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

COVID-19 Anticoagulation Domain Version 1.0 dated 19 March 2024

TABLE OF CONTENTS

1.   COVID-19 ANTICOAGULATION DOMAIN SAP

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

1.1.   Version history

Version 1:   Finalized on 19th March 2024

1.2.   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

2.   INTRODUCTION

This statistical plan for 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 (critically ill). This plan details the statistical analyses in the original REMAP-CAP core SAP and the pandemic stratum SAP applied to the analysis of the Intermediate and Conventional low dose anticoagulation interventions of the Anticoagulation Domain within the pandemic infection suspected or proven (PISOP) (COVID-19) stratum.

The analysis of continuation of therapeutic-dose anticoagulation (TAC) intervention in the prior TAC stratum was previously completed and results are published *(Bradbury CA et al Intensive Care Med. 2023 Jul;49(7):873-875. doi: 10.1007/s00134-023-07095-8).* The TAC intervention closure on April 29, 2022 was based on this treatment reaching a prespecified trigger for futility. To preserve the blind of the other interventions in the domain, the TAC intervention was reported compared to a pooled group of low and intermediate interventions in the prior TAC stratum. Since then, recruitment to the anticoagulation domain continued with randomization to conventional low dose or intermediate dose heparin stratified by whether the patient previously received therapeutic dose anticoagulation with heparin for COVID-19 treatment when moderately ill before becoming critically ill and recruitment to this domain (prior TAC strata). Although a statistical trigger had not been reached for these 2 remaining interventions (low and intermediate dose heparin), the anticoagulation DWG and ITSC decided to stop recruitment to the PISOP anticoagulation domain due to operational futility. This recommendation was based on the reasonable number of participants having been recruited (>1300), ongoing slow recruitment (due to declining severe case numbers) and the absence of meeting a statistical trigger at the most recent adaptive analysis. A series of simulations were undertaken to inform the decision to stop, and the simulations suggested that a substantially larger number of patients were needed to have a reasonable likelihood of meeting a futility or superiority trigger. These simulations are provided below in **Appendix A**. The anticoagulation DSWG therefore recommended to the ITSC that we stop recruitment to the PISOP anticoagulation domain and report the findings. An important driver of this decision was to report the data regarding COVID-19 in the public domain while it has relevance. This was supported by the ITSC. Accordingly, on December 1st 2023, recruitment stopped to the remaining interventions in the anticoagulation domain.

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. For this analysis, in the absence of a platform conclusion, data for the remaining interventions (low and intermediate dose heparin) within the anticoagulation domain will be unblinded and made public.

The authors of this document are blinded to the treatment assignments and comparative effectiveness of low and intermediate dose heparin. In the previous analysis of the continuation of TAC interventions, the authors of this document were unblinded to individual patient data for the continuation of TAC group and the pooled group of patients randomized to either low or intermediate dose heparin. The primary analysis for this SAP will be conducted after the patient last randomized, before closing the domain, reaches 21 days of follow-up (completion of the primary end-point).

3.   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 (conventional low and intermediate dose heparin) 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:

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 severe patients in the prior TAC or no prior TAC strata, this would trigger domain superiority of that intervention for that stratum.

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 prior TAC or no prior TAC strata, this would trigger domain inferiority of that intervention for that stratum.

3. **Intervention Efficacy**. If an intervention is deemed to have at least a 99% posterior probability of being superior to conventional low dose thromboprophylaxis in the prior TAC or no prior TAC strata, then a declaration of efficacy of that intervention would be declared for that stratum.

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 dose intervention in the prior TAC or no prior TAC strata, then a declaration of futility of that intervention would be declared for that stratum.

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 low dose intervention, then it will be deemed to be harmful in this population.

4.   UNBLINDING

REMAP-CAP has multiple domains in which patients can be randomized and multiple interventions within domains. At the unblinding of the anticoagulation domain, there is only one domain remaining within the PISOP stratum to which patients have been randomized that will not be unblinded at this analysis. Because almost all domains and interventions have been unblinded at this point, the prespecified analyses in this report will not be conducted by the fully unblinded Statistical Analysis Committee (SAC) but instead the ITSC Statistical Analysis committee. These analyses are conducted with only knowledge of the unblinded anticoagulation allocation status for patients or the allocation status to other unblinded interventions. These analyses are identified below.

5.   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

There are two interventions within no Prior TAC stratum of the Anticoagulation Domain. These are:

1. Intermediate dose heparin
2. Conventional low dose heparin

The primary analysis will estimate separate intervention treatment effects by Prior TAC stratum with dynamic borrowing across strata. A key sensitivity analysis will estimate a pooled effect of each intervention in the Prior TAC and no Prior TAC strata patients.

6.   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.

7.   ANALYSIS POPULATIONS

1. Unblinded ITT. All PISOP patients randomized in the Anticoagulation Domain or to any other unblinded interventions/domains within the PISOP stratum.
2. Anticoagulation specific ITT. This population consists of only patients randomized in the second phase of the Anticoagulation Domain within the severe PISOP stratum.

Each of these analysis populations will include only the patients randomized on or before the anticoagulation domain was halted on December 1st 2023.

8.   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.

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 B 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. **Progression to intubation and mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or death**

   a. A dichotomous endpoint of whether a patient progresses to intubation and mechanical ventilation, ECMO or death in hospital.

   b. This endpoint will be reported descriptively.

5. **Vasopressor/Inotrope Free-Days**

   a. An ordinal outcome of the number of days free of Vasopressor/Inotropes. This is the exact calculation of OSFD, with Vasopressor/Inotropes as the only organ support category. In-hospital death is considered a −1.

   b. This endpoint will be reported descriptively (or graphically).

6. **Respiratory support-free Days**

   a. An ordinal outcome of the number of days free of respiratory support. This is the exact calculation of OSFD, with respiratory support as the only qualifying organ support category. In-hospital death is considered a −1.

   b. This endpoint will be reported descriptively (or graphically).

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.

    d. This endpoint will be reported descriptively (or graphically).

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 events.

    c. Patients still in the hospital at data snapshot will be considered censored.

    d. This endpoint will be reported descriptively (or graphically).

9. **At least one serious adverse event (SAE)**

    a. A dichotomous endpoint of SAE.

10. **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.

11. **Total red blood cell units transfused between randomization and the end of study day 15**

    a. A numerical endpoint

    b. The endpoint is censored at 14 days to correspond with the intervention duration.

    c. This endpoint will be reported descriptively.

12. **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 arterial or venous thrombotic event diagnosed at any time during the index hospitalization.

    b. This endpoint will be reported descriptively using proportions.

13. **Arterial thrombotic events (events confirmed by blinded adjudication)**

c. A composite dichotomous endpoint of ischemic cerebrovascular event, myocardial infarction, systemic arterial thromboembolism or other arterial thrombotic events including mesenteric ischemia and limb ischemia diagnosed at any time during the index hospitalization.

d. This endpoint will be reported descriptively using proportions.

14. **Venous thrombotic events (events confirmed by blinded adjudication)**

e. A composite dichotomous endpoint of deep vein thrombosis, pulmonary embolism or other venous thrombotic event diagnosed at any time during the index hospitalization.

f. This endpoint will be reported descriptively using proportions.

15. **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.

16. **Heparin induced thrombocytopenia (laboratory confirmed)**

a. This endpoint will be reported descriptively using proportions.

9.   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.

10.   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.

11.   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.

12.   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.

12.1. 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.

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

• The treatment effect of intermediate dose compared to low dose is estimated separately for the Prior TAC and No Prior TAC strata as specified in the Current State document and DSA. The priors on the treatment effects of intermediate compared to low dose by strata will incorporate borrowing through a hierarchical prior.

$$\beta_j \sim N(\mu, \tau^2) \text{ for } j \in [\text{Prior TAC, No Prior TAC}]$$
$$\mu \sim N(0,1)$$
$$\tau^2 \sim IG(0.125, 0.00281)$$

• In a sensitivity analysis, the Prior and No Prior TAC strata results will be pooled for comparison of the low and intermediate dose interventions. A standard normal prior distribution (mean 0, variance 1) will be used for the effect of intermediate dose heparin in this sensitivity analysis.

12.1.1.   **Proportional Odds Assumption**

The primary analysis model assumes a proportional effect of treatment across the scale of the ordinal outcome. 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.

12.2. **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).

12.3. 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.

12.4. 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.

12.5. 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.

12.6. 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 (or Bayesian equivalents):

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.

13.   SPECIFIC PROSPECTIVE ANALYSES

Table 1. Prospective analyses

#	Status	Population	Endpoint	Other
1	Primary	Unblinded ITT population	OSFD	Includes all unblinded interventions and pre-specified interactions.
2	Primary	Unblinded ITT population	In-Hospital Mortality	Includes all unblinded interventions and pre-specified interactions.
3	Sensitivity	Unblinded ITT population	Dichotomized OSFD	The odds ratio for intermediate dose heparin will be reported for each dichotomization of OSFD in the severe state.
4	Sensitivity	Unblinded ITT population	OSFD	Intervention effects are pooled across prior TAC and no prior TAC strata
5	Sensitivity	Unblinded ITT population	In-Hospital Mortality	Intervention effects are pooled across prior TAC and no prior TAC strata
6	Sensitivity	Unblinded ITT population	OSFD	Intervention effects are independent across prior TAC and no prior TAC strata
7	Sensitivity	Unblinded ITT population	In-Hospital Mortality	Intervention effects are independent across prior TAC and no prior TAC strata

8	Sensitivity	Anticoagulation specific ITT	OSFD	
9	Sensitivity	Anticoagulation specific ITT	In-Hospital Mortality	
10	Secondary	Unblinded ITT	90-day Mortality	
11	Safety Analysis	Anticoagulation specific ITT	Serious adverse events per patient	Time effects removed from model.
12	Primary safety analysis	Anticoagulation specific ITT	Major bleeding	Time effects removed from model.
13	Secondary	Anticoagulation specific ITT	All thrombotic events or death	
14	Subgroup	Unblinded ITT population	OSFD	Including differential treatment effect by subgroup: age (<50, 50-70, 70+)
15	Subgroup	Unblinded ITT population	In-Hospital Mortality	Including differential treatment effect by subgroup: age (<50, 50-70, 70+)
16	Subgroup	Unblinded ITT population	OSFD	Including differential treatment effect by subgroup: invasive mechanical ventilation at baseline (yes/no)
17	Subgroup	Unblinded ITT population	In-Hospital Mortality	Including differential treatment effect by subgroup: invasive mechanical ventilation at baseline (yes/no)
18	Subgroup	Unblinded ITT population	OSFD	Including differential treatment effect by subgroup: baseline use of antiplatelets
19	Subgroup	Unblinded ITT population	In-Hospital Mortality	Including differential treatment effect by subgroup: baseline use of antiplatelets
20	Subgroup	Unblinded ITT population	All thrombotic events or death	Including differential treatment effect by subgroup: baseline use of antiplatelets
21	Subgroup	Unblinded ITT population	Major bleeding	Including differential treatment effect by subgroup: baseline use of antiplatelets
22	Graphical Summaries	Anticoagulation specific ITT	All endpoints	Including combinations across unblinded domains.

14.   REPORTING OF ANALYSIS RESULTS

For each analysis model, the following summaries of parameters will be reported when applicable.

All summaries of Intermediate dose treatment effect will be reported relative to low dose:

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				
Intermediate dose heparin (relative to low dose heparin)				
Continuation of TAC (relative to low dose heparin)				
Main effects of unblinded interventions included in interaction w/ anticoagulation therapy				
Anticoagulation therapy*Unblinded intervention interaction				
Anticoagulation therapy*Unblinded intervention combination				
Main effect of subgroup				
Anticoagulant therapy by subgroup				

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

- Intermediate dose heparin will be compared to conventional low 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.

- Intermediate dose heparin will be compared to conventional low dose heparin for futility. A 95% probability of a smaller than 1.2 odds-ratio for Intermediate dose heparin relative to low dose heparin 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 intermediate dose heparin and interventions from other domains.

- The posterior probability that the OR>1 for the interaction effect will be reported for each interaction between intermediate dose heparin 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.

14.1. Graphical summaries

The following graphical summaries will be provided for all endpoints:

- Population: Anticoagulation specific ITT

- Endpoint: All endpoints

- Factors: Intermediate dose heparin and conventional low dose heparin interventions

Appendix A. Simulations

This appendix describes simulations performed during enrolment of the anticoagulation domain to inform the operational decision of whether to continue enrolment. As of June 2023, 1339 PISOP patients were randomized to the 2nd phase of the anticoagulation domain (1250 no prior TAC) with no statistical trigger met at the most recent adaptive analysis. Given the lack of a conclusion and the slow enrolment of PISOP patients, this simulation study was conducted to evaluate the possible treatment effect sizes that would not satisfy futility/superiority triggers at the current sample size and the likelihood of making a conclusion at future analyses if enrolment continues. In summary, if we continue enrolling an additional 250 patients (which under the current enrolment rate could take 9-12 months), the probability we will make a conclusion is 14% given the fact that we have not yet met a conclusion at previous interims.

Figure 1. Cumulative recruitment of critically ill patients with COVID-19 to the 2nd phase of the anticoagulation domain to June 2023 demonstrating slowing of recruitment in 2023. Recruitment to prior therapeutic dose anticoagulation (TAC) stratum: 89 (high vs low vs intermediate, 26 high-dose already reported), no Prior TAC stratum: 1250 (low vs intermediate).
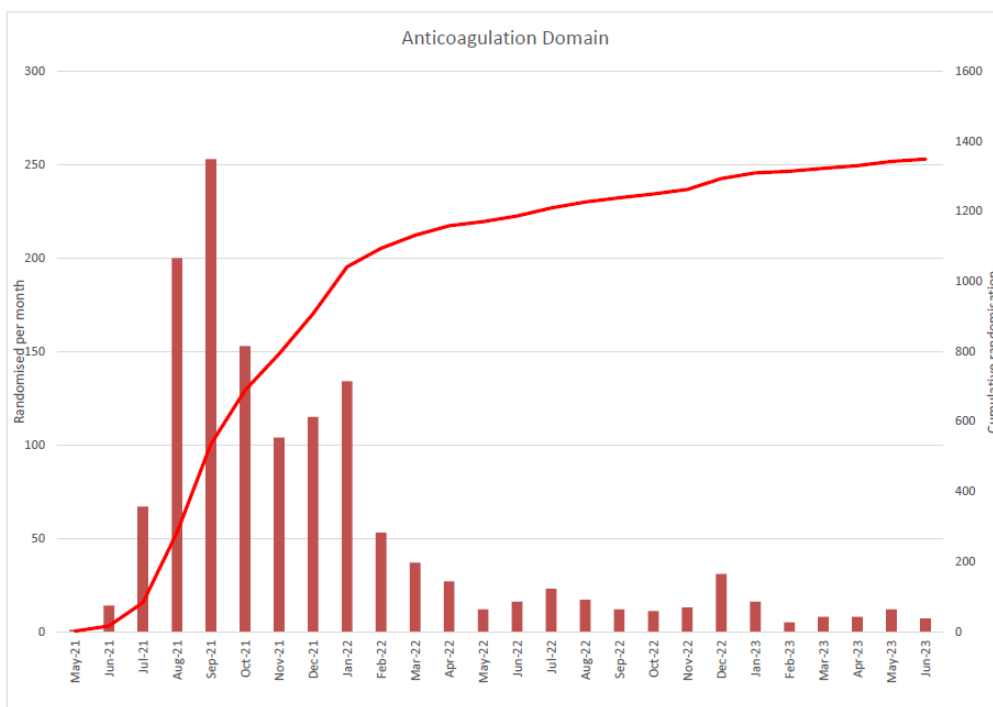
Simulation assumptions

This simulation study of the anticoagulation domain in the severe state for the no prior TAC stratum makes the following assumptions:

- We assume that the distribution of OSFD is similar to the proportions observed in the unblinded no antiplatelet intervention in the Antiplatelet domain. The 23-level OSFD outcome is collapsed into 5 categories with the following proportions:

OSFD level	-1 (death)	0-5	6-10	11-15	16-21
Probability	0.318	0.170	0.066	0.148	0.297

- We simulate a range of anticoagulation treatment effects relative to control: odds ratios (ORs) of 1, 1.05, 1.1, 1.15, 1.2 and 1.25. We focus on this range of moderate effect sizes since larger/smaller effect sizes are highly likely to have reached a statistical trigger by the current sample size.
- We assume no borrowing between the no-prior TAC and prior TAC strata. Given the small sample size in the prior TAC stratum, the dynamic borrowing would have little influence on the treatment effect estimate in the no-prior TAC stratum.

In the simulations, interims were conducted when 500, 1000, 1250, 1500, and 1750 patients have complete outcomes. At each interim, RAR probabilities are updated and decision rules for futility and superiority of intermediate dose to low dose are assessed. To reflect the current status of the domain (1250 no prior TAC patients), the summaries below summarize the outcome of the 1250 interim for trials that did not reach a conclusion at an earlier interim. For trials that continue to the 1250 interim, 61.9% of simulated trials have not yet met a conclusion across all treatment effect scenarios. Figure 2 displays those simulated trials with the x-axis displaying the estimated OR and the y-axis the posterior probability of superiority. Each point on the plot is a simulated trial and the color of each point represents what action that trial will take at this 1250 interim. In summary,
- 7.7% stop for futility
- 7.7% stop for superiority
- 84.6% continue enrolling

Figure 3 shows the same simulated trials and describes the observed effects that meet each conclusion. Observed OR less than 1 met futility and observed ORs greater than 1.3 met superiority. Observed ORs between 1 and 1.3 will typically continue enrolling to the next interim.

Figures 4-5 repeats this exercise for the interim when 1500 patients with complete data. These plots now summarize the simulated trials that had not yet met a futility or superiority decision (the green points from Figure 2). At this interim,
- 6.0% stop for futility
- 7.9% stop for superiority
- 86.2% continue enrolling

Therefore in summary, we would have a 6% chance of declaring futility, 8% chance of declaring superiority and an 86% chance of needing to continue enrolling if we enrolled an additional 250 patients and performed an interim at 1500 patients.

Figure 4-6 summarize the operating characteristics for the assumed scenarios. Figure 4 summarizes the cumulative proportion of meeting superiority by treatment effect and sample size. Figure 5 summarizes the cumulative proportion of meeting superiority by treatment effect and sample size. Figure 6 summarizes the cumulative proportion of meeting either conclusion by treatment effect and sample size.

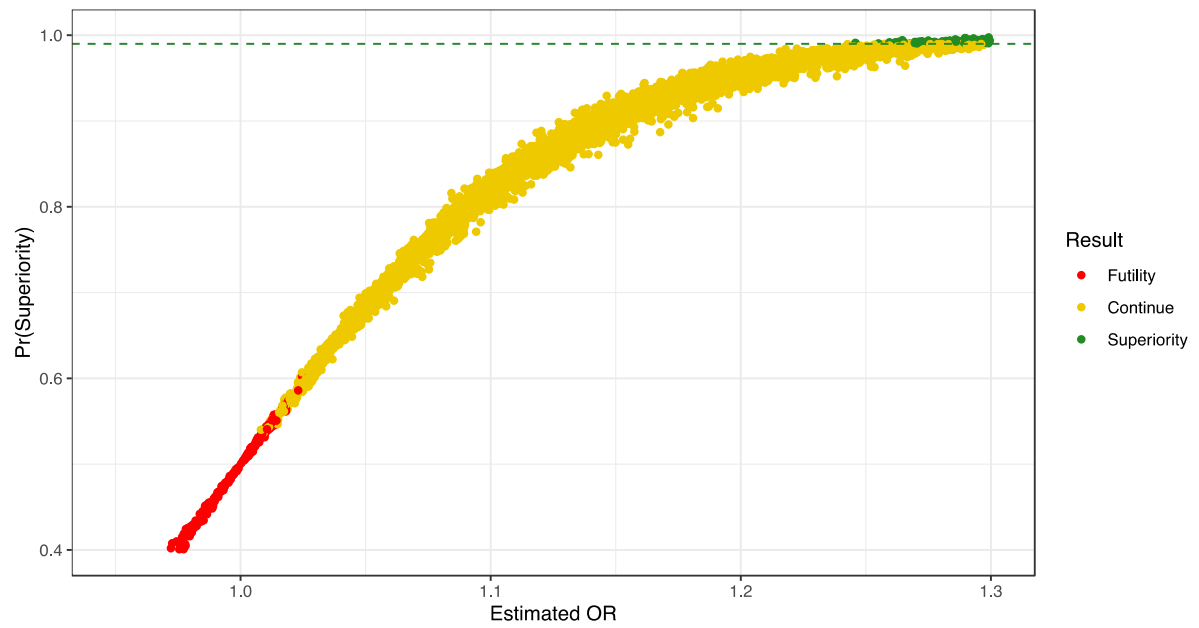**Figure 2:** Plot of simulated trials that are still enrolling at the interim when 1250 patients have complete data.

Figure 3: Proportion of each conclusion by observed OR buckets at the interim when 1250 patients have complete data.
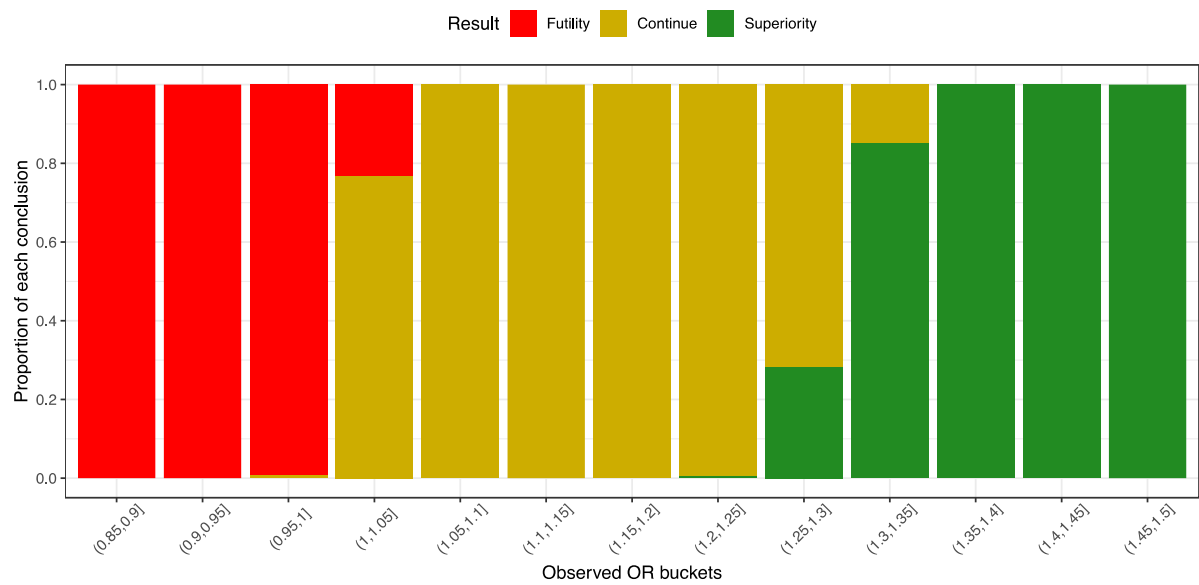
Figure 4: Plot of simulated trials that are still enrolling at the interim when 1500 patients have complete data.
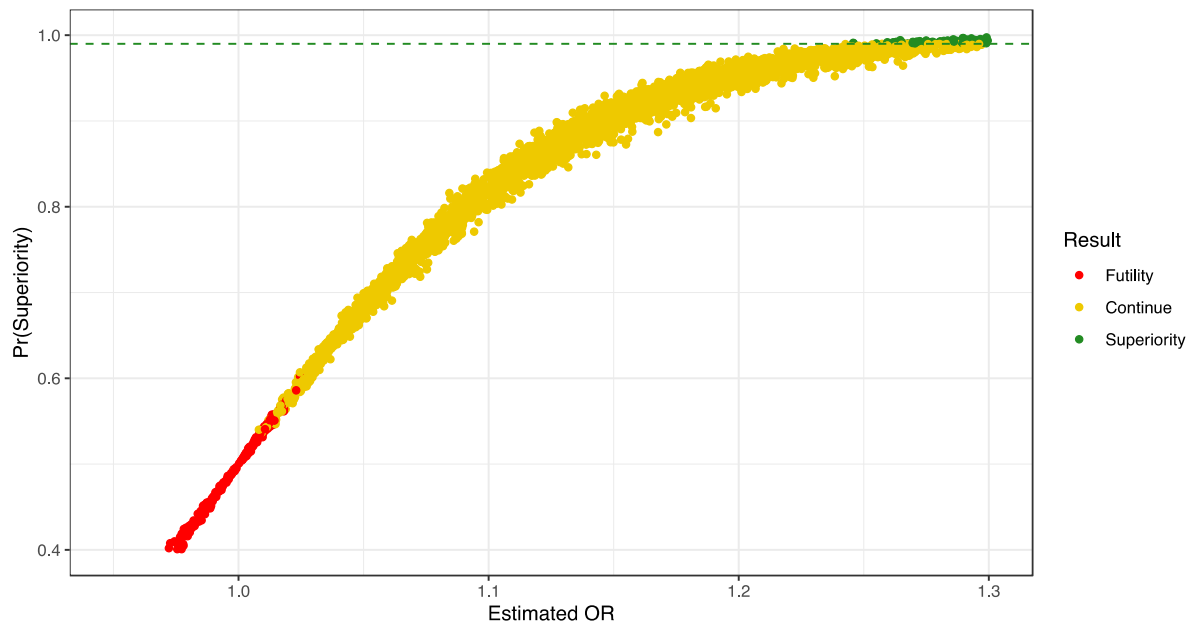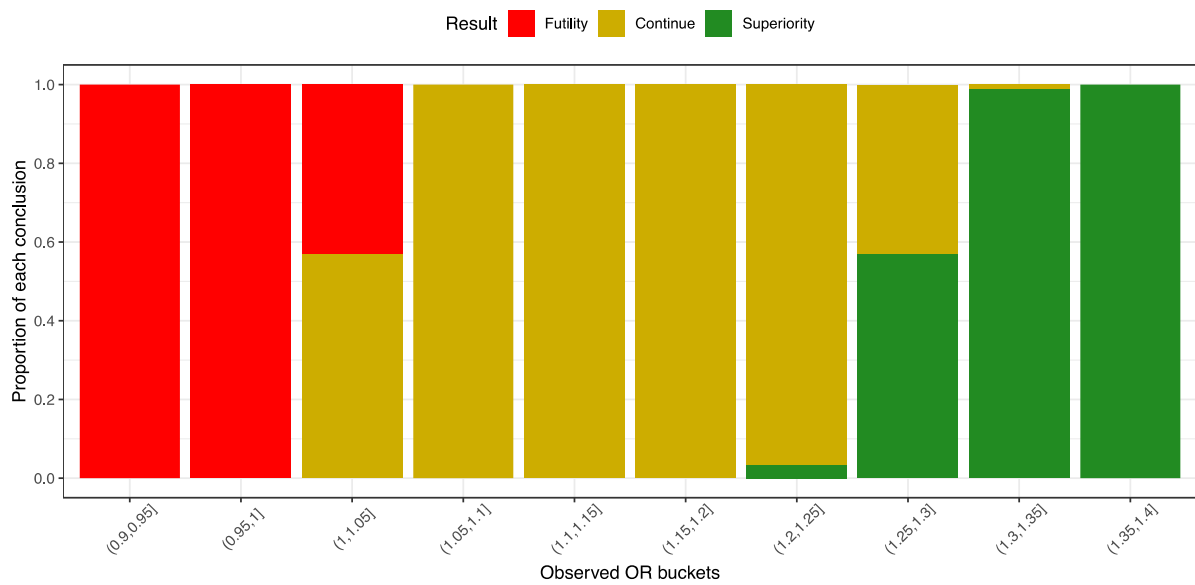

Figure 5: Proportion of each conclusion by observed OR buckets at the interim when 1500 patients have complete data.

Figure 6: Cumulative probability of superiority by number of patients with complete outcome and assumed treatment effect.
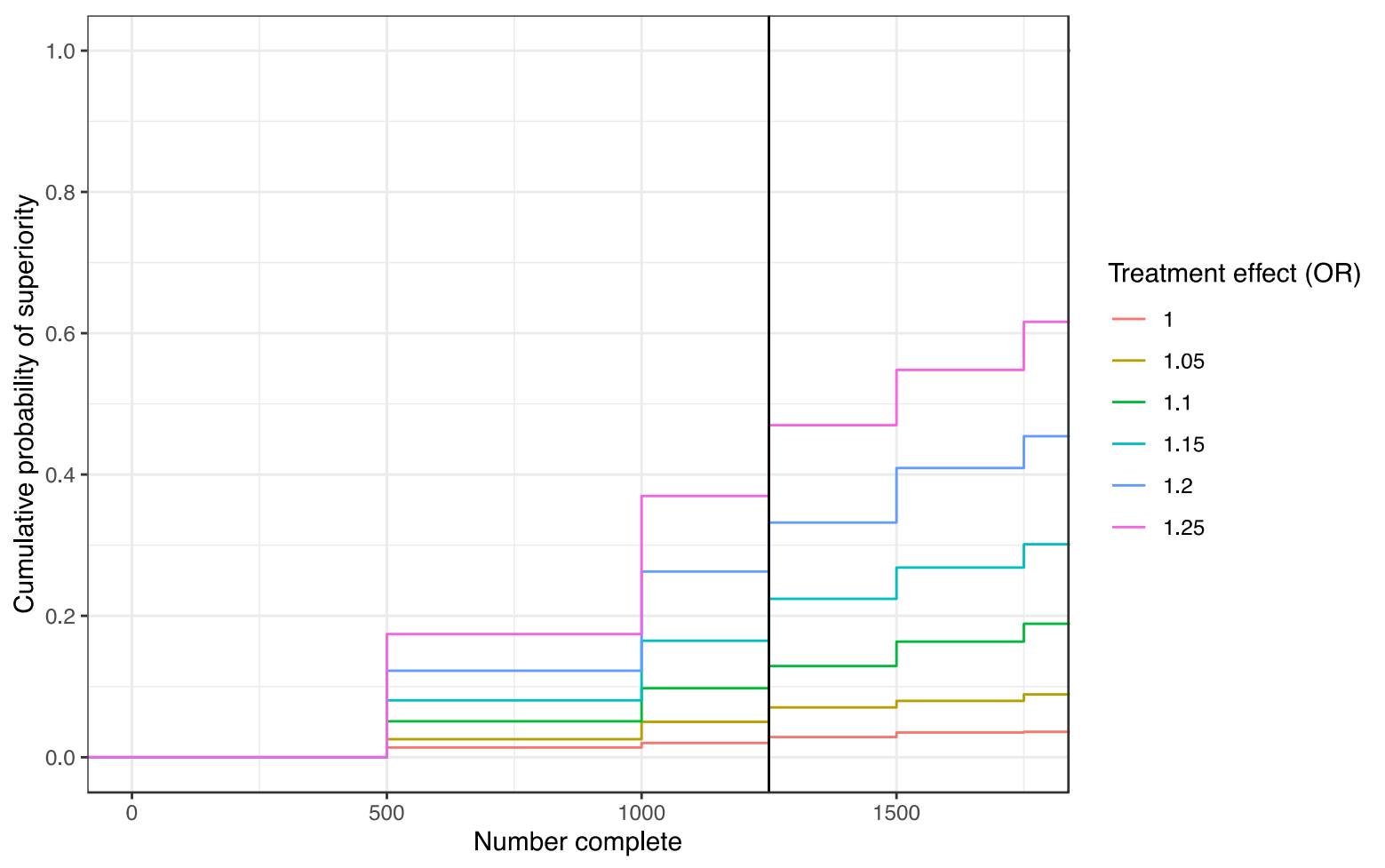
Figure 7: Cumulative probability of futility by number of patients with complete outcome and assumed treatment effect.
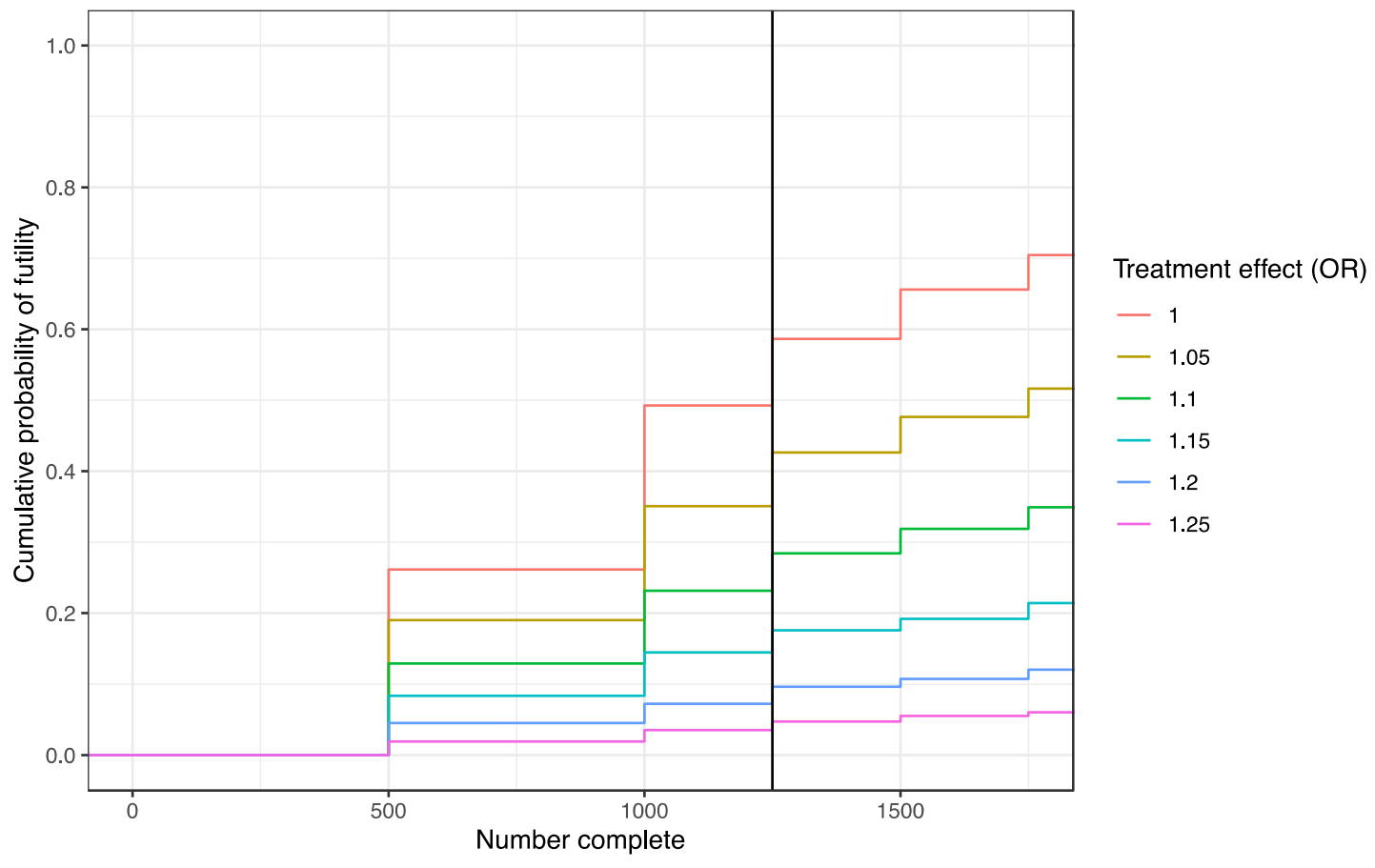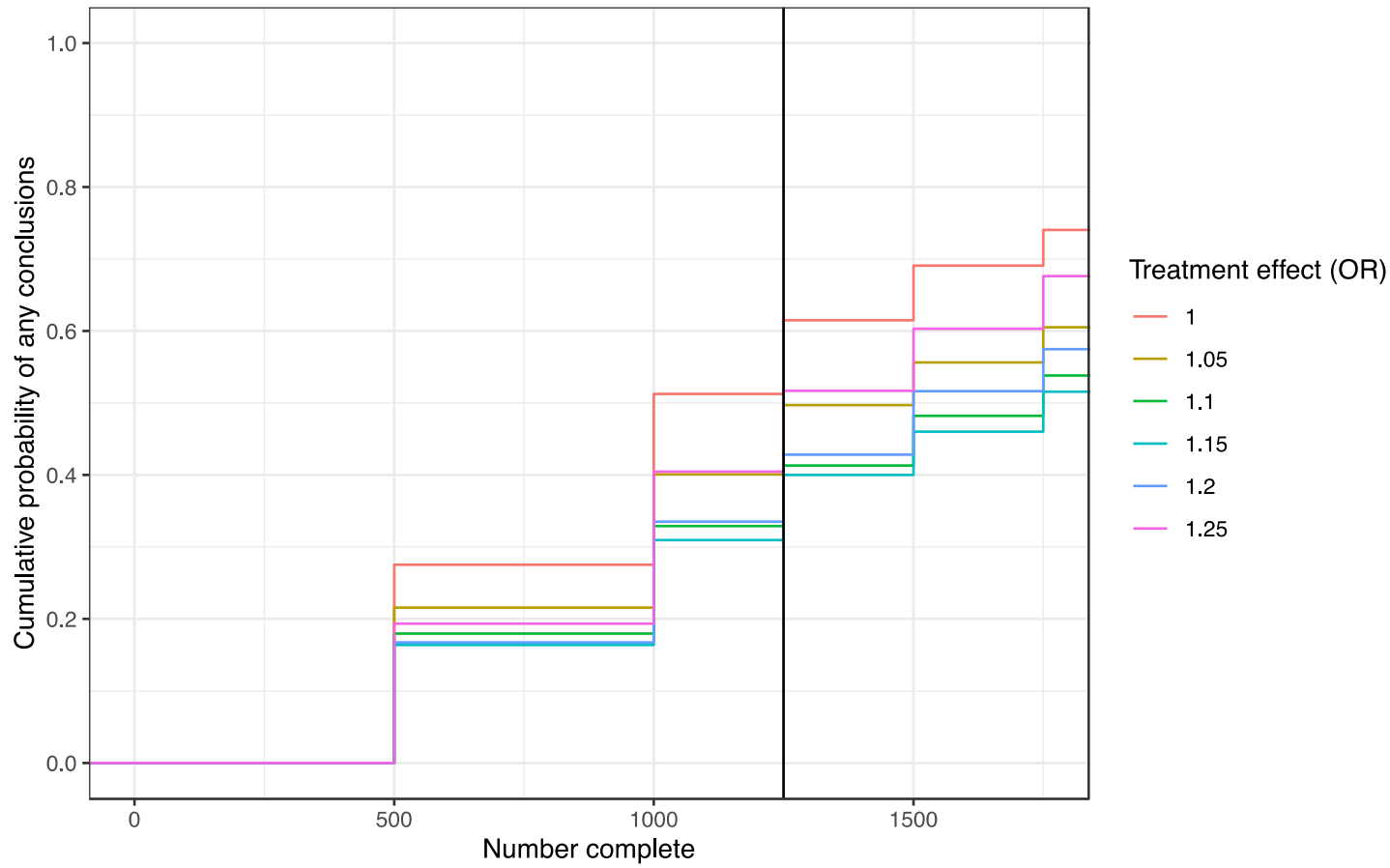
Figure 8: Cumulative probability of any conclusion (superiority or futility) by number of patients with complete outcome and assumed treatment effect.

Appendix B. 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.