration arm. These interventions were originally nested, which allows their pooling, and very few patients were randomized to high-dose 7-day hydrocortisone.
5. Antiviral specific ITT population. All patients within the PISOP stratum randomized in the severe state to Lopinavir/ritonavir, Hydroxychloroquine, Hydroxychloroquine and lopinavir/ritonavir, or no antiviral for COVID-19.
6. Immunoglobulin specific ITT population. All patients within the PISOP stratum randomized in the severe state to convalescent plasma or no immunoglobulin against COVID-19.
7. Anticoagulation specific ITT population. All patients randomized in the severe state to usual care thromboprophylaxis anticoagulation or therapeutic anticoagulation in the Anticoagulation Therapy Domain within the PISOP stratum only.
8. Antiplatelet specific ITT populations. All patients randomized in the severe state to Aspirin, P2Y12 inhibitor or no antiplatelet in the Antiplatelet Domain.

9. ENDPOINTS

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

1. 180-day Mortality

- a. This is the primary endpoint for the longer-term outcomes analysis
- b. This is a time-to-event endpoint through 180-days. This will maximise use of available data due to some sites and regions not collecting data on patient status following 90 days post randomization.
- c. Any patient without 180-day mortality data recorded will be censored at their last known status alive.

2. 90-day Mortality

- a. This is a secondary outcome. While some domains reported follow-up through 90 days, not all did, and it is anticipated that additional data will be available.
- b. This is analyzed as a dichotomous endpoint of whether a patient is alive at 90 days following randomization.

3. EQ-5D-5L

The EQ5D-5L is a preference-based QoL instrument comprised of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Respondents are asked to choose the most appropriate option from five alternatives (no, slight, moderate, severe or extreme problems). In addition, respondents are asked to indicate their present health state on a visual analogue scale (EQ VAS) ranging from the worst imaginable health state (“0”) to the best imaginable health state (“100”)

a. Utility score

This is a secondary outcome analyzed as a continuous endpoint.

Utility scores will be calculated where a valid response (1 to 5) is available for each of the 5 EQ5D5L domains, and the EQ5D5L was conducted within the 12 weeks following day 180.

Scores will be calculated using the crosswalk link function and the individual responses to the EQ-5D-5L descriptive system, using the UK time trade off (TTO) value set. Values will lie between -0.594 and 1.00. Among those with an EQ-5D score (alive at 6 months), available data will be presented visually and the distribution summarized with descriptive statistics. For the purposes of modeling treatment effects, patients who are known to be deceased at day 180 will be given a score of 0; this acknowledges that there are some utility states ranked worse than death. The inclusion of a value for death allows this continuous outcome to account for the competing risk of death in one composite endpoint.

For the modeling of treatment interactions, unknown values of EQ-5D utility scores will be multiply imputed within the Bayesian model based on the individual’s mortality status and covariates.

b. VAS

This is a secondary outcome analyzed as a continuous endpoint of self-reported health status ranging from 0 to 100. This endpoint will be summarized by treatment arm visually, and through descriptive statistics and not analyzed. Only values where that were determined within the 12 weeks following day 180 will be included.

4. WHODAS

The 12-item WHODAS 2.0 which covers six domains of functioning with scores from 0 (no difficulty) to 4 (extreme difficulty) and a total score ranging from 0 to 48, with higher scores representing greater disability.

a. Percentage score

The total score is divided by 48 and multiplied by 100 to convert it to a percentage of maximum disability. Where a single WHODAS item was missing, the mean value of the remaining 11 items is assigned to the missing item. Higher numbers represent a higher level of disability. Score will only be calculated where the WHODAS was conducted within the 12 weeks following day 180.

b. Disability category

WHODAS percentage scores can be used to determine mutually exclusive disability categories: 1) no disability (0–4.5%); 2) mild disability (4.5–24.5%); 3) moderate disability (24.5–49.5%); 4) severe disability (49.5–95.5%); and 5) complete disability (95.5–100%).

In addition to the categories above, graphical/descriptive summaries may include categories for patients that die and those alive with unknown disability.

To account for missing data and the competing risk of death, this endpoint will be analyzed jointly with 180-day mortality, as detailed below. Unknown values of disability category will be multiply imputed within the Bayesian model based on the individual's mortality status and covariates.

10. GRAPHICAL DATA SUMMARIES

1. Dichotomous endpoints will be plotted using bar plots or plots of the proportion point estimate and uncertainty interval.
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.
3. Ordinal endpoints will be plotted using stacked cumulative bar plots and cumulative probability plots.

11. DESCRIPTIVE STATISTICS

1. Dichotomous or categorical endpoints will be summarized by the proportion in each category.
2. Time-to-event outcomes will be summarized by the 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles from the Kaplan-Meier estimates, as available.
3. Continuous endpoints will be summarized by the median, mean, IQR, and standard deviation.
4. Ordinal endpoints will be summarized by the cumulative frequency of each outcome. The 25th, 50th, and 75th percentiles will be summarized.

12. BASELINE CHARACTERISTICS

The following demographics will be summarized. More may be added as baseline summaries: Age, sex, BMI, ethnicity, APACHE II score (measured from hospital admission to randomization), confirmed SARS CoV-2 infection, preexisting conditions, baseline use of high-frequency nasal oxygenation, non-invasive ventilation, invasive mechanical ventilation, ECMO, vasopressors/inotropes, renal replacement therapy, and miscellaneous physiological values and laboratory values. It is recognized as a potential limitation that no data on baseline QOL/health status is available.

13. ANALYTIC APPROACH

Each inferential analysis will be done using a Bayesian model. Some default frequentist methods may be used for exploration and description. A summary of the analyses methods is provided below. In addition to the models described below, as noted above, descriptive statistics will be presented.

13.1. Modeling Conventions

Each analysis model will include patient-level covariates including baseline patient characteristics and covariates representing randomized treatment assignment across domains. Each model will include the same set of covariates that are included in the primary analysis model for the pandemic stratum of REMAP-CAP. This set of covariates includes patient age category, patient sex, enrollment site nested within country, time of enrollment, indicators of randomization to unblinded interventions, and indicators of domain randomization and domain ineligibility. Specific details of the model formulation for covariates and prior distributions are provided in the Current State Document for the Pandemic Statistical Model, Version 3.2 dated 17 May 2021.

In addition, the analyses in this SAP will use the following conventions:

- 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
- The tocilizumab arm will be combined with the sarilumab arm (unless otherwise specified). They were originally nested, which allows their pooling, and they met the prespecified trigger for equivalence
- The aspirin arm will be combined with the P2Y12 inhibitor arm (unless otherwise specified). They were originally nested, which allows their pooling, and they met the prespecified trigger for equivalence
- All sites within a country that have <5 patients randomized will be combined into a single site within that country

13.2. Analytic Approach for 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 as piecewise constant. The underlying hazard will be modeled with a hazard rate for each 15-day period up to day 90 and the 90-day period from day 90 to 180. The prior distribution for the hazard rate is a gamma distribution with 1 day of exposure and a mean equal to the total exposure (in days) 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 rate through an additive linear model of the log-hazard. The default prior for each factor is the same as for the log-odds in the ordinal model. If other variables are added to the model and no prior distribution is specified elsewhere, then a normal distribution with mean 0 and standard deviation 10 will be utilized.

Time to event endpoints will be summarized with Kaplan Meier curves. In addition to the unadjusted KM curves, fitted survival curves will be presented to summarize the model fit on a cohort of patients adjusting for covariates. Predicted survival curves will be produced for each patient in a cohort of interest, and then the average of these curves will be taken to summarize the average survival of the cohort. To assess the difference in fitted survival curves by treatment, the average fitted survival curves will be shown for the combined cohort (control+treatment patients) first assuming the cohort received control and then assuming they received the treatment of interest. Given the use of response adaptive randomization, imbalances may exist in these baseline variables, and as such adjustment may provide a more accurate estimate of association.

The proportional hazards assumption will be assessed for each intervention using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals. Residuals will be assessed for each intervention in the domain-specific ITT population defined in Section 8. If evidence of non-proportionality is present, sensitivity analyses with non-proportional effects may be considered to assess the sensitivity of model results to the proportional hazards assumption.

13.3. Analytic Approach for Dichotomous Endpoints

A Bayesian logistic regression model will be used for each dichotomous outcome. The model is the standard logistic link function model:

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

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) and the prior distribution for covariate effects is a normal distribution with mean 0 and variance 10.

13.4. Analysis of EQ5D Utility Score

The EQ5D utility score is analyzed with a mixture model including two components: 1) a continuous distribution of utility scores for patients that survive to day 180, and 2) a point mass at 0 for patients that die before day 180. For patients with known day 180 vital status, their mixture component assignment is known. However some patients are censored alive before day 180, so their mixture component assignment is unknown. For this subset of patients censored before day 180, we treat this mixture assignment as an unknown variable and estimate a posterior distribution for the unknown time of death for each patient that is censored. As a result, unknown values of EQ5D utility score are multiply imputed as a weighted average of zero and a continuous distribution that is a function of the patient's covariates. The weight of each component in this imputation is based on the probability that a censored patient dies before day 180; patients censored closer to day 180 will have a smaller probability of dying before day 180 than those censored earlier. Patients known to be dead at day 180 will have EQ5D utilities of 0, and patients known to be alive on day 180 will be imputed from a non-zero continuous distribution based on their covariates.

We specify a joint model of time-to-death up to 180 days and EQ5D utility score conditional on 180-day vital status. First, we model the time to death up to day 180 as described in Section 13.2. This model will produce an estimated hazard ratio effect for each intervention in the unblinded domains. In addition, this model will produce a posterior distribution for the time of death of censored patients.

Next, we model the utility score conditional on whether the time of death is before or after day 180. Let Y_i denote the EQ5D utility score for individual i . We model the EQ5D utility score conditional on the variable $d_i \in \{0,1\}$ which is an indicator taking on value 1 if individual i dies before day 180 and value 0 otherwise. Note that, since d_i is unknown for censored patients, we will draw multiple possible values for d_i from the posterior distribution of the imputed time of death. We model the utility score as follows:

$$Y_i = \begin{cases} 0, & d_i = 1 \\ \alpha + x_i' \beta + \epsilon_i, & d_i = 0 \end{cases}$$

where α is the intercept, x_i is the vector of covariate values for individual i , β is the vector of unknown coefficients, and ϵ_i is the normally distributed residual error. We place normal priors with mean zero and variance 1 on α and each coefficient β and a Gamma(0.5,0.5) prior on the residual noise. This subcomponent of the model will produce an estimate of a treatment effect for each unblinded intervention in terms of a mean change in utility for survivors.

This model will produce distinct treatment effects within each subcomponent of the joint model: an effect on mortality and an effect on the utility score of survivors. In addition to presenting these separate summaries, the overall expected effect on the utility score of all patients will be summarized for each intervention.

13.5. Analysis of WHODAS Disability Category

WHODAS disability category is analyzed with a mixture model including two components: 1) an ordinal model of disability category for patients that survive to day 180, and 2) the worst category of “death” for patients that die before day 180. For patients with known day 180 vital status, their mixture component assignment is known. However, some patients are censored alive before day 180, so their mixture component assignment is unknown. For this subset of patients censored before day 180, we treat this mixture assignment as an unknown variable and estimate a posterior distribution for the unknown time of death for each patient that is censored. As a result, unknown values of disability category are multiply imputed with some probability on the “Death” category and some probability on the disability categories that is a function of the patient’s covariates. The weight of each component in this imputation is based on the probability that a censored patient dies before day 180; patients censored closer to day 180 will have a smaller probability of dying before day 180 than those censored earlier.

To include information about 180-day mortality in the imputation of disability category, we specify a joint model of 180-day mortality and disability category conditional on 180-day mortality. First, we model 180-day mortality as a time to event outcome as described in Section 13.2. This model will produce an estimated hazard ratio effect for each intervention in the unblinded domains. In addition, this model will produce a posterior distribution for the time of death of censored patients. Next, we model the disability category conditional on whether the time of death is before or after day 180. Let Z_i denote the disability category for individual i . We model the disability category conditional on the variable $d_i \in \{0,1\}$ which is an indicator taking on value 1 if individual i dies before day 180 and value 0 otherwise. Note that, since d_i is unknown for censored patients, we will draw multiple possible values for d_i from the posterior distribution of the imputed time of death. If $d_i = 1$, we model the disability score as the worst category of “Death”. If $d_i = 0$, we model the disability score through a proportional odds model as a five-level ordinal variable from “complete disability” to “no disability”. The proportional odds model will include the model factors described in Section 13.1. Unless otherwise specified, covariate effects will have normal priors with mean 0 and variance 1. The prior for the ordinal outcome distribution will be a Dirichlet distribution with a total weight of one patient and equal probability across each category. This subcomponent of the model will produce a treatment effect estimate for each intervention in terms of an odds ratio effect on disability category for survivors.

This model will produce distinct treatment effects within each subcomponent of the joint model: an effect on mortality and an effect on the disability category of survivors. In addition to presenting these separate summaries, the overall expected effect on the disability category (including death as a category) of all patients will be summarized for each intervention.

13.6. Subgroup Analyses

Post-trial sub-groups will be used in analysis. The patient sub-groups of interest are:

- Ventilatory status at baseline – mechanical ventilation vs non-mechanical ventilation
- Patients with known immunodeficiency – patients with an immunodeficiency (defined as on immunosuppressive drugs or underlying disease causing immune deficiency) versus those who do not.

Subgroup analyses will be performed by independently running the analysis model within each group of patients defined by the subgroup variable.

13.7. Markov Chain Monte Carlo (MCMC) Model Stability

The Bayesian models have many parameters and there may be risk of poor model stability, including convergence and mixing behavior of the MCMC sampler. 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 interpretation but provide reliable model diagnostics and scientific rigor. Any alterations will be noted.

13.8. 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 be equal-tailed intervals, so 95% credible intervals will range from the 2.5th percentile to the 97.5th percentile of the posterior distribution). In addition, density plots of the prior and posterior distributions of model parameters may be presented to provide a visualization of the entire distributions. For ordinal endpoints, the odds-ratios will be summarized. For dichotomous endpoints, the odds-ratio will be summarized. For the time-to-event endpoints, the hazard ratios will be summarized. The direction of benefit for the relative effects may vary by endpoint based on the clinical interpretation. Relative effects for negative events (i.e., mortality) will be presented so that <1 implies patient benefit. Relative effects for positive events (i.e., survival) will be provided so that $OR > 1$ implies benefit.

In some cases, relative effects may be converted to average absolute effects. In these instances, it should be noted that the absolute effect for an individual will vary based on baseline risk. The average absolute effects are intended to summarize adjusted across-group differences in outcome rather than the absolute effect for an individual. For dichotomous endpoints, absolute effects will be computed based on the posterior distribution of the odds ratio and the observed proportion of events in the control/reference group. For ordinal endpoints, absolute effects may be presented as a shift in a quantile (i.e., median) of the distribution or as an absolute difference in the cumulative probability for a clinically meaningful dichotomization of the ordinal scale. For time to event endpoints, absolute effects may be presented as a shift in a quantile of the fitted survival curve or as an absolute difference in the estimated proportion of patients that survive to some landmark.

For each inferential model, a posterior probability that one arm is superior will be provided for each comparison between arms. This posterior probability has been identified as the primary analysis metric between arms.

13.9. Exploratory Analyses

Exploratory analyses will not be considered inferential and no p-values will be presented. Post-hoc exploratory analyses may use the following methods:

1. Time-to-Event analyses will utilize a Cox proportional hazards model, summarizing the hazard ratios and 95% confidence intervals.
2. Dichotomous proportions will be compared using logistic regression 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.
3. Ordinal endpoints will be compared using a cumulative proportional odds model with summaries of the odds-ratio, 95% confidence intervals, and Wilcoxon tests for robustness against a lack of proportional odds.
4. Continuous endpoints will compare means with 95% confidence intervals based on two-sample t-test procedures. Frequentist linear regression models may be used to compare outcomes while adjusting for covariates.

14. SPECIFIC PLANNED ANALYSES

The specific planned analyses are summarized in the table and described in detail below.

#	Status	Population	Endpoint	Other
14.1	Primary	Unblinded population ITT	180-day Mortality	Includes all interventions and pre-specified interaction between anticoagulation and antiplatelet
14.2	Secondary	Unblinded population ITT	90-day Mortality	Includes all interventions and pre-specified interaction between anticoagulation and antiplatelet
14.3	Secondary	Unblinded population ITT	EQ5D5L utility score	Includes all interventions and pre-specified interaction between anticoagulation and antiplatelet
14.4	Secondary	Unblinded population ITT	WHODAS	Includes all interventions and pre-specified interaction between anticoagulation and antiplatelet
14.5	Sensitivity analysis	Unblinded non-negative COVID-19	180-day Mortality	Includes all interventions Includes pre-specified interaction between anticoagulation and antiplatelet
14.6	Sensitivity analysis	Immune modulation specific ITT population	180-day Mortality	
14.7	Sensitivity analysis	Unblinded population ITT	180-day Mortality	Independent effects of IL-6ra interventions and antiplatelet interventions
14.8	Sensitivity analysis	Corticosteroid specific ITT population	180-day Mortality	
14.9	Sensitivity analysis	Antiviral specific ITT population	180-day Mortality	
14.10	Sensitivity analysis	Immunoglobulin specific ITT population	180-day Mortality	
14.11	Sensitivity analysis	Anticoagulation specific ITT population	180-day Mortality	Includes pre-specified interaction between anticoagulation and antiplatelet
14.12	Sensitivity analysis	Antiplatelet specific ITT population	180-day Mortality	Includes pre-specified interaction between anticoagulation and antiplatelet
14.13	Sensitivity analysis	Unblinded population ITT	EQ5D5L utility score	Includes all interventions and pre-specified interaction between anticoagulation and antiplatelet; no imputation of missing utility scores
14.14	Sensitivity analysis	Unblinded population ITT	WHODAS	Includes all interventions and pre-specified interaction between anticoagulation and antiplatelet; no imputation of missing WHODAS scores

14.15	Subgroup	Unblinded population ITT	90-day Mortality	Baseline use of mechanical ventilation (Non-MV vs MV)
14.16	Subgroup	Unblinded population ITT	180-day Mortality	Baseline use of mechanical ventilation (Non-MV vs MV)
14.17	Subgroup	Unblinded population ITT	90-day Mortality	Patient with known immunodeficiency versus those without
14.18	Subgroup	Unblinded population ITT	180-day Mortality	Patient with known immunodeficiency versus those without
14.19	Graphical Summaries	Unblinded population ITT	All endpoints	Including combinations across unblinded domains.

14.1. Reporting of Analysis Results

For each analysis model, the following summaries of hazard/odds ratios will be presented (where applicable):

Model 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				
Main effects of unblinded interventions				
Antiplatelet*anticoagulation intervention interaction				
Antiplatelet*anticoagulation intervention combination				
Main effects of subgroup variable				
Effects of intervention by subgroup				

For each analysis model, the following comparisons will be made (when applicable):

- Each active intervention will be compared to the control arm. The posterior probability of efficacy (or harm in the case where the effect of the intervention is markedly worse than control) will be provided for each active intervention and by subgroup (if applicable).
- Each active intervention will be compared to the control arm for futility. In models where the OR/HR >1 implies benefit, this will be the posterior probability the relative effect falls below 1.2. In models where the OR/HR <1 implies benefit, this will be the posterior probability that the relative effect exceeds 1/1.2.
- Active interventions may be compared for equivalence. For this comparison, the posterior probability that the relative effect is between 1/1.2 and 1.2 will be provided.
- The treatment effects for each endpoint may be compared to the previously published treatment effects on OSFD and hospital survival. For 180-day mortality, a graph will be produced showing the hazard ratio/log hazard ratio (y-axis) versus the OSFD odds ratio/log odds ratio (x-axis) for each intervention. The relationship between the two effects may be summarized by fitting a linear model to the distribution of points.
- The “Antiplatelet*Anticoagulation intervention combination” term is an odds ratio composed of the main effect of antiplatelet, the main effect of anticoagulation, and the interaction effect between the two. The “Antiplatelet* Anticoagulation intervention interaction” term is the odds ratio for the interaction effect – without the main effects of the interventions included.

14.2. Graphical summaries

The following graphical summaries will be provided for all endpoints:

- Population: REMAP-CAP COVID-19 unblinded population severe state ITT
 - Additional summaries may be provided in sensitivity analysis populations
- Endpoint: all endpoints
- Factors: All unblinded domain interventions (i.e., steroids, antiviral, immune modulation, immunoglobulin, anticoagulation, antiplatelet)