Statistical Analysis Plan
for the Analysis of the Continuation of TAC Intervention in the Anticoagulation Domain
for Patients with COVID-19 Pandemic Infection Suspected Or Proven (PISOP)

COVID-19 Anticoagulation Domain Prior TAC SAP Version 1.0 dated 12th August 2022
# TABLE OF CONTENTS

1. **COVID-19 ANTICOAGULATION Domain Prior TAC SAP Version** ................................. 3  
   1.1. Version history ........................................................................................................ 3 
2. **SAP Authors** ........................................................................................................... 3  
3. **Introduction** ............................................................................................................. 4 
4. **Design Considerations** ........................................................................................... 5 
5. **Unblinding** ............................................................................................................... 6 
6. **Interventions** .......................................................................................................... 7 
7. **Disease States** ......................................................................................................... 7 
8. **Analysis Populations** .............................................................................................. 8 
9. **Endpoints** ............................................................................................................... 8 
10. **Graphical Data Summaries** .................................................................................... 10 
11. **Descriptive Statistics** ............................................................................................ 10 
12. **Baseline Characteristics and Co-interventions** ..................................................... 10 
13. **Analytic Approach** ................................................................................................ 10  
   13.1. Primary Analysis of Primary Endpoint .................................................................. 11  
   13.1.1. Proportional Odds Assumption ........................................................................ 12  
   13.2. Analytic Approach for Secondary Dichotomous Endpoints ............................... 12  
   13.3. Analytic Approach for Secondary Time-To-Event Endpoints .............................. 12  
   13.4. Markov Chain Monte Carlo (MCMC) Model Stability ........................................ 13  
   13.5. Model Outputs ...................................................................................................... 13  
   13.6. Exploratory Analyses ............................................................................................ 13 
14. **SPECIFIC PROSPECTIVE ANALYSES** ................................................................. 14 
16. **Reporting of Analysis Results** ................................................................................. 15 
   Appendix A. Definition of organ support-free days .................................................... 18
1. COVID-19 ANTICOAGULATION DOMAIN PRIOR TAC SAP VERSION

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

1.1. Version history

Version 1: Finalized on 12th August 2022

2. SAP AUTHORS

Scott Berry, Berry Consultants, Austin, TX, USA
Lindsay Berry, Berry Consultants, Austin, TX, USA
Elizabeth Lorenzi, Berry Consultants, Austin, TX, USA
Steven Webb, Monash University, Melbourne, Victoria, Australia
Colin McArthur, Auckland City Hospital, Auckland, New Zealand
Anthony Gordon, Imperial College, London, UK
Patrick Lawler, University of Toronto, Toronto, CA
Paul Mouncey, ICNARC DCC, UK
Bryan McVerry, University of Pittsburgh
Zoe McQuilten, Monash University, Melbourne, Victoria, Australia
Ewan Goligher, University of Toronto, Toronto, Canada
Ryan Zarychanski, University of Manitoba, Winnipeg, Canada
Charlotte Bradbury, University of Bristol, UK
3. INTRODUCTION

This statistical plan for the initial analysis of the second phase of the Anticoagulation Domain in the pandemic stratum of the REMAP-CAP trial is an appendix to the Pandemic Appendix to Core (PATC) Statistical Analysis Plan (SAP). Of note, the second phase of the Anticoagulation Domain has only been open for recruitment of patients in the severe state. This plan details the statistical analyses in the original REMAP-CAP core SAP and the pandemic stratum SAP applied to the analysis of the continuation of therapeutic-dose anticoagulation (TAC) intervention in the prior TAC stratum of the Anticoagulation Domain within the pandemic infection suspected or proven (PISOP) (COVID-19) stratum.

On April 28, 2022, the DSMB advised the International Trial Steering Committee (ITSC) that the continuation of TAC intervention in the Prior TAC stratum of the Anticoagulation Domain met the statistical trigger for futility in the state of the PISOP stratum. As a result of meeting the futility trigger, recruitment to the TAC intervention in the severe state stopped on April 29, 2022, whilst randomization to the conventional low and intermediate dose heparin interventions continued.

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 TAC intervention closure was based on this treatment reaching a prespecified trigger for futility, relative to one or more other interventions in the domain. Data for this futile intervention within the domain will be unblinded and made public. This document prespecifies the analysis plan for this unblinding. Two distinct futility triggers were defined for TAC in the Prior TAC stratum relative to low and intermediate dose heparin, respectively, and investigators remain blinded to which comparator led to the futility trigger. To preserve blinding of investigators to the treatment effects of ongoing comparator interventions in the domain, the treatment effect summaries for this treatment will be reported relative to data from all severe state patients in both other randomization groups combined. In addition to the treatment effect summaries relative to the pooled comparator, posterior probabilities of futility for TAC will be reported from the primary analysis in which the low and intermediate dose interventions are separate since this was the model that triggered the platform conclusion. However, investigators will remain blinded to the individual comparator in posterior probabilities relative to a single intervention. Every effort will be taken to avoid unblinding of the ongoing interventions. This initial analysis will only include patients recruited in the prior TAC stratum up to April 29, 2022 and will only include a limited number of preliminary analyses. For all
reported treatment effect summaries, the conventional low and intermediate heparin dose interventions will be pooled into a single “control group”. When an additional platform conclusion is reached, a subsequent SAP will be developed for the rest of the anticoagulation domain (including a comparison of conventional low versus intermediate dose heparin) and will include additional analyses in the prior TAC stratum.

The authors of this document are blinded to all individual data and are only aware that the statistical trigger for futility has been reached for continuation of TAC in the prior TAC stratum of the severe state. The primary analysis for this SAP will be conducted after the patient last randomized, before closing of the continuation of TAC intervention, 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 analyze the anticoagulation interventions (continuation of TAC, conventional low and intermediate dose heparin) in the prior TAC stratum of the Anticoagulation Domain within the state 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 may lead to adaptation of 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 Anticoagulation Domain in the severe state for the prior TAC stratum:

1. **Domain Superiority.** If a single intervention within the Anticoagulation Domain has at least a 99% posterior probability of being in the best regimen for patients in the PISOP stratum, this would trigger domain superiority of that intervention for that state.

2. **Domain Inferiority.** If a single intervention within the Anticoagulation Domain has less than a 1% posterior probability of being in the best regimen for patients in the PISOP stratum, this would trigger domain inferiority of that intervention for that state and stratum.

3. **Intervention Efficacy.** If an intervention is deemed to have at least a 99% posterior probability of being superior to low dose thromboprophylaxis, then a declaration of efficacy of that intervention would be declared. For the purposes of this SAP, the efficacy trigger will be reported relative to the pooled low and intermediate dose interventions.

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 low or intermediate dose interventions, then a declaration of futility of that intervention would be declared for that state. For the purposes of this SAP, the futility trigger may be reported relative to low or intermediate interventions individually or pooled.

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. In this case, the control arm will be the pooled low and intermediate dose interventions.

5. **UNBLINDING**

REMAP-CAP has multiple domains in which patients can be randomized and to multiple interventions within domains. At the unblinding of the continuation of TAC intervention of the anticoagulation domain, there may be other interventions to which patients have been randomized that will not be unblinded at this analysis unless a statistical trigger is reached 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 anticoagulation 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 Prior TAC stratum of the Anticoagulation Domain. These are

1. Continuation of therapeutic-dose anticoagulation (TAC)
2. Intermediate dose heparin
3. Conventional low dose heparin

Importantly, given that this initial analysis is only intended to include the reporting of the continuation of TAC findings, to preserve blinding of relative treatment effects for ongoing treatments in the domain, both the intermediate dose and low dose groups will be pooled and reported as one aggregate “control” group. It is understood that this was not how the domain was designed, but is intended to allow timely reporting of a potentially clinically important finding while preserving blinding of ongoing intervention effects. A full comparison of the treatment effects for each distinct intervention will follow at the time of closure of all interventions in the stratum or domain.

The additional secondary analyses completed by the blinded investigators will estimate and report the interaction effects of the interventions in the Anticoagulation Domain with the other unblinded interventions based on the adequacy of data support. To determine which interactions between anticoagulation and unblinded interventions will be estimated, cross-tabulations of the Anticoagulation 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.

7. DISEASE STATES

There are two disease states in the PAtC, which are moderate and severe. This second phase of the Anticoagulation Domain has been open for randomization of patients in the severe state only.
The primary analysis model will estimate the effect of continuation of TAC compared with the conventional low and intermediate dose heparin interventions. 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) and will estimate the effect of continuation of TAC compared with the pooled effect of the conventional low and intermediate dose heparin interventions to preserve blinding.

8. ANALYSIS POPULATIONS

1. REMAP-CAP COVID-19 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 Anticoagulation Domain within the prior TAC stratum or to any other unblinded interventions/domains within the PISOP stratum.

3. Anticoagulation specific ITT. This population consists of only patients randomized in the prior TAC stratum of the Anticoagulation Domain within the PISOP stratum.

Each of these analysis populations will include only the patients randomized on or before the continuation of TAC intervention was halted on April 29, 2022.

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. In this SAP, only a limited selection of endpoints will be analyzed for patients recruited and randomized in the prior TAC stratum of the severe state for continuation of TAC versus conventional low and intermediate dose heparin. At a later stage, when the domain reaches a platform conclusion, there will be a subsequent more detailed SAP that incorporates all the pre-specified endpoints in the DSA.

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.

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. At least one serious adverse event (SAE)
   a. A dichotomous endpoint of SAE.

5. 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.

6. 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.

7. 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

8. Heparin induced thrombocytopenia (laboratory confirmed)
a. This endpoint will be reported descriptively using proportions.

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 for the continuation of TAC intervention and pooled low/intermediate dose interventions: 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. Additionally, exposure to relevant drugs as usual care (antiplatelet agents, steroids, immunomodulatory therapies and remdesivir) at baseline will be compared across anticoagulation interventions.

13. **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.
As few patients have been recruited into the Prior TAC stratum, numbers of infrequent events may be too low to allow reliable models to be run. In these cases only counts and descriptive statistics will be reported.

13.1. Primary Analysis of Primary Endpoint

The primary analysis model is a Bayesian cumulative logistic model for the ordinal primary endpoint. An overview of the model is provided below. The full details of the primary analysis model are specified in the Current State of The Statistical Model, Version 4.3 dated July 28, 2022.

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 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 Anticoagulation 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.
• As prespecified in the Current State document, the low and intermediate dose interventions will be modeled separately in the primary analysis. Only restricted summaries of the TAC treatment effect will be reported from the primary analysis models to maintain blinding of the low and intermediate dose interventions. In all secondary analyses performed by blinded investigators, the low and intermediate dose interventions will be pooled into a single “control” 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.

13.1.1. 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.

13.2. 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).

13.3. 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.

13.4. **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. If sparse data prohibits reliable estimation of model parameters, descriptive summaries may be provided instead of model summaries.

13.5. **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.

13.6. **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.

14. **SPECIFIC PROSPECTIVE ANALYSES**

Table 1. Prospective analysis of the prior TAC stratum in the severe state

<table>
<thead>
<tr>
<th>#</th>
<th>Status</th>
<th>Population</th>
<th>Endpoint</th>
<th>Anticoagulation Interventions</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.1</td>
<td>Primary</td>
<td>REMAP-CAP COVID-19 severe state ITT</td>
<td>OSFD</td>
<td>Separate but de-identified low and intermediate dose, Continuation of TAC</td>
<td>Includes all interventions and pre-specified interactions.</td>
</tr>
<tr>
<td>15.2</td>
<td>Primary</td>
<td>REMAP-CAP COVID-19 severe state ITT</td>
<td>In-Hospital Mortality</td>
<td>Separate but de-identified low and intermediate dose, Continuation of TAC</td>
<td>Includes all interventions and pre-specified interactions.</td>
</tr>
<tr>
<td>15.3</td>
<td>Secondary</td>
<td>Unblinded ITT population</td>
<td>OSFD</td>
<td>Pooled low and intermediate dose, Continuation of TAC</td>
<td></td>
</tr>
<tr>
<td>15.4</td>
<td>Secondary</td>
<td>Unblinded ITT population</td>
<td>In-Hospital Mortality</td>
<td>Pooled low and intermediate dose, Continuation of TAC</td>
<td></td>
</tr>
<tr>
<td>15.5</td>
<td>Secondary</td>
<td>Anticoagulation specific ITT</td>
<td>OSFD</td>
<td>Pooled low and intermediate dose, Continuation of TAC</td>
<td></td>
</tr>
<tr>
<td>15.6</td>
<td>Secondary</td>
<td>Anticoagulation specific ITT</td>
<td>In-Hospital Mortality</td>
<td>Pooled low and intermediate dose, Continuation of TAC</td>
<td></td>
</tr>
<tr>
<td>15.7</td>
<td>Secondary</td>
<td>Unblinded ITT</td>
<td>90-day Mortality</td>
<td>Pooled low and intermediate dose, Continuation of TAC</td>
<td></td>
</tr>
</tbody>
</table>
15.8 Primary Safety Analysis

<table>
<thead>
<tr>
<th>Primary Safety Analysis</th>
<th>Anticoagulation specific ITT</th>
<th>Serious adverse events per patient</th>
<th>Pooled low and intermediate dose, Continuation of TAC</th>
<th>Time effects removed from model.</th>
</tr>
</thead>
</table>

15.9 Secondary safety analysis

<table>
<thead>
<tr>
<th>Secondary safety analysis</th>
<th>Anticoagulation specific ITT</th>
<th>Major bleeding</th>
<th>Pooled low and intermediate dose, Continuation of TAC</th>
</tr>
</thead>
</table>

15.10 Secondary

<table>
<thead>
<tr>
<th>Secondary</th>
<th>Anticoagulation specific ITT</th>
<th>All thrombotic events or death</th>
<th>Pooled low and intermediate dose, Continuation of TAC</th>
</tr>
</thead>
</table>

15.11 Graphical Summaries

<table>
<thead>
<tr>
<th>Graphical Summaries</th>
<th>Anticoagulation specific ITT</th>
<th>All endpoints</th>
<th>Pooled low and intermediate dose, Continuation of TAC</th>
<th>Including combinations across unblinded domains.</th>
</tr>
</thead>
</table>

16. Reporting of Analysis Results

The unblinded SAC will provide blinded investigators with a restricted set of summaries from the primary analysis models (15.1-15.2) to maintain the blinding of low and intermediate dose interventions. For these models, the SAC will report the following summary:

- Continuation of TAC will be compared to both the low and intermediate dose interventions separately for futility. The SAC will report the highest probability of futility (OR<1.2) across these two comparators and will not reveal the specific comparator intervention.

For the remaining analysis models, the following summaries of parameters will be reported when applicable. All summaries of TAC treatment effect will be reported relative to pooled low and intermediate dose:

<table>
<thead>
<tr>
<th>Odds/Hazard-Ratio Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>95% Credible Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 39</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 40-49</td>
<td></td>
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<tr>
<td>Age 50-59</td>
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<tr>
<td>Age 70-79</td>
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<tr>
<td>Age 80+</td>
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</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Time Bucket 1</td>
<td></td>
<td></td>
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</tbody>
</table>
For each analysis model (except 15.1 and 15.2), the following comparisons will be made by state, when applicable:

- Continuation of TAC will be compared to the control arm (pooled conventional low dose and intermediate dose heparin) for superiority. A posterior probability of superiority of 99% will be used as the statistical threshold to declare efficacy. In subgroup models, this probability will be provided by subgroup.

- Continuation of TAC will be compared to the control arm (pooled conventional low dose and intermediate dose heparin) for futility. A 95% probability of a smaller than 1.2 odds-ratio for continuation of TAC relative to the control will be used as the statistical threshold to declare futility. In subgroup models, this probability will be provided by subgroup.

- The posterior probability that the OR>1 for combinations will be reported for continuation of TAC and interventions from other domains.

- The posterior probability that the OR>1 for the interaction effect will be reported for each interaction between continuation of TAC and interventions from other domains.

- The “Anticoagulant*Unblinded intervention combination” term is an odds ratio composed of the main effect of anticoagulant, the main effect of the unblinded intervention, and the interaction effect between the two. The “Anticoagulant*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 anticoagulant therapy ORs will be reported for each dichotomization of OSFD.

**16.1 Graphical summaries**

The following graphical summaries will be provided for all endpoints:

- Population: Anticoagulation specific ITT
- Endpoint: all endpoints
● Factors: Continuation of TAC and control (pooled conventional low and intermediate dose heparin) interventions

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

● Population: Anticoagulation specific ITT
● Endpoint: OSFD, in-hospital mortality
● Factors:
  o Continuation of TAC and control (pooled conventional low and intermediate dose heparin) interventions interacted with antiplatelet domain

Analysis: Conducted by the blinded Design Team
Appendix A. Definition of organ support-free days

This outcome is an ordinal scale of integers from –1 to 22 for the Moderate state, or -1 to 21 for the Severe state. It is derived from a composite of the patient’s vital status at the end of acute hospital admission (censored at day 90 after each randomization) and duration of organ failure support while admitted to an ICU (including a re-purposed ICU) during the 21 days (504 hours) after randomization in that state. The outcome of -1 indicates a patient death in hospital prior to the end of 90 days after their last randomization.

Patients 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.

Final OSFD decimals are rounded up or down to nearest whole day

If the patient has received allocations in both the Moderate and Severe states, and is alive at the end of both the Moderate and Severe censoring time points (i.e. day 90 after each randomization), the outcomes will be calculated as above. If the patient dies after the end of the Moderate censoring day 90 time point but before the Severe censoring day 90 time point, and before hospital discharge, the endpoint values will be updated to “–1” for BOTH ModerateOutcomeDay21 and SevereOutcomeDay21 endpoints. For patients who receive an allocation in both the Moderate and Severe states, if SevereOutcomeDay21 = -1, then ModerateOutcomeDay21 must therefore also be -1.

Outcome values are updated to -1 if the patient dies during the acute hospital stay and before day 90 after their last randomization. For a patient who remains admitted to an acute hospital and is still alive at the end of day 90 after their last randomization, no further changes to coding will be made.