ASCOT-ADAPT

Anticoagulation Domain Statistical Analysis Plan

Australasian COVID-19 Trial: An Adaptive Platform Trial

16 May 2022

Anticoagulation SAP Version: 1.0

Protocol Version: ASCOT-ADAPT 6.0

PROTOCOL TITLE	Australasian COVID-19 Trial - Adaptive Platform Trial (ASCOT-ADAPT)
PROTOCOL NUMBER	ERM62646-A
PROTOCOL VERSION	Version 6.0 - 30 Mar 2022
TRIAL REGISTRATION	ACTRN12620000445976
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Contents

Version History

Version 0.1

May 2021: Draft anticoagulation statistical analysis plan (JT)

Version 0.2

April 2022: Restructuring content and adding additional detail throughout (MJ)

Version 1.0

May 2022: Release for imminent analyses of anticoagulation domain (MJ)

Abbreviations

Abbreviation	Definition
COVID-19	Coronavirus Disease-19
CRF	Case report form
DSA	Domain-specific appendix
FAS	Full analysis set
ISTH	International Society of Thrombosis and Haemostasis
ITT	Intention-to-treat
MCMC	Markov chain Monte Carlo
mMRC	Modified Medical Research Council
PP	Per-protocol
RAR	Response-adaptive randomisation
RT-PCR	Reverse transcription - polymerase chain reaction
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SAR	Serious Adverse Reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TMT	Trial Management Team

Domain-specific synopsis

TITLE	Australasian COVID-19 Trial: An Adaptive Platform Trial (ASCOT-ADAPT). A multi-centre randomised adaptive platform clinical trial to assess clinical, virological and immunological outcomes in patients with SARS-CoV-2 infection (COVID-19)
PRIMARY OUTCOME	As per the core protocol - a binary variable indicating: ▪ Death from any cause, or ▪ Requirement of new intensive respiratory support (invasive or non-invasive ventilation), or ▪ Vasopressor/inotropic support in the 28 days after randomisation.
SECONDARY OUTCOMES	As per the core protocol: 1. Time to clinical recovery during the first 28 days after enrolment 2. WHO 8-point ordinal outcome scale at day 28 3. All-cause mortality at 28 and 90 days. 4. Days alive and free of hospital by 28 days. 5. Days alive and free of ventilation by 28 days. 6. Presence of patient reported outcome of shortness of breath at days 28 and 90. 7. Quality of life as measured by EQ-5D-5L questionnaire at days 28 and 90.

DOMAIN-SPECIFIC SECONDARY OUTCOMES	1. Confirmed deep venous thrombosis up to 28 days after randomisation 2. Confirmed pulmonary embolus up to 28 days after randomisation 3. Confirmed acute myocardial infarction up to 28 days after randomisation 4. Confirmed ischemic cerebrovascular event up to 28 days after randomisation 5. Any clinically relevant bleeding (non-major or worse), censored at 28 days after randomisation 6. Major bleeding (as defined by ISTH), censored at 28 days after randomisation 7. Clinically relevant non-major bleeding (as defined by the ISTH), censored at 28 days after randomisation 8. Heparin-induced thrombocytopenia during index hospitalisation, censored at 28 days after randomisation 9. Other confirmed thrombotic event up to 28 days after randomisation 10. Any confirmed thrombotic event up to 28 days after randomisation
STUDY DOMAINS	The following domains were open to recruitment at participating sites: 1. Antiviral 2. Anticoagulation
STUDY DURATION	November 2020 onward

SAMPLE SIZE	Flexible (see protocol and statistical appendices for details)
INCLUSION CRITERIA	1. Age ≥ 18 years 2. Admitted to an acute-care hospital 3. Confirmed SARS-CoV-2 by nucleic acid testing in the past 14 days 4. Able to be randomised within 14 days of symptom onset 5. At least one symptom or sign attributable to SARS-CoV-2 infection
EXCLUSION CRITERIA	1. Currently receiving acute intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support 2. Previous participation in the trial 3. Treating team deems enrolment in the study is not in the best interest of the patient 4. Death is deemed to be imminent and inevitable within the next 24 hours 5. Either the patient or their primary treating clinician are not committed to active treatment
DOMAIN-SPECIFIC INCLUSION CRITERIA	None

DOMAIN-SPECIFIC EXCLUSION CRITERIA	1. Receiving dual antiplatelet therapy 2. The treating clinician intends to continue or commence therapeutic anticoagulation 3. Contraindication to receiving low molecular weight heparin or unfractionated heparin, including the known or suspected history of heparin exposure such as hypersensitivity 4. Severe thrombocytopenia (platelet count less than 30×10^9/L) 5. History of intracranial haemorrhage in the previous 3 months 6. Severe renal impairment, defined as estimated glomerular filtration rate less than $15/\text{ml/min}/1.73^2$ 7. A current or recurrent condition with a high risk of major bleeding (e.g. bleeding disorder), or a baseline coagulation profile (within the previous 3 days) that indicates a high risk of bleeding, that would be considered a contraindication to receive thromboprophylaxis
BLINDING	This will be an open-label study.

1 Introduction

1.1 Background

ASCOT-ADAPT is an investigator-initiated, multi-centre, open-label, randomised controlled Bayesian adaptive platform trial. Patients enrolled in ASCOT-ADAPT and who progress to requiring invasive or non-invasive ventilation can be enrolled in REMAP-CAP (with follow-up data continuing to be collected from these patients for ASCOT).

The anticoagulation domain was developed because COVID-19 is associated with a prothrombotic state, which can manifest as microvascular thrombosis, venous or arterial thrombosis. Identifying interventions that reduce thrombotic complications is therefore a management priority. Specifically, in ASCOT-ADAPT, eligible patients enrolled within the anticoagulation domain are administered low molecular weight heparin at varying dosage. Recent meta-analyses have summarised the knowledge on higher-dose anticoagulation therapy for COVID-19 (Jorda et al., 2022; Kow et al., 2022; Reis et al., 2022; Yasuda et al., n.d.) with Jorda et al. (2022) suggesting: *"there is currently insufficient evidence of survival benefit of therapeutic-dose or intermediate-dose anticoagulation compared with prophylactic-dose anticoagulation in non-critically ill and in critically ill patients hospitalised with COVID-19"*.

1.2 Objectives of domain

The primary objective of the anticoagulation domain is to determine the effectiveness of anticoagulation therapy for patients with COVID-19. Specifically, we hypothesise that the proportion of patients alive and not requiring intensive respiratory or vasopressor support at 28 days after enrolment (primary endpoint for ASCOT-ADAPT) will vary according to anticoagulation dose.

The domain includes a pre-specified objective of evaluating the interactions associated with the combined delivery of anticoagulation and antiviral therapy, which is still active. Therefore, given the relative sample size randomised within each domain, it is more appropriate to report the interaction at the time of revealing the antiviral domain. Additionally, combined reporting would result in the potential risk of revealing information that may compromise the antiviral domain.

1.3 Status

Figure 1 provides a summary of the cumulative enrolment into ASCOT-ADAPT and the progression of the treatment arms for the anticoagulation domain. Nearly all participants in the platform have been randomised within the anticoagulation domain. The vertical dashed lines indicate the times that the interim analyses occurred, which also corresponds to the (approximate) times at which updates to the response adaptive randomisation could be made. The horizontal lines in the lower panel represent the period that each arm was open to enrolment.

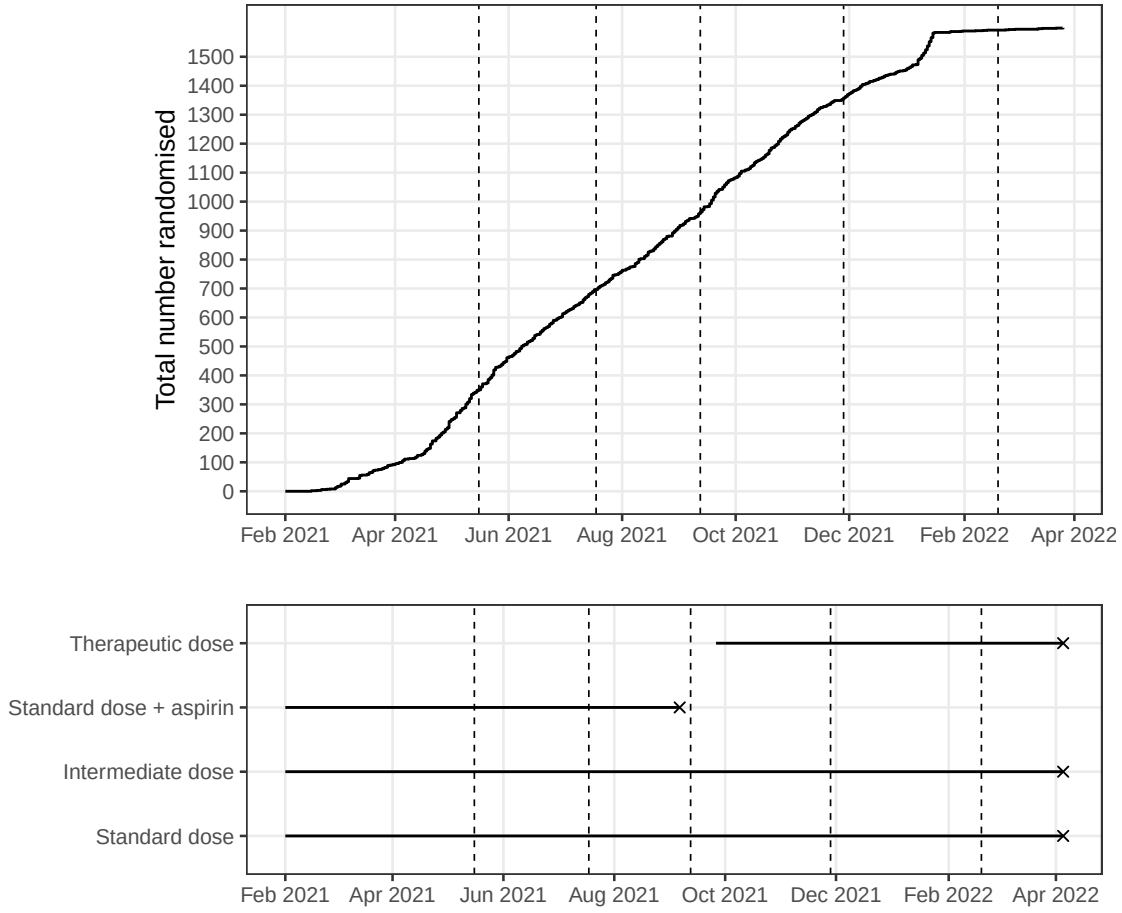

Figure 1: Evolution of anticoagulation domain - dates and adaptation points (vertical lines show time of interim analyses, crosses show time at which arm stopped).

The anticoagulation domain opened for enrolment on 4 Feb 2021 and included treatment arms: standard (prophylactic) dose thromboprophylaxis, intermediate dose thromboprophylaxis and standard dose thromboprophylaxis co-administered with aspirin. On 10 Sept 2021, the prophylactic dose with

aspirin was stopped as a result of external evidence[1] of no benefit (RECOVERY Collaborative Group, 2021). An intermediate dose with aspirin and therapeutic anticoagulation were both proposed, but only therapeutic anticoagulation was activated (late Sep 2021). The introduction of the therapeutic anticoagulation arm was motivated by the findings from the ATTACC, ACTIV-4a and REMAP-CAP collaboration (ATTACC Investigators et al., 2021). On 3 March 2022, the DSMB met and requested that the unblinded DSMB statistician perform a predictive probability assessment of the trial being able to meet pre-specified decision criteria with the scenarios of an additional 260 (expected maximal enrolment with existing funding) or 1,440 (expected maximal enrolment if additional funding secured) enrolments within the anticoagulation domain. Based on these simulations, the DSMB recommended on 21 Mach 2022 that the therapeutic anticoagulation arm be stopped. On 8 April 2022, as a combined result of funding constraints and likely futility, the TMT made the decision to stop enrolment to the anticoagulation domain and complete a definitive analysis for this domain. At the time of the decision, the antiviral (nafamostat and standard of care) and the anticoagulation domains were active, the antiviral domain had enrolled approximately 149 participants and the anticoagulation domain had enrolled 1575 participants. The database components related to the anticoagulant domain will be locked when the last enrolled participant in the anticoagulant domain has reached the 28 day follow up and the data checks/cleaning are completed.

1.4 Purpose and scope of plan

This domain-specific statistical analysis plan (SAP) identifies the data and outlines the procedures for assessing the effectiveness and safety of the anticoagulation domain in ASCOT-ADAPT. The domain-specific SAP is not a standalone document; it is intended to be read in conjunction with the core protocol, the domain specific protocol and the statistical appendix to the core protocol (versions below) all of which are publicly available at the trial website (https://www.ascot-trial.edu.au/pages/resources). The primary analysis, the core secondary analyses and the domain-specific secondary analyses all fall within the scope of this plan. The planned analyses will be included in future trial reports and manuscripts. Exploratory analyses not necessarily identified in this SAP may be performed to support the planned analyses. However, any *post-hoc* or unplanned analyses not

[1]The following reference is the original pre-print source.

specified herein will be identified as such in any statistical reports and manuscripts for publication.

This SAP was written and reviewed by members of the statistical committee and comments were also provided by the trial management team and the domain specific working group members. All contributors were blinded to individual treatment allocations and to the results from each interim analysis that are reported to the Data Safety and Monitoring Board (DSMB) at the time of their contributions.

The following documents were reviewed when preparing this SAP:

- Core protocol for ASCOT-ADAPT Version 6.0
- ASCOT-ADAPT Statistical Analysis Appendix Version 2.2
- Domain-specific appendices to the core protocol
  - Anticoagulation Version 5.0
  - Antiviral Version 5.0

As noted, this SAP is not a standalone document and readers are therefore encouraged to read the core protocol and associated appendices for further details on the conduct of this study, the operational aspects of clinical assessments, the timing for completing a patient in this study, and other design aspects.

2 Study design

2.1 Overview

The generalised study design is outlined in the core protocol and further details are provided in the statistical appendix to the core protocol. The design adopts a Bayesian framework for all analyses. The statistical model (and extensions) for the primary analysis is specified in the statistical appendix to the core protocol. Decision criteria based on posterior probabilities associated with primary analysis model parameters drive all trial adaptations. The primary model will be used in reporting the results for the anticoagulation domain. While there are no within-domain interactions for this domain, an interaction between the anticoagulation and antiviral (nafamostat) domains was pre-specified. However, given that the antiviral domain is still actively recruiting, the between-domain interaction will not be incorporated into the primary model for reporting the anticoagulation domain.

In the statistical appendix to the core protocol, the following statistical decision rules were defined as applicable for adaptations in all domains in the trial:

- **Domain Superiority**: if a single intervention within a domain has posterior probability of being in the best regimen exceeding 99%, then a decision of superiority will be made for that intervention in the domain.
- **Intervention Effectiveness**: if a single non-control intervention within a domain has posterior probability of being more effective than control exceeding 99%, then a decision of effectiveness will be made for that intervention.
- **Intervention Futility**: if a single non-control intervention within a domain has posterior probability less than 5% of being more effective than control by at least an odds ratio of 1.2, then a decision of futility will be made for that intervention.
- **Intervention Equivalence**: if two non-control interventions have a 90% posterior probability of equivalence (odds ratio between $1/1.2$ and 1.2), then a decision of equivalence may be made for those two interventions.

With the exception of the equivalence criteria, the actions associated with each of these decision rules are outlined in the statistical appendix to the core protocol. The decision rule thresholds

were selected accounting for the multiple interim analyses and interventions, based on average trial operating characteristics over a range of trial scenarios generated by statistical simulation and documented in the statistical appendix.

Statistical decisions trigger reporting to the DSMB in closed sessions, who then determine whether the proposed action should be taken, or if there is justification for delaying the action in light of the existing data and/or external evidence. However, while the decision rules direct adaptation, in settings where stopping arises due to other reasons (such as evidence that is external to the trial) emphasis will be placed on the posterior probabilities and parameter summaries.

2.2 Study population

For the platform eligibility, refer to the synopsis presented earlier, the core protocol and the domain-specific appendix. There are no domain-specific inclusion criteria beyond those defined in the core protocol, however, there are domain specific exclusion criteria for the anticoagulation domain. These exclusion criteria apply in addition to those criteria listed in the core protocol. Specifically, participants will be excluded from the anticoagulation domain if any of the following are met:

- Receiving dual antiplatelet therapy
- The treating clinician intends to continue or commence therapeutic anticoagulation
- Contraindication to receiving low molecular weight heparin or unfractionated heparin, including the known or suspected history of heparin exposure such as hypersensitivity.
- Severe thrombocytopenia (platelet count less than 30 $\times 10^9$/L)
- History of intracranial haemorrhage in the previous 3 months
- Severe renal impairment, defined as estimated glomerular filtration rate less than $15/\text{ml}/\text{min}/1.73^2$.
- A current or recurrent condition with a high risk of major bleeding (e.g. bleeding disorder), or a baseline coagulation profile (within the previous 3 days) that indicates a high risk of bleeding, that would be considered a contraindication to receive thromboprophylaxis.

There are also intervention specific exclusion criteria for the standard thromboprophylaxis plus aspirin arm:

- Receiving an antiplatelet agent
- Hypersensitivity to aspirin

2.3 Outcomes

For all core outcomes, refer to the synopsis presented earlier, the core protocol and the domain-specific appendix. In addition to the core outcomes, the domain-specific outcomes (all of which will consider death when reported) include:

- Confirmed deep venous thrombosis (DVT) up to 28 days after randomisation
- Confirmed pulmonary embolus (PE) up to 28 days
- Confirmed acute myocardial infarction up to 28 days
- Confirmed ischemic cerebrovascular event up to 28 days
- Major bleeding (as defined by ISTH) censored at 28 days after randomisation
- Clinically relevant non-major bleeding (as defined by ISTH), censored at 28 days
- Heparin-induced thrombocytopenia during index hospitalisation, censored at 28 days
- Other confirmed thrombotic event up to 28 days after randomisation

The clinical criteria for each of the above has been captured in the domain-specific appendix. While it was not defined in the anticoagulation domain specific appendix, two aggregated outcome were defined. The first was *any thrombotic event (or death) up to 28 days after randomisation* corresponding to the occurrence of any of the following:

- Confirmed DVT
- Confirmed PE
- Confirmed ischemic cerebrovascular event
- Confirmed acute myocardial infarction
- Confirmed other thrombotic event

The second was *any clinically relevant bleeding (non-major or worse), up to 28 days after randomisation*.

All of the domain-specific outcomes are binary variables. If patients have been discharged from

hospital before day 28, a history of domain specific secondary outcomes will be sought from the patient, person responsible, or supervising medical practitioner during the day 28 follow-up telephone call. Confirmation of diagnosis will be required from hospital medical records, radiological reports, or a supervising medical practitioner.

In addition to core serious adverse reactions, domain-specific adverse events that should be reported as serious adverse reaction (SAR) include:

- Major bleeding (as defined by ISTH definition)
- Heparin-induced thrombocytopenia (HIT)

2.4 Subgroups

The following subgroups (replicated from the statistical appendix to the core protocol) include:

- country/region
- days since symptom onset $\leq$ 7 days or $>$ 7 days
- $<$ 60 years of age or $\geq$ 60 years of age
- receipt of corticosteroid
- receipt of remdesivir
- receipt of other agent intended to be an antiviral agent against SARS-CoV-2
- required supplemental oxygen at time of randomisation or oxygen saturation less than 94% at room air
- participants receiving ACE inhibitor/ATII blocker therapy at the time of presentation

However, we note that data on ACE inhibitor/ATII blocker therapy was not collected.

Pre-specified domain-specific patient subgroups of interest to be explored in the context of the primary analysis include:

- D-dimer above (versus below) upper limit of normal at baseline
- Weight less than 120kg versus greater than 120kg
- Patients already on aspirin or not on aspirin at enrolment

3 Analysis sets

3.1 General principles

The primary analysis population consists of all participants that are randomised to at least one of the interventions in the **anticoagulation domain** and have passed 28 days after randomisation with their primary endpoint status either known or known to be missing. The definitive analysis (that will be reported as the primary result) will be based on both concurrent and non-concurrent controls, using model-based approaches to bridge the overlap between multiple treatments arms, adjust for time trends and make appropriate comparisons (see statistical appendix to the core protocol for detail). However, only the data for those participants who were enrolled into the domain prior to the date that the domain closed will be used. This primary analysis population will be used for all outcomes with participants analysed by the regimen to which they were assigned (see ACS-ITT below).

When a platform conclusion is reached for a specific intervention within the anticoagulation domain, and randomisation to that intervention stops, follow-up of participants receiving that intervention will be completed to day 28 and a definitive analysis undertaken for the domain.

For each of the analysis sets (ITT and per protocol) described below, there may be a subset used for the definitive analysis of an intervention. These subsets are determined by the participants randomisation date, eligibility criteria and the platform conclusion date.

3.2 Intention-to-treat

The intention-to-treat (ITT) population is intended to represent patients reflective of what might be seen if the treatment was used in clinical practice. In the ITT analyses, participants will be analysed according to the regimen and interventions to which they were randomised, irrespective of what they received and their adherence. Participants who were randomised to at least one domain will be included in the Full Analysis Set (FAS) ITT dataset. Participants who were randomised in a specific domain, but subsequently found to be ineligible will be included in the ITT set for that domain.

The datasets applicable to the anticoagulation domain analyses are listed in Table 1. When epoch-specific datasets need to be referred to, we will denote them using a subscript. For example, ACS-ITT$_{t=1}$ denotes the subset of the FAS-ITT dataset that were randomised within the anticoagulation domain in the most recent epoch relative to the current time (each epoch spans a 4 week window, counting backwards in time). The intersection between the anticoagulation and antiviral sets (those that were assigned to both domains) is relevant primarily for the evaluation of the interactions between the anticoagulation and antiviral domains. However, as noted earlier, as the antiviral domain is ongoing, the interaction will be reported in the publication of that domain.

3.3 Per-protocol

The per-protocol (PP) population aims to support identifying treatment effects under ideal (or at least near-ideal) conditions. The domain-specific appendix has outlined how the intervention should be delivered (in terms of dose and duration). The per-protocol population will be represented as participants who were commenced on their allocated treatment arm and received the expected dose on more than 75% of study days. Participants who discontinued their allocated treatment arm due to death, requirement for intensive respiratory or inotropic support, clinically significant bleeding or suspected or confirmed thrombosis are included in the per protocol population (as this was allowed in the protocol).

The datasets applicable to the anticoagulation analyses are listed in Table 2. Epoch-specific datasets are denoted in an analogous manner to those for the ITT datasets.

3.4 Sample size

As the aim of the platform was for perpetual recruitment until a conclusion could be made for all interventions under consideration, no pre-specified sample size was defined. Additionally, given the adaptive design, sample size is a random variable that is conditional on the realised/observed design. To evaluate the platform operating characteristics, simulations assumed a maximum total sample size of 5000 participants.

Table 1: Dataset definitions for use in intention-to-treat analyses.

Name	Abbreviation	Description
Full Analysis Set (ITT)	FAS-ITT	All participants who were randomised to at least one study domain. Participants will be analysed as randomised, irrespective of withdrawal, treatment compliance, or other protocol deviations.
Anticoagulation Set	ACS-ITT	Subset of FAS-ITT who were randomised to the anticoagulation domain.
Antiviral Set	AVS-ITT	Subset of FAS-ITT who were randomised to the antiviral domain.
Anticoagulation ∩ Antiviral	ACS-AVS-ITT	Intersection of ACS-ITT and AVS-ITT.
Intervention specific set	<Intervention>-ITT	Subset of anticoagulation specific ITT who were eligible to be randomised to the intervention of interest and randomised either to that intervention or control

Table 2: Dataset definitions for use in per-protocol analyses.

Name	Abbreviation	Description
Full Analysis Set (PP)	FAS-PP	All participants who were randomised to at least one study domain and satisfied platform, domain, and intervention protocol requirements.
Anticoagulation Set	ACS-PP	Subset of FAS-PP who were randomised to the anticoagulation domain and completed the treatment originally allocated.
Antiviral Set	AVS-PP	Subset of FAS-PP who were randomised to the antiviral domain.
Anticoagulation ∩ Antiviral	ACS-AVS-PP	Intersection of ACS-PP and AVS-PP.
Intervention specific set	<Intervention>-PP	Subset of anticoagulation specific PP who were eligible to be randomised to the intervention of interest and randomised either to that intervention or control

4 Data management

4.1 Data sources

Data will be cleaned blind by members of the TMT and access/extracts will be provided to the analytic team following the protocols used to date for interim analyses.

5 Analysis - general considerations

In the interests of time, the primary analysis and all 28 day secondary outcomes will be implemented and reported publicly prior to all participants reaching the 90 day endpoints. The 90 day outcomes will be analysed subsequently, as soon as practical after the data is available.

5.1 Participant progression

A CONSORT (CONsolidated Standards of Reporting Trials) diagram will be used to show the patient progression for the anticoagulation domain (specific details on other domains will be omitted). A summary of the screening information will be provided dependent on availability. Number (and percentage) of participants randomised to each intervention will be given for all randomised participants by interim analysis. Reasons for ineligibility to the platform and anticoagulation domain and domain-specific interventions will be tabulated. Reasons for study withdrawal will be presented by intervention group.

5.2 Enrolment

Enrolment by site and domain-specific intervention will be tabulated.

5.3 Participant characteristics

Baseline data, as per the statistical appendix to the core protocol will be summarised by domain-specific intervention, including demographics, co-morbidities and prognostic variables (see table template section 12.3). Grouping will be based on the treatments arms involved in the anticoagulation domain and overall.

5.4 Protocol adherence

The protocols for intervention dosing are provided in the relevant sections of the anticoagulation domain appendix to the core protocol. Adherence to the intervention protocol will be summarised

descriptively for each intervention in the domain.

5.5 Visual summaries

Visual summaries will be provided for:

- Cumulative frequency of participants randomised and timepoints at which adaptations occurred (per Figure 1)
- Proportion with the primary outcome by interim analysis and anticoagulant intervention group (showing date of analysis and number of new enrolments) based on concurrent controls and cumulative non-concurrent controls
- Cumulative randomisation charts (overall and by study site)
- Age class distribution
- Temporal evolution of the empirical distribution of the WHO eight-point ordinal outcome scale
- Forest plot of primary outcome in pre-defined subgroups

Additional visual summaries may be requested to support reports or publications.

5.6 Descriptive statistics

Descriptive summaries will be provided for:

- All primary and secondary outcomes
  - Descriptive statistics will be provided for components that make up composite outcomes. For example, the primary outcome is a composite and so descriptive summaries will be provided for the variables that make up the composite, namely, the number of participants requiring vasopressor/inotropic support, the number requiring new intensive respiratory support and the number of deaths.
- Drugs received during hospital stay (participants with discharge records)
- Discharge outcomes

Dichotomous outcomes will be summarised by counts and proportions in each category. Ordinal outcomes will be summarised by the frequency and proportions in each outcome category. Time-

to-event outcomes will be presented using Kaplan-Meier plots and summarised by percentiles of the Kaplan-Meier estimates where available and appropriate.

5.7 Model summaries

Model outputs for each parameter estimate in the linear predictor will be the mean, median, standard deviation, and 95% credible intervals (all credible intervals be equal-tailed percentiles, e.g. 95% credible intervals will range from the 2.5th percentile to the 97.5th percentile). For tabulated summaries, random effects may be integrated out. While model parameters will be adjusted for assignment in other domains, the only intervention effects to be reported will relate to the anticoagulation domain.

The extent of overlap will be considered in comparisons between treatment arms. For example, there is no temporal overlap between the standard dose + aspirin arm and the therapeutic arms.

All models will be parameterised so that an odds-ratio (or relevant parameter) greater than 1 (or other appropriate reference value) indicates that there is an increase in the likelihood of the outcome.

5.8 Missing data

Missingness in the participant characteristics will be explored and reported. Patterns and number of missing data for the primary, secondary and domain specific outcomes will be reported/visualised. Patterns and number of missing data for the covariates involved in the primary model linear predictor will also be reported/visualised. Variables with missingness in excess of 10% will be identified, but no formal imputation model developed. Exploratory analyses examining the associations attributed to missingness may be implemented. For example, intervention specific missingness may be considered. Worst/best scenarios may be assessed for the primary outcome (see 10).

5.9 Diagnostics

Where possible, models will be validated on simulated data. Convergence of MCMC chains will be inspected using standard approaches including traceplots and the Gelman-Rubin diagnostic (R-hat values). Diagnostics reported by Stan (e.g. divergent transitions) will be addressed. Posterior

predictive checks will be used to scrutinise relevant aspects of the models. Should model specification or other issues/concerns arise, the analysts have discretion to make necessary adjustments, subject to ensuring that all changes or updates to the pre-specified models are documented in the clinical trial report and manuscripts.

5.10 Quality assurance

Data verification will be implemented (blinded) via a combination of manual and scripted (automated) checks. All code associated with the analyses will be reviewed by a second unblinded statistician. Results from analyses documented within the trial report will be reviewed and discussed by the statistics WG.

5.11 Software

All data analyses will be performed using R (R Core Team, 2022). Models will be fit in R using Stan (Carpenter et al., 2017) via the `rstan` or `cmdstanr` packages.

6 Primary analysis

The primary analysis (including the priors) will be implemented and reported as specified in the statistical appendix to the core protocol and run on the ACS-ITT population (see earlier). In brief, the primary analysis model is a Bayesian logistic regression model for the binary primary endpoint. The linear predictor includes terms for:

- treatment (all domains)
- ineligibility
- region
- site
- time
- age

For further detail, refer to the statistical appendix to the core protocol. While the model parameters are conditional on intervention assignment within other domains, only intervention contrasts relating to the anticoagulation domain will be made available.

The probabilities for each decision criteria (2.1) will be computed, that is, we will provide the probability of effectiveness, futility, superiority and inferiority based on the pre-specified definitions of these quantities. In addition, the probabilities of each arm being the best intervention in the domain will be provided.

As a minimum, we will also produce summaries of model estimates for comparisons between:

- standard dose vs standard dose + aspirin
- standard dose vs intermediate
- standard dose vs therapeutic
- intermediate vs therapeutic

Other comparisons such as standard vs (pooled intermediate & therapeutic) and therapeutic vs (pooled standard & intermediate) may be produced.

No interactions between intervention domains will be included in the linear predictor.

7 Secondary analysis

Secondary analyses will adopt a linear predictor that has an analogous structure to that used in the primary analysis.

7.1 Time to clinical recovery during the first 28 days after enrolment

Per the core protocol, clinical recovery is defined as the first day, during the 28 days after enrolment, on which a patient satisfies categories 1, 2, or 3 on the WHO eight-point ordinal outcome scale (it will be assumed that the participant is not hospitalised on the first day following discharge and that on the day of discharge the participant is still considered hospitalised but not requiring supplemental oxygen nor ongoing medical care if the site has mistakenly indicated the patient was not hospitalised). This outcome will be modelled per the statistical appendix to the core protocol, specifically, we will use a discrete-time-to-event proportional continuation ratio logistic model.

7.2 WHO 8-point ordinal outcome scale at day 28 after randomisation

The WHO 8-point ordinal outcome ranges from "Not hospitalised, no limitations on activities" (1) to "Death" (8) assessed at day 28 of follow up. Note that admission to a Hospital in the Home unit is not counted as hospitalisation for the purposes of this ordinal scale. Additionally, patients who have been admitted to hospital and transferred to a Hospital in the Home unit will be assessed as either ordinal score 1 or 2. This outcome will be modelled per the statistical appendix to the core protocol, specifically, we will use a cumulative logistic regression model. The proportional odds assumption will be assessed by fitting independent logistic regression models to successive cutpoints.

7.3 All-cause mortality at 28 and 90 days after randomisation

The outcomes was defined as death with the relevant time window and will be modelled per the statistical appendix to the core protocol. Specifically, we will use a logistic regression model.

7.4 Days alive and free of hospital by 28 days after randomisation

This outcome was defined as the number of days alive and free of hospital from randomisation to 28 days, calculated as 28 minus the number of days in the hospital. All patients dying within 28 days will be assigned zero free days. Note that days spent in a Hospital in the Home unit will not be counted as days in hospital as hospital means 'acute-care hospital' for the purposes of this endpoint. The outcome will be modelled per the statistical appendix to the core protocol, specifically, we will use a cumulative logistic regression model. The proportional odds assumption will be assessed by fitting independent logistic regression models to successive cutpoints.

7.5 Days alive and free of invasive or non-invasive ventilation by 28 days after randomisation

This outcome was defined as the number of days alive and free of positive pressure ventilation (invasive or noon-invasive) to 28 days, calculated as 28 minus the number of days on ventilatory support. All patients dying within 28 days will be assigned zero free days. The outcome will be modelled per the statistical appendix to the core protocol, specifically, we will use a cumulative logistic regression model. The proportional odds assumption will be assessed by fitting independent logistic regression models to successive cutpoints.

7.6 Presence of patient reported outcome of shortness of breath at days 28 and 90 post randomisation

This outcome will be modelled per the statistical appendix to the core protocol, specifically, we will use a logistic regression model.

7.7 Modified Medical Research Council (mMRC) breathlessness scale at days 28 and 90 post randomisation

The Medical Research Council (mMRC) breathlessness scale ordinal outcome ranges from "I only get breathless with strenuous exercise" (0) to "I am too breathless to leave the house or I am breathless

when dressing or undressing" (4). This outcome will be modelled per the statistical appendix to the core protocol, specifically, we will use a cumulative logistic regression model. The proportional odds assumption will be assessed by fitting independent logistic regression models to successive cutpoints.

7.8 Quality of life as measured by EQ-5D-5L questionnaire at days 28 and 90 post randomisation

Health-Related Quality of Life (HRQoL) as measured by the EuroQol 5 dimension, 5 level (EQ-5D-5L) questionnaire, and the visual analogue scale (VAS), will be reported descriptively. HRQoL utility values will be calculated using the appropriate population algorithms.

8 Domain-specific secondary analysis

8.1 Any thrombotic event (or death) to day 28

This outcome corresponds to the occurrence of any of the following thrombotic events:

- DVT
- PE
- Acute myocardial infarction
- Ischemic cerebrovascular event
- Other thrombotic event

and will account for the risk of death. This outcome will be reported descriptively and analysed by logistic regression.

8.2 Confirmed deep venous thrombosis up to 28 days

This outcome will be reported descriptively.

8.3 Confirmed pulmonary embolus up to 28 days

This outcome will be reported descriptively.

8.4 Confirmed acute myocardial infarction up to 28 days

This outcome will be reported descriptively.

8.5 Confirmed ischemic cerebrovascular event up to 28 days

This outcome will be reported descriptively.

8.6 Any clinically relevant bleeding (non-major or worse), censored at 28 days after randomisation

This outcome will be analysed by logistic regression.

8.7 Major bleeding (as defined by ISTH) censored at 28 days

This outcome will be reported descriptively.

8.8 Clinically relevant non-major bleeding (as defined by ISTH), censored at 28 days

This outcome will be reported descriptively.

8.9 Heparin-induced thrombocytopenia during index hospitalisation, censored at 28 days

This outcome will be reported descriptively.

8.10 Other confirmed thrombotic event up to 28 days after randomisation

This outcome will be reported descriptively.

9 Safety analyses

Safety analyses will be restricted to descriptive summaries by domain-specific intervention group and overall.

10 Sensitivity analyses

Several sensitivity analyses were identified in the statistical appendix to the core protocol. For this domain, we will run the following sensitivities:

- The primary analysis will be re-run based on the FAS-ITT dataset
- The primary analysis will be re-run based solely on those participants eligible for all interventions in the anticoagulation domain
- The primary analysis will be re-run based solely on concurrently randomised controls
- The primary analysis will be re-run under worst-case scenarios whereby all participants with missing primary outcomes will be set to having met the primary outcome (death or requirement of new intensive respiratory support or vasopressor/inotropic support)
- The primary analysis will be re-run under best-case scenarios whereby all participants with missing primary outcomes will be set to having NOT met the primary outcome (death or requirement of new intensive respiratory support or vasopressor/inotropic support)
- The primary analysis will be re-run on the ACS-PP population (see earlier)
- Secondary analyses will be re-run based solely on contemporaneous controls
- Domain-specific secondary analyses will be re-run based solely on contemporaneous controls

Deviations from the above are at the analysts' discretion but must be reported with a reason for the deviation.

11 Subgroup analyses

Subgroups (see 2.4) will be analysed for the primary outcome per the approach detailed in the statistical appendix to the core protocol. Any additional subgroup analyses will be considered *post-*

hoc and reported as such.

As noted earlier, subgroups analyses are (a) subject to analyst discretion based on their assessment of the suitability of the data (b) will not be explored in any secondary outcome and (c) not contingent on the results from the primary analysis. The rationale for any variation to the approach will be documented in the trial report.

12 Reporting

In the interests of time, the primary results will report only the primary outcome and the 28 day secondary outcomes. The 90 day outcomes will be reported in subsequent manuscripts.

12.1 Blinding

Only information pertaining to the anticoagulation domain will be reported. For example, information on the proportions allocated to other domains will not be disclosed when reporting baseline characteristics.

12.2 Clinical trial report

All results will be documented in a single clinical trial report, which will be used as the basis for the content in all manuscripts to be published.

12.3 Tables

An **indicative** set of shell tables to be reported are specified in the following sections. Statistical tests for comparisons of groups will not be provided.

12.3.1 Participant characteristics at baseline

Table 3: Participant characteristics at baseline

Variable	Std (n = xx)	Std+Aspirin (n = xx)	Int (n = xx)	Thera (n = xx)	Overall (n = xx)
Age					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Sex					
Male, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Female, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Weight					
Median, (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Vaccinated					
Yes, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity					
Indian, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Smoking					
Current, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Former, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Never, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

12.3.2 Baseline co-morbidities

Table 4: Baseline co-morbidities

Variable	Std (n = xx)	Std+Aspirin (n = xx)	Int (n = xx)	Thera (n = xx)	Overall (n = xx)
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hypertension, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Diabetes, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Obesity, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asthma, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Chronic lung disease, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Chronic cardiac disease, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Obstructive sleep apnoea, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Iatrogenic immunosuppression, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Chronic kidney disease, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Malignant neoplasm, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate or severe liver disease, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Dialysis, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
HIV infection, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Dementia, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

12.3.3 Baseline prognostic variables

Table 5: Baseline prognostic variables

Variable	Std (n = xx)	Std+Aspirin (n = xx)	Int (n = xx)	Thera (n = xx)	Overall (n = xx)
Was the patient on room air for any of the preceding 24 hours?					
Yes, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Was the patient's GCS < 15?					
Yes, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Peripheral oxygen saturation (SpO2) on room air (Lowest)					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Highest respiratory rate (breaths/minute)					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Highest recorded Urea in the last 24 hours (mmol/L)					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Highest recorded CRP in the last 24 hours (mg/L)					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
APTT					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
INR					
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Fibrinogen1 (g/L)					
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prothrombin time (sec)					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Taking aspirin					
Yes, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Interventions					
None	xx	xx	xx	xx	xx
Antiviral	xx	xx	xx	xx	xx
Corticosteroids	xx	xx	xx	xx	xx
Anti-inflammatory	xx	xx	xx	xx	xx
Time from onset of symptoms to hospitalisation					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)

Table 5: Baseline prognostic variables *(continued)*

Variable	Std (n = xx)	Std+Aspirin (n = xx)	Int (n = xx)	Thera (n = xx)	Overall (n = xx)
Time from hospitalisation to randomisation					
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)

12.3.4 Summary of primary outcome observations

Table 6: Summary of primary outcome observations

Event	Std (n = xx)	Std+Aspirin (n = xx)	Int (n = xx)	Thera (n = xx)	Overall (n = xx)
Overall (n = xx)					
Proportion with primary outcome	xx.x	xx.x	xx.x	xx.x	xx.x
Death, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Intensive respiratory support, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Vasopressor/inotropic support, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Interim 1 (n = xx)					
Proportion with primary outcome	xx.x	xx.x	xx.x	xx.x	xx.x
Death, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Intensive respiratory support, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Vasopressor/inotropic support, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Interim 2 (n = xx)					
Proportion with primary outcome	xx.x	xx.x	xx.x	xx.x	xx.x
Death, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Intensive respiratory support, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Vasopressor/inotropic support, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note:

Interim sections show primary outcome for those enrolled in the current interval.

12.3.5 Compliance to study drug

Table 7: Compliance to study drug

Variable	Std (n = xx)	Std+Aspirin (n = xx)	Int (n = xx)	Thera (n = xx)	Overall (n = xx)
Time from randomisation to administration of study drug					
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing, n (%)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)
Time on study treatment (days)					
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing, n (%)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)
Cumulative dose of study drug received (ml)					
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing, n (%)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)
Cumulative dose duration (hours)					
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing, n (%)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)
Overall compliance (%)					
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing, n (%)	xx (x)	xx (x)	xx (x)	xx (x)	xx (x)

12.3.6 Summary of secondary outcomes for anticoagulation domain

Table 8: Summary of secondary outcomes for anticoagulation domain

Event	Std (n = xx)	Std+Aspirin (n = xx)	Int (n = xx)	Thera (n = xx)	Overall (n = xx)
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Died on or prior to day 28, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Acute myocardial infarction, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ischemic cerebrovascular event, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Deep vein thrombosis, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pulmonary embolism, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other thrombotic event (arterial or venous), n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Clinically relevant non-major bleeding, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other thrombotic event, n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

12.3.7 Summary of safety outcomes for anticoagulation domain

Table 9: Summary of safety outcomes for anticoagulation domain

Event	Std (n = xx)	Std+Aspirin (n = xx)	Int (n = xx)	Thera (n = xx)	Overall (n = xx)
None, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Major bleeding as per the ISTH definition, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Clinically relevant non major bleeding, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Heparin-induced thrombocytopenia (HIT), n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note:

Table will be modified as required. For example, serious adverse reactions may be included.

12.3.8 Summary of parameter estimates for primary outcome

Table 10: Summary of parameter estimates for primary outcome

Parameter (Odds-ratio)	Median	95% Credible interval	Mean (SD)	Pr(OR > 1)
Standard + aspirin	x.xx	x.xx - x.xx	0.91 (0.07)	x.xx
Intermedi...	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx
Therapeutic	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx
Age >= 60	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx
Epoch-0 (referant)	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx
Epoch-1	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx
...	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx
Corticosteroids	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx
Remdesivir	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx
Standard + aspirin	x.xx	x.xx - x.xx	x.xx (x.xx)	x.xx

Note:

Other contrasts may be reported as will decision summaries.

Analogous tables will be provided for secondary outcomes and decision summaries. Analysts have discretion to vary tables from these definitions where deemed necessary.

12.4 Figures

Figures as listed in 5.5 will be reported.

13 References

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