
# Statistical Analysis Plan for the Analysis of the Antiplatelet Domain for Patients with COVID-19 Pandemic Infection Suspected Or Proven (PISOP)

REMAP-CAP COVID-19 Antiplatelet Domain SAP Version 1.0 dated 1st July 2021

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# 1. COVID-19 ANTIPLATELET THERAPY DOMAIN SAP VERSION

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

## 1.1. Version history

Version 1: Finalized on 1st July 2021

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# 3. INTRODUCTION

This statistical plan for the analysis of the Antiplatelet 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 plan details the statistical analyses in the original REMAP-CAP core SAP and the pandemic stratum SAP applied to the analysis of the antiplatelet interventions in the Antiplatelet Domain. This plan is prespecified for the imminent unblinding of the data for the Aspirin, P2Y12 and control interventions in the Antiplatelet Domain within the pandemic infection suspected or proven (PISOP) (COVID-19) stratum.

On April 8, 2021, the DSMB disclosed that the aspirin and P2Y12 inhibitor interventions met the statistical trigger for equivalence in the severe state of the PISOP stratum. Since no trigger for futility/efficacy was met at this time, randomization continued to the three antiplatelet interventions. As a result of hitting the equivalence trigger, the aspirin and P2Y12 inhibitor interventions were pooled in the severe state of the primary analysis model and subsequent statistical triggers in the severe state were defined for the pooled interventions. Severe state RAR proportions were based on the posterior distribution for the pooled intervention and randomization was split equally between aspirin and the P2Y12 inhibitor.

The Antiplatelet Domain was halted in the PISOP stratum following the disclosure from the DSMB that the pooled aspirin and P2Y12 inhibitor interventions had met the pre-specified threshold for futility in the severe state. The REMAP-CAP ITSC publicly disclosed the futility of pooled aspirin and P2Y12 in the severe state on 23 June 2021 (Greenwich Mean Time (GMT)) coinciding with the closure of the Antiplatelet Domain within the PISOP stratum of REMAP-CAP. Enrollment to the moderate state of the Antiplatelet domain was also halted on 23 June 2021 based on accumulating external evidence and the limited recruitment numbers enrolled in the moderate state. The external evidence considered came from two RCTs assessing antiplatelet therapy in COVID-19 patients; the preprint of aspirin results from the RECOVERY trial of approximately 15,000 patients showing futility and the closure of the P2Y12 randomization in moderate hospitalized patients of the ACTIV 4A trial due to the futility trigger being met.

REMAP-CAP explores multiple treatment domains 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. The Antiplatelet domain closure was based on both *internal and external results*; hence the data for the Antiplatelet domain will be unblinded and made public. This document prespecifies the analysis plan for this unblinding.

The authors of this document are blinded to all individual data other than publicly disclosed results and that the statistical triggers for equivalence and futility have been reached for aspirin and P2Y12 inhibitor in the severe state. The primary analysis for this SAP will be conducted when the patient last randomized, before closing of the Antiplatelet domain, reaches 21 days of follow-up (completion of the primary end-point).

# 4. DESIGN CONSIDERATIONS

REMAP-CAP is designed with a Bayesian analysis as the primary analysis method for the trial. There is one overarching Bayesian model, prespecified in the SAP, driving all adaptations, statistical triggers, and result summaries. That primary statistical analysis model will be used to report the results for the antiplatelet interventions (aspirin and P2Y12 inhibitor) in the Antiplatelet Domain within the moderate and severe states of the PISOP stratum.

The decision to use a Bayesian analysis 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 Antiplatelet Domain within each state:

1. **Domain Superiority**. If a single intervention within the Antiplatelet Domain has at least a 99% posterior probability of being in the best regimen for patients in the moderate or severe state of the PISOP stratum, this would trigger domain superiority of that intervention for that state.
2. **Intervention Efficacy**. If an intervention is deemed to have at least a 99% posterior probability of being superior to the control in the moderate or severe state, then a declaration of efficacy of that intervention would be declared in that state. This statistical trigger is active for each of the non-control arms in the Antiplatelet Domain.
3. **Intervention Equivalence**. If Aspirin and P2Y12 inhibitor have at least a 90% probability of equivalence (within a 20% odds ratio difference) in the moderate or severe state, this would trigger a public disclosure of intervention equivalence for that state.

4. **Intervention Futility**. If an intervention is deemed to have a less than 5% probability of at least a 20% odds ratio improvement compared to the control in the moderate or severe state, then a declaration of futility of that intervention would be declared for that state.

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).

Although not a statistical trigger at adaptive analyses, if an active intervention has a greater than 90% probability of being inferior to the control, then it will be deemed to be harmful in this population.

# 5. UNBLINDING

REMAP-CAP has multiple domains to which patients can be randomized and multiple interventions within domains. At the unblinding of the antiplatelet domain in the moderate and severe state, there are other interventions to which patients have been randomized that will not be unblinded at this analysis unless a statistical trigger is hit at the time of the primary analysis. This includes interventions within other domains that are not yet unblinded. In the analysis plan, there will be analyses conducted by the Statistical Analysis Committee (SAC) using additional randomizations and unblinding of other randomizations. The SAC is unblinded to all interventions and domains as part of their role for REMAP-CAP. There will be other analyses that are conducted with only knowledge of the unblinded antiplatelet/control allocation status for patients or the allocation status to other unblinded interventions. These may be conducted by investigators who are blinded to information about other interventions and domains. These analyses are identified below.

# 6. INTERVENTIONS

There are three interventions within the Antiplatelet Domain. These are

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

The primary analysis model will estimate the interaction effects of the interventions in the Antiplatelet Domain with the Anticoagulation Domain interventions; the interaction, combination, and main effects from this analysis will be reported.

The additional secondary analyses completed by the blinded investigators will estimate and report the interaction effects of the interventions in the Antiplatelet Domain with the other unblinded interventions based on the adequacy of data support. To determine which interactions between antiplatelet and unblinded interventions will be estimated, cross-tabulations of the antiplatelet and each unblinded domain will be created. If there is sufficient data support to estimate interaction (e.g. greater than approx. 20 in each cell), the interaction and combination effect will be estimated and reported.

Initially, the aspirin and P2Y12 inhibitor interventions were nested in the severe and moderate states. After meeting the statistical trigger for equivalence, the two interventions were pooled into a single intervention effect in the severe state. In the primary analysis, Aspirin and P2Y12 inhibitor were nested in the moderate state.

## 7. DISEASE STATES

There are two disease states in the PAtC, which are **moderate** and **severe**. The Antiplatelet Domain has been open for randomization in patients in the moderate and severe states. The DSMB recommendation could suggest continuation or termination of recruitment for the disease states individually based on the statistical triggers defined in section 4.

The primary analysis model will estimate the pooled effect of the antiplatelet interventions in the severe state and the nested effect of the antiplatelet interventions in the moderate states; only the intervention effects for the unblinded intervention(s) and state(s) will be reported. The secondary analysis models run by blinded investigators will be run on only the unblinded intervention(s) and state(s).

## 8. ANALYSIS POPULATIONS

1. REMAP-CAP COVID-19 severe and moderate state intent-to-treat (ITT). This population consists of all PISOP patients in the moderate or severe state randomized within at least one domain.
2. Unblinded ITT. All PISOP patients randomized in the Antiplatelet Domain or to any other unblinded interventions/domains within the PISOP stratum.
3. Unblinded non-negative COVID-19. All patients in the Unblinded ITT population after removing those with $\geq$1 negative test for COVID-19 **and** no positive tests.
4. Antiplatelet specific ITT. This population consists of only patients randomized to the Antiplatelet Domain within the PISOP stratum.

5. Antiplatelet specific per protocol. This consists of the patients in the Antiplatelet ITT population who have been treated as per protocol. In this analysis, that is defined as patients randomized to aspirin or P2Y12 inhibitor, **and** received at least one dose within 48 hours of randomization, or randomized to no antiplatelet therapy **and** did not receive any antiplatelet therapy within 48 hours of randomization. Based on the possibility of crossover, this population is limited to patients with the opportunity to complete 14 days of treatment prior to the domain closure on June 23, 2021. In addition to a per-protocol analysis, protocol adherence will be reported in the aspirin and P2Y12 arms as the proportion of patients receiving at least one dose of the randomized antiplatelet agent in the first 48 hours following randomization, and in the control arm as the proportion not receiving any antiplatelet agents in the first 48 hours following randomization.

Each of these analysis populations will include only the patients randomized on or before the antiplatelet domain was halted on 23 June 2021.

# 9. ENDPOINTS

The following endpoints will be analyzed, displayed graphically, and summarized through descriptive statistics. Depending on data availability, some outcomes may be presented in subsequent reports. All endpoints will be analyzed for patients recruited and randomized in the severe state for the pooled antiplatelet interventions versus no antiplatelet, whereas, only a limited selection of endpoints will be analyzed for the separate antiplatelet interventions (aspirin and P2Y12 inhibitor). In addition, only a limited selection of endpoints will be analyzed for patients recruited and randomized in the moderate state due to the smaller sample size.

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 organ support considered is cardiovascular (vasopressor/inotrope support) and respiratory support. See Appendix A for a detailed description.
    b. In the moderate state, the primary outcome will be presented both across the long ordinal scale, as well as trichotomized into three level ordinal outcome: survival to hospital discharge without receipt of organ support (the best outcome), survival to hospital discharge with the receipt of organ support (an intermediate outcome), and in-hospital death with or without receipt of organ support.

2. **Survival to Hospital Discharge**
    a. A dichotomous endpoint of in-hospital death where the death component corresponds to a –1 on the OSFD endpoint. Follow-up for this outcome is censored at 90 days.
    b. This endpoint will be reported as "survival to hospital discharge" where an odds ratio > 1 indicates patient benefit for consistency with the direction of the OSFD odds ratio.

3. **90-day 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 assumed to be alive at 90 days, if 90-day mortality data are not yet recorded.

4. **Progression to invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or death**
    a. A dichotomous endpoint of whether a patient progresses to invasive mechanical ventilation, ECMO or death in hospital. This endpoint is defined for patients that are not on invasive mechanical ventilation or ECMO at baseline.

5. **Vasopressor/Inotrope-Free Days**
    a. An ordinal outcome of the number of days free of Vasopressor/Inotropes through 21 days. 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 the number of days free of respiratory support through 21 days. This is the exact calculation of OSFD, with mechanical respiratory support as the only organ support category (includes high flow nasal oxygen, non-invasive and invasive mechanical ventilation). In-hospital death is considered a –1.

7. **Duration 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. **Duration 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 discharge event.
    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:
        i. 0 + 1 + 2 = No longer hospitalized
        ii. 3 = Hospitalized, no oxygen therapy
        iii. 4 = Oxygen by mask or nasal prongs
        iv. 5 = Non-invasive ventilation or high-flow oxygen
        v. 6 = Intubation and mechanical ventilation
        vi. 7 = Ventilation + additional organ support: vasopressors, renal replacement therapy (RRT), ECMO
        vii. 8 = Death

11. **Major bleeding on or before day 14 (events confirmed by blinded adjudication)**
    a. A dichotomous endpoint of major bleeding as defined according to International Society of Thrombosis and Hemostasis (ISTH) criteria in non-surgical patients.
    b. The endpoint is censored at 14 days to correspond with the intervention duration.

12. **Fatal bleeding on or before day 14**
    a. A dichotomous endpoint of fatal bleeding defined as death attributable to bleeding according to the site investigator reporting or as judged via central adjudication.
    b. The endpoint is censored at 14 days to correspond with the intervention duration.

13. **Intracranial hemorrhage on or before day 14**

a. A dichotomous endpoint of intracranial haemorrhage.
b. The endpoint is censored at 14 days to correspond with the intervention duration.

**14. Deep venous thrombosis (events confirmed by blinded adjudication)**

a. A dichotomous endpoint of clinically detected radiologically confirmed proximal deep venous thrombosis diagnosed at any time during the index hospitalization.
b. This endpoint will be reported descriptively using proportions.

15. **Pulmonary embolism (events confirmed by blinded adjudication)**

a. A dichotomous endpoint of clinically detected radiologically confirmed pulmonary embolism diagnosed at any time during the index hospitalization.
b. This endpoint will be reported descriptively using proportions.

16. **Ischemic cerebrovascular event (events confirmed by blinded adjudication)**

a. A dichotomous endpoint of ischemic cerebrovascular event (stroke).
b. This endpoint will be reported descriptively using proportions.

17. **Acute myocardial infarction (events confirmed by blinded adjudication)**

a. A dichotomous endpoint of acute myocardial infarction defined according to the universal definition of myocardial infarction.
b. This endpoint will be reported descriptively using proportions.

18. **All thrombotic events (events confirmed by blinded adjudication)**

a. A composite dichotomous endpoint of deep vein thrombosis, pulmonary embolism, ischemic cerebrovascular event, myocardial infarction, systemic arterial thromboembolism or other thrombotic event diagnosed at any time during the index hospitalization.
b. This endpoint will be reported descriptively using proportions.

19. **Venous thrombotic event (events confirmed by blinded adjudication)**

a. A composite dichotomous endpoint of pulmonary embolism, deep vein thrombosis, and other venous thromboembolic event diagnosed at any time during the index hospitalization.
b. This endpoint will be reported descriptively using proportions.

**20. Arterial thrombotic event (events confirmed by blinded adjudication)**

a. A composite dichotomous endpoint of acute myocardial infarction, ischemic cerebrovascular event, mesenteric ischemia, limb ischemia, or other arterial thrombotic event diagnosed at any time during the index hospitalization
b. This endpoint will be reported descriptively using proportions.

21. **All thrombotic events or death (thrombotic events confirmed by blinded adjudication)**
    a. A composite dichotomous endpoint of deep vein thrombosis, pulmonary embolism, ischemic cerebrovascular event, myocardial infarction, or systemic arterial thromboembolism diagnosed at any time during the index hospitalization or death in hospital
22. **Venous thrombotic event or death (thrombotic events confirmed by blinded adjudication)**
    a. A composite dichotomous endpoint of pulmonary embolism, deep vein thrombosis, and other venous thromboembolic event diagnosed at any time during the index hospitalization or death in-hospital
23. **Arterial thrombotic event or death (thrombotic events confirmed by blinded adjudication)**
    a. A composite dichotomous endpoint of acute myocardial infarction, ischemic cerebrovascular event, mesenteric ischemia, limb ischemia, or other arterial event diagnosed at any time during the index hospitalization or death in-hospital

## 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 proportion in each category.
3. 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.
4. Composite endpoints will be summarized overall and for each component individually.

## 12. BASELINE CHARACTERISTICS AND CO-INTERVENTIONS

The following demographics will be summarized across arms. More may be added as baseline summaries: Age, sex, BMI, race, ethnicity, illness severity at admission, pre-existing conditions, baseline use of high-flow nasal oxygenation, non-invasive ventilation, invasive mechanical

ventilation, ECMO, vasopressors/inotropes, renal replacement therapy, and miscellaneous physiological values and inflammatory biomarker laboratory values (see Appendix A). Additionally, exposure to relevant drugs as usual care (e.g., anticoagulation agents, steroids, immunomodulatory therapies), at baseline, and during the treatment period will be compared across antiplatelet interventions. Dosing of concurrent anticoagulation interventions at baseline will be summarized based on the following dosing equivalents categorization: (1) standard prophylactic, (2) intermediate prophylactic, (3) subtherapeutic/therapeutic. The highest anticoagulant dose received over the first 48 hours from randomisation will be taken as the baseline concurrent anticoagulation dose.

# 13. COMPLIANCE

The compliance to Antiplatelet use over the first 48 hours from randomisation 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 analyses 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 severe state has 23 and the moderate state has 24 possible ordered outcomes respectively. Let the outcome for a patient be 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. A cumulative logistic model is specified. The model is structured so that an odds-ratio >1 implies clinical benefit. The full details of the model are specified in the Current State of The Statistical Model, Version 3.2 dated May 17, 2021. The model has factors for:

- Each level of the ordinal endpoint
- State at randomization
- Each global site, nested within country
- Age; ≤39, 40-49, 50-59, 60-69 (reference), 70-79, 80+
- Sex; Male (reference) or female
- 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
- Specified interactions in the model between interventions across domains

The primary analysis for the Antiplatelet domain uses the following rules:

- All sites within a country that have <5 patients randomized will be combined into a single site within that country.
- If there is an outcome in the ordinal scale that did not occur in the data in a given state, then that outcome will be combined with a neighboring outcome (the worse outcome). This is done for model stability. For example, if the outcome 11 never occurred in the severe state, then a combined outcome of 10 & 11 will be modeled for the severe state in that analysis.
- Time buckets with <5 randomized subjects in a state may be combined with the more recent neighboring bucket for that state
- The interventions, aspirin and P2Y12, will be pooled into a single treatment effect in the severe state and nested in the moderate state.
- In addition to the rules above, the secondary analyses will use the following conventions:
- Unless otherwise specified, aspirin and P2Y12 inhibitor will be pooled into a single treatment effect in analyses of secondary endpoints.
- In subgroup analyses, aspirin and P2Y12 will be pooled into a single “antiplatelet therapy” intervention.

The primary analysis model 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. No statistical test of proportional odds is conducted.

This sensitivity analysis will be run in models including both the severe and moderate states. The aspirin and P2Y12 inhibitors will be pooled in the severe state and nested in the moderate state.

## 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 and be parameterized so that an odds-ratio >1 implies benefit to patients. The model is the standard logistic link function model:

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

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 the hazard rate for each day 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 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 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 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.

## 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 be equal-tailed intervals, so 95% credible

intervals will range from the 2.5th percentile to the 97.5th percentile of the posterior distribution). For the ordinal endpoints, the odds-ratios will be summarized. For the dichotomous endpoints, the odds-ratio will be summarized. For the time-to-event endpoints, the hazard ratios will be summarized. For consistency, all models will be parameterized so that an odds-ratio or hazard-ratio greater than 1 indicates clinical benefit.

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. 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 be clearly labeled as exploratory and will use the following methods:

1. Ordinal endpoints will be compared using a cumulative proportional odds model with summaries of the OR, 95% confidence intervals, and Wilcoxon tests 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 regression summarizing the OR 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

Table 1. Prospective analysis

| # | Status | Population | Endpoint | State(s) | Antiplatelet Intervention | Other |
|---|---|---|---|---|---|---|
| 15.1 | Primary | REMAP-CAP COVID-19 moderate and severe state ITT | OSFD | Nested | Pooled in severe; | Includes all interventions and pre-specified interactions. |

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|---|---|---|---|---|---|---|
| | | | | | nested in moderate | |
| **15.2** | Primary | REMAP-CAP COVID-19 moderate and severe state ITT | In-Hospital Mortality | Nested | Pooled in severe; nested in moderate | Includes all interventions and pre-specified interactions. |
| **15.3** | Sensitivity | REMAP-CAP COVID-19 moderate and severe state ITT | Dichotomized OSFD | Nested | Pooled in severe; nested in moderate | A logistic regression will be run for each dichotomization of OSFDs as a robustness check. |
| **15.4** | Secondary | Unblinded ITT population | OSFD | Separate models | Nested in each state | The posterior probability of equivalence between Aspirin and P2Y12 inhibitor will be reported as a descriptive summary but will not overturn the prior equivalence trigger. |
| **15.5** | Secondary | Unblinded ITT population | In-Hospital Mortality | Separate models | Nested in each state | |
| **15.6** | Sensitivity | Unblinded ITT population | OSFD | Separate models | Independent | Independent N(0,1) prior on aspirin and P2Y12 inhibitor |
| **15.7** | Sensitivity | Unblinded ITT population | In-Hospital Mortality | Separate models | Independent | Independent N(0,1) prior on aspirin and P2Y12 inhibitor |
| **15.6** | Sensitivity | Unblinded ITT population | OSFD | Separate models | Pooled | |
| **15.7** | Sensitivity | Unblinded ITT population | In-Hospital Mortality | Separate models | Pooled | |
| **15.8** | Secondary | Unblinded population ITT Non-negative COVID-19 | OSFD | Separate models | Pooled | |
| **15.9** | Secondary | Unblinded population ITT Non-negative COVID-19 | In-Hospital Mortality | Separate models | Pooled | |
| **15.10** | Secondary | Antiplatelet specific ITT | OSFD | Separate models | Pooled | |

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|---|---|---|---|---|---|---|
| **15.11** | Secondary | Antiplatelet specific ITT | In-Hospital Mortality | Separate models | Pooled | |
| **15.12** | Sensitivity | Antiplatelet specific per protocol | OSFD | Separate models | Pooled | |
| **15.13** | Sensitivity | Antiplatelet specific per protocol | In-Hospital Mortality | Separate models | Pooled | |
| **15.14** | Sensitivity | Unblinded ITT population | OSFD | Separate models | Pooled | Remove site and time effects |
| **15.15** | Sensitivity | Unblinded ITT population | In-Hospital Mortality | Separate models | Pooled | Remove site and time effects |
| **15.16** | Sensitivity | Unblinded ITT population | OSFD | Separate models | Pooled | Includes all interventions and pre-specified interactions. Includes exploratory interaction effects for antiplatelet therapy and unblinded domains with sufficient data support. Less informative standard normal priors will be used in estimating the interaction effects. |
| **15.17** | Sensitivity | Unblinded ITT population | In-Hospital Mortality | Separate models | Pooled | Includes all interventions and pre-specified interactions. Includes exploratory interaction effects for antiplatelet therapy and unblinded domains with sufficient data support. Less informative standard normal priors will be used in estimating the interaction effects. |
| **15.18** | Secondary | Unblinded ITT | 90-day Mortality | Separate models | Pooled | Pooled aspirin/P2Y12 inhibitor in severe state |
| **15.19** | Secondary | Unblinded ITT population not on MV, ECMO at baseline | Progression to intubation, ECMO, death | Separate models | Pooled | |

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|---|---|---|---|---|---|---|
| **15.20** | Secondary | Unblinded ITT population | Days-Free of vasopressor/inotropes | Separate models | Pooled | |
| **15.21** | Secondary | Unblinded ITT population | Respiratory support-free days | Separate models | Pooled | |
| **15.22** | Secondary | Unblinded ITT population | Duration of ICU Stay | Separate models | Pooled | |
| **15.23** | Secondary | Unblinded ITT population | Duration of Hospital Stay | Separate models | Pooled | |
| **15.24** | Secondary | Unblinded ITT population | WHO Scale at 14 days | Separate models | Pooled | |
| **15.25** | Primary Safety Analysis | Antiplatelet specific ITT | Serious adverse events per patient | Separate models | Independent | Time effects removed from model. |
| **15.26** | Secondary safety analysis | Unblinded ITT population | Major bleeding | Separate models | Independent | |
| **15.27** | Secondary | Unblinded ITT population | All thrombotic events or death | Separate models | Pooled | Primary dichotomous model with additional interactions between antiplatelet interventions and IL-6ra and anti-coag. Standard normal prior on interaction. |
| **15.28** | Secondary | Unblinded ITT population | Venous thrombotic event or death | Separate models | Pooled | Primary dichotomous model with additional interactions between antiplatelet interventions and IL-6ra and anti-coag. Standard normal prior on interaction. |
| **15.29** | Secondary | Unblinded ITT population | Arterial thrombotic | Separate models | Pooled | Primary dichotomous model with additional interactions between antiplatelet |

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|---|---|---|---|---|---|---|
| | | | event or death | | | interventions and IL-6ra and anti-coag. Standard normal prior on interaction. |
| **15.30** | Secondary | Unblinded ITT population | All thrombotic events or death | Separate models | Independent | Primary dichotomous model with additional interactions between antiplatelet interventions and IL-6ra. Standard normal prior on interaction. |
| **15.31** | Secondary | Unblinded ITT population | Venous thrombotic event or death | Separate models | Independent | Primary dichotomous model with additional interactions between antiplatelet interventions and IL-6ra. Standard normal prior on interaction. |
| **15.32** | Secondary | Unblinded ITT population | Arterial thrombotic event or death | Separate models | Independent | Primary dichotomous model with additional interactions between antiplatelet interventions and IL-6ra. Standard normal prior on interaction. |
| **15.33** | Secondary | Unblinded ITT population | All thrombotic events | Separate models | Independent | Primary dichotomous model with additional interactions between antiplatelet interventions and IL6-ra. Standard normal prior on interaction. |
| **15.34** | Secondary | Unblinded ITT population | Venous thrombotic event | Separate models | Independent | Primary dichotomous model with additional interactions between antiplatelet interventions and IL6-ra. Standard normal prior on interaction. |
| **15.35** | Secondary | Unblinded ITT population | Arterial thrombotic event | Separate models | Independent | Primary dichotomous model with additional interactions between antiplatelet |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | interventions and IL6-ra. Standard normal prior on interaction. |
| **15.36** | Subgroup | Unblinded ITT population | OSFD | Severe only | Pooled | Including differential treatment effect by age (<50, 50-70, 70+) |
| **15.37** | Subgroup | Unblinded ITT population | Major bleeding | Severe only | Pooled | Including differential treatment effect by age (<50, 50-70, 70+) |
| **15.38** | Subgroup | Unblinded ITT population | OSFD | Severe only | Pooled | Including differential treatment effects by invasive mechanical ventilation at baseline (yes/no) |
| **15.39** | Subgroup | Unblinded ITT population | In-Hospital Mortality | Severe only | Pooled | Including differential treatment effects by invasive mechanical ventilation at baseline (yes/no) |
| **15.40** | Subgroup | Unblinded ITT population | OSFD | Severe only | Pooled | Including differential treatment effects by terciles of troponin. (Low/middle/high/unknown) |
| **15.41** | Subgroup | Unblinded ITT population | OSFD | Severe only | Pooled | Including differential treatment effects by alternative coding of baseline anticoagulation doses (low, intermediate, sub-therapeutic/therapeutic, and unknown) |
| **15.42** | Subgroup | Unblinded ITT population | All thrombotic events | Severe only | Pooled | Including differential treatment effects by alternative coding of baseline anticoagulation doses (low, intermediate, sub-therapeutic/therapeutic, and unknown) |
| **15.43** | Subgroup | Unblinded ITT population | Arterial thrombotic events | Severe only | Pooled | Including differential treatment effects by alternative coding of baseline anticoagulation doses (low, intermediate, sub-therapeutic/therapeutic, and unknown) |

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|---|---|---|---|---|---|---|
| **15.44** | Subgroup | Unblinded ITT population | Venous thrombotic events | Severe only | Pooled | Including differential treatment effects by alternative coding of baseline anticoagulation doses (low, intermediate, sub-therapeutic/therapeutic, and unknown) |
| **15.45** | Subgroup | Unblinded ITT population | Major bleeding | Severe only | Pooled | Including differential treatment effects by alternative coding of baseline anticoagulation doses (low, intermediate, sub-therapeutic/therapeutic, and unknown) |
| **15.46** | Subgroup | Unblinded ITT population | OSFD | Severe only | Pooled | Including differential treatment effect by baseline chronic kidney disease |
| **15.47** | Graphical Summaries | Antiplatelet specific ITT | All endpoints | | | Including combinations across unblinded domains. |

## 15.1. Reporting of Analysis Results

For each analysis model, the following odds/hazard ratio summaries will be reported when applicable:

| **Odds/Hazard-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 | | | | |
| Moderate to severe transition | | | | |
| Antiplatelet therapy (Aspirin/P2Y12 separately or pooled) | | | | |
| Main effects of unblinded interventions included in intervention in interaction w/ antiplatelet therapy | | | | |
| Antiplatelet*Unblinded intervention interaction | | | | |
| Antiplatelet*Unblinded intervention combination | | | | |

| | | | | |
|---|---|---|---|---|
| Main effect of subgroup | | | | |
| Antiplatelet therapy by subgroup | | | | |

For each analysis model, the following comparisons will be made by state, when applicable:

- Antiplatelet therapy will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. In subgroup models, this probability will be provided by subgroup.
- Antiplatelet therapy and no antiplatelet interventions will be compared for futility. A 95% probability of a smaller than 1.2 odds-ratio for antiplatelet therapy relative to no antiplatelet therapy will be used as a statistical trigger for futility. In subgroup models, this probability will be provided by subgroup.
- If aspirin and P2Y12 are not pooled, the posterior probability of equivalence of aspirin and P2Y12 inhibitor will be reported.
- The posterior probability that P2Y12 is superior to aspirin will be reported for models in which the two interventions are not pooled
- The posterior probability that the OR>1 for combinations will be reported for each combination between P2Y12/ aspirin and interventions from other domains.
- The posterior probability that the OR>1 for the interaction effect will be reported for each interaction between P2Y12/ aspirin and interventions from other domains.
- The “Antiplatelet*Unblinded intervention combination” term is an odds ratio composed of the main effect of antiplatelet, the main effect of the unblinded intervention, and the interaction effect between the two. The “Antiplatelet*Unblinded intervention interaction” term is the odds ratio for the interaction effect – without the main effects of the interventions included.

For the sensitivity analysis assessing the proportional odds assumption, the antiplatelet therapy ORs will be reported for each dichotomization of OSFD and each unblinded state.

## 15.2. Graphical summaries

The following graphical summaries will be provided for all endpoints:

- Population: Antiplatelet specific ITT
- Endpoint: all endpoints
- Factors: Antiplatelet and no antiplatelet interventions

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

- Population: Antiplatelet specific ITT
- Endpoint: OSFD, in-hospital mortality
- Factors:
    - Antiplatelet and no antiplatelet interventions interacted with anticoagulation domain (therapeutic anticoagulation, standard care thromboprophylaxis)
- 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 randomization.

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 randomization, 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 OutcomeDay21 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.