Statistical Analysis Plan for the Randomized Clinical Trial of Anti-platelet Treatment for Covid-19

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1.1. Version history

Version 1: Draft 3/30/2021

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3. Introduction

This is the statistical plan for the analysis of the ACTIV4A antiplatelet treatment trial. This plan has been pre-specified by the investigators prior to unblinding of the data.

3.1. Reporting strategy

This SAP describes the planned analyses for the study. As outlined below, two cohorts (moderate illness, severe illness) may report at different times. Multiple reports describing the results of analysis may be prepared and published to ensure expedited dissemination of the study findings. It is anticipated that for each cohort, expedited, potentially preliminary reports will describe key primary and secondary findings and limited subgroup analyses. Endpoints to be reported in these reports include:

- Organ support-free days to day 21 (primary endpoint)
- In-hospital mortality (key secondary endpoint)
- Major thrombotic events or death (key secondary endpoint)
- ISTH major bleeding (key safety endpoint)

Comprehensive reports providing complete characterization of trial results may subsequently be prepared and published.

4. Design Considerations

The study was designed with a Bayesian analysis as the primary analysis method for the trial. There is one overarching Bayesian model, pre-specified in the SAP, driving all adaptations, statistical triggers, and result summaries. The decision to use a Bayesian analysis was driven in part by the uncertainty of the extent of the pandemic. The required sample size could have been small or large. Given the expected evolution of the design and uncertain sample size, a Bayesian approach is more appropriate.

In this section we describe the basic defined structure of the analysis plan. This includes definitions for the patient subtypes, referred to as cohorts, the interventions, the primary endpoint, and the adaptive design.

4.1. Patient Cohorts

There are two *illness states* defined for this analysis; the severe and moderate illness cohorts. The *severe illness state* is defined as a hospitalized patient on ICU-level organ-support at time of randomization. The *moderate illness state cohort* is defined as a hospitalized patient that is not in the severe illness state.

The primary analysis for the study creates two distinct populations to analyze potential differential benefit of the interventions. In this study these distinct groups are labeled as *cohorts*. The two cohorts are: 1) patients in the severe illness state; 2) patients in the moderate illness state at randomization.

4.2. Interventions

The two interventions for this study are labeled as *antiplatelet agent* (P2Y12 inhibitor), which plays the inferential role of the investigational treatment and no antiplatelet agent

referred to as *control*, which plays the inferential role of the control arm. These interventions are defined as:

1. Antiplatelet agent (P2Y12 inhibitor) to achieve a high level of platelet inhibition in addition to usual care anticoagulation at a level recommended for the illness state.
2. No Antiplatelet agent: usual care strategies, including anticoagulation at a level recommended for the illness state.

4.3. Primary Endpoint

The primary endpoint for the study is *organ support-free days* (OSFD). The endpoint is the number of days, out of the first 21 days after randomization, that a patient is alive and free of ICU-level organ support. For the purposes of the calculation of OSFDs, if a patient dies during their index hospitalization they will be considered the status of dead even if the death occurs after the first 21 days, through 90 days. If a patient dies during their acute index hospitalization they are coded as having –1 OSFDs, which is the worst outcome for the measure. Any patient on ICU-level organ support for all of the first 21 days that does not die, will be labeled as 0 OSFDs, the second worst outcome. The number of days is rounded to the nearest day, creating an integer valued outcome. The values of 0, 1, …, 21 refer to the number of days alive and free of organ support, with smaller values being worse outcomes. Therefore, the primary outcome OSFDs is an ordinal outcome with 23 possible outcomes for each patient, –1, 0, 1, 2, …, 21. The details for the calculation of the endpoint is detailed in the data dictionary.

ICU-level of organ support is defined as high flow nasal cannula, non-invasive ventilation, invasive ventilation, extracorporeal life support, vasopressors, and/or inotropes delivered in an ICU or repurposed critical care area; high flow nasal cannula is considered to be organ support when applied inspiratory flow is ≥20 L/min and $FiO_2 \geq 0.4$. Due to the varying provision of organ-support in potentially repurposed areas during the pandemic, ACTIV-4a defines any hospitalized area able to deliver the above organ-support as an ICU. The details for the calculation of the endpoint is detailed in the data dictionary.

This primary endpoint is an ordinal outcome and the primary analysis model analyzes the outcome as ordinal, with a cumulative logistic proportional odds model. The details of the primary analysis model are presented in Section 12.1. The measure of relative efficacy for the interventions is an odds ratio (OR) which captures the effect of having improved outcomes in OSFDs across the scale between the two interventions. The model is structured so that for P2Y12 an OR > 1 implies improved outcomes on OSFDs for the P2Y12 intervention compared to the control.

4.4. Adaptive Design

There is a prospective adaptive analysis plan for the study. The plan is to have approximately monthly analyses of the study for potential adaptive conclusions. There are two potential prospective adaptive conclusions that can be reached for the comparison of the therapeutic anticoagulation to the prophylactic anticoagulation: *superiority* and *futility*. Superiority of P2Y12 to usual care is defined as a high probability of an OR greater than 1 for P2Y12 and hence improved outcomes in OSFDs for the P2Y12 intervention. Futility will be declared if there is a high probability that the effect of P2Y12 is below a small relative effect of a 1.20 OR. Prospective analyses have been created where statistical thresholds for

claiming superiority or futility have been defined. These statistical thresholds are referred to as *statistical triggers*.

The study defines two statistical triggers within the trial that, at any analysis of the trial, would result in a declaration of superiority or futility as trial conclusions.

The following statistical triggers were defined at the onset of the trial before unblinding:

1. *Superiority*. If P2Y12 has at least a 99% posterior probability of OR>1 for organ support-free days this would trigger a claim of superiority for P2Y12.
2. *Futility*. If P2Y12 has less than 5% posterior probability of at least a 1.20 OR compared to usual care for organ support-free days, then a claim of futility of that intervention would be declared.

For the purpose of this analysis plan, *inferiority* (harm) for P2Y12 is defined as an OR>1 with a posterior probability of 1% or less.

At each adaptive and final analysis of the study each statistical trigger will be separately checked for the two cohorts:

1. Severe state cohort
2. Moderate state cohort

The antiplatelet domain includes pre-specified subgroups/cohorts defined by their classification at baseline with the most recent data available about the patient state at baseline with potentially different outcomes.

4.5. Endpoint adjudication

Thrombosis and bleeding endpoints will be centrally adjudicated. Preliminary reports may describe data available prior to completion of adjudication where necessary.

5. Unblinding

The development of the analysis plan was carried out prior to unblinding of study investigators. Using guidance from the Data and Safety Monitoring Board, the NHLBI will decide when the Investigators will be unblinded to study outcomes by treatment.

6. Analysis Populations

For the purpose of this SAP, several analysis populations are defined.

1. **study confirmed (Primary)**. The study's primary analysis population includes all enrolled patients with confirmed COVID-19 randomized to either intervention and analyzed according to the intention-to-treat principle (i.e. according to randomly assigned treatment status, irrespective of actual treatment receipt).

It is recognized that the primary analysis includes both patient cohorts, moderate and severe. This analysis population will remain primary even if one cohort has a trigger before the other cohort. This is because the primary analysis uses Bayesian borrowing in which the

outcomes from both cohorts are used to estimate the separate ORs for each cohort. The primary analysis will be conducted by the unblinded statistician and the results for the cohorts with statistical triggers will be reported to the DSMB.

If both cohorts achieve a superiority or futility threshold at the same time, a sensitivity analysis including a common odds ratio, adjusted for severity will be conducted, in addition to the primary analysis of each cohort.

The following analysis populations will be defined for each public disclosure corresponding to each cohort being unblinded.

2. **study confirmed unblinded.** The subset of patients in the study confirmed population that belong to the cohort(s) being reported (i.e. those specific cohort(s) that have been unblinded for reporting). This population consists entirely of patients with laboratory-confirmed COVID-19 randomized to P2Y12 or usual care and analyzed according to the intention-to-treat principle.
3. **study confirmed and suspected unblinded** (exploratory sensitivity analyses only)**.** The study population including patients with suspected but unconfirmed COVID-19 who belong to the cohorts that are unblinded for reporting.
4. **study per protocol for P2Y12.** This consists of the patients in the study confirmed unblinded population who have been treated as per protocol. In this analysis that is defined as 1) patients randomized to P2Y12 and who received at least 1 dose by Day zero (day of randomization) or Day 1 (first full day after randomization, **and** 2) patients randomized to usual care who did not receive a P2Y12 dose on or by the end of first full study day after randomization (Day 1).
5. **Study per protocol for P2Y12 and heparin.** This consists of the patients in the study confirmed unblinded population who have been treated as per protocol for P2Y12 and with the suggested dose of heparin anticoagulation according to illness severity at the time of randomization. In this analysis that is defined as 1) patients randomized to P2Y12 and who received at least 1 dose by day zero (day of randomization) or Day 1 (first full day after randomization, **and** 2) patients randomized to usual care who did not receive a P2Y12 dose on or by the end of first full study day after randomization (Day 1) , **and** 3) patients who received at least 1 dose of therapeutic anticoagulation by Day 1 if in moderate severity, or at least one dose of prophylactic anticoagulation by Day 1 if severe illness state.

7. Endpoints

The following endpoints will be analyzed, displayed graphically, and summarized with descriptive statistics.

1. **Organ Support-Free Days** (OSFDs)
   - This is the primary endpoint for the study, and is a composite ordinal endpoint reflecting the number of days alive and off organ support, with in-hospital mortality from any cause as the worst possible outcome. Organ support considered is cardiovascular (vasopressor/inotrope support) and respiratory support (high flow nasal cannula, invasive or non-invasive ventilation, or ECMO).

In-hospital death is considered a –1 and may occur after study day 21 as long as it occurs during the index hospitalization through day 90.

- Detailed definitions for OSFDs are specified in the study data dictionary.
- Missing values for organ support-free days will be treated as "missing and will not be included in the analyses". We will conduct a sensitivity analysis on the primary endpoint treating missing values using the "last known status carried forward" approach.

2. **In-Hospital Mortality**
   - A dichotomous endpoint of in-hospital death from any cause where the death component corresponds to a –1 on the OSFD endpoint. The measurement of in-hospital mortality is truncated at 90 days.

3. 28-day Mortality
   - A dichotomous endpoint of death from any cause. The measurement of mortality is not dependent on the location of the patient.

4. **Mortality**
   - This is a time-to-event endpoint through 90 days.
   - 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, regardless of location at the time of that last assessment.
   - Any patient successfully discharged from hospital, alive, without organ support, will be censored at the date of discharge if 90-day mortality data are not yet recorded.

5. **Vasopressor/inotrope-free days to day 28**
   - An ordinal outcome of the number of days alive and 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 0 (consistent with ACTIV-4A protocol 1.0).
   - All platforms compute vasopressor-free days based on integer days on which vasopressors/inotropes were not received at any time
   - Vasopressor/inotrope-free days will be computed based on the duration of time from the initiation of vasopressors/inotropes to the final cessation of vasopressors/inotropes during the 28-day period; intervening days on which patients are not on vasopressors/inotropes will be ignored

6. **Ventilator-free days to day 28**
   - An ordinal outcome of the number of days alive and free of ventilation. This is the exact calculation of OSFD, with invasive or non-invasive ventilation as the only organ support category. In-hospital death is considered a 0 (consistent with ACTIV-4A protocol 1.0).
   - All platforms compute ventilator-free days based on integer days on which invasive or non-invasive ventilation were not received at any time.
   - Ventilator-free days will be computed based on the duration of time from the initiation of invasive or non-invasive ventilation to the final cessation of invasive

or non-invasive ventilation during the 28-day period; intervening days on which patients are not on ventilatory support will be ignored.

7. **Renal replacement-free days to day 28**
    - Restricted to patients not on Renal Replacement Therapy at baseline
    - An ordinal outcome of the number of days free of renal replacement therapy in the hospital. Death is considered a 0 (consistent ACTIV-4A protocol 1.0).
    - Compute renal replacement-free days based on integer days on which renal replacement therapy was not received at any time
    - Renal replacement-free days will be computed based on the duration of time from the initiation of renal replacement therapy to the final cessation of renal replacement therapy during the 28-day period; intervening days on which patients are not on renal replacement therapy will be ignored

8. **Time to ICU Liberation**
    - Time until the last day in the ICU (including days between ICU stays not in the ICU).This variable will be truncated at 90 days.
    - Patients who die in ICU at any time will be considered censored at 90 days.
    - Patients still in the ICU at data snapshot will be considered censored at the time of exposure (at the time the snapshot was taken).

9. **Duration of hospital stay**
    - A time-to-event endpoint of leaving the hospital alive. If a patient is known to leave and return to the hospital within 21 days that intervening time will be ignored.
    - This variable will be truncated at 90 days.
    - Patients who die in hospital at any time will be considered censored at 90 days.
    - Patients still in the hospital at data snapshot will be considered censored at the time of exposure. (at the time the snapshot was taken).

10. **Major bleeding on or before day 15**
    - A dichotomous endpoint of major bleeding as defined according to the "International Society of Thrombosis and Hemostasis (ISTH) criteria in non-surgical patients."
    - The endpoint is censored at 15 days to correspond to the intervention duration.

11. **Fatal bleeding 5**
    - A dichotomous endpoint of fatal bleeding defined as death attributable to bleeding according to the site investigator reporting or as judged via central adjudication.
    - The endpoint is counted only for bleeding events occurring within 15 days to correspond to the intervention duration. Death from that bleeding event occurring after 15 days is included here.

12. **Heparin-induced thrombocytopenia (HIT)**
    - A dichotomous endpoint of laboratory-confirmed HIT.

- The endpoint is censored at 15 days to correspond to the intervention duration.

13. **Deep venous thrombosis**
    - A dichotomous endpoint of clinically detected deep venous thrombosis diagnosed at any time during the index hospitalization.

14. **Pulmonary embolism**
    - A dichotomous endpoint of clinically detected pulmonary embolism diagnosed at any time during the index hospitalization.

15. **Ischemic cerebrovascular event**
    - A dichotomous endpoint of ischemic cerebrovascular event (stroke).
    - Assessed during the index hospitalization, up to 28 days

16. **Acute myocardial infarction**
    - A dichotomous endpoint of acute myocardial infarction defined according to the universal definition of myocardial infarction.
    - Assessed during the index hospitalization, up to 28 days

17. **Systemic arterial thromboembolism**
    - A dichotomous endpoint of clinically diagnosed systemic arterial thrombosis or embolism
    - Assessed during the index hospitalization, up to 28 days

18. **Major thrombotic event or death**
    - A composite dichotomous endpoint of pulmonary embolism, ischemic cerebrovascular event, myocardial infarction, or systemic arterial thromboembolism diagnosed at any time during the index hospitalization or death in hospital

19. **All thrombotic events or death**
    - 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

20. **Intracranial hemorrhage**
    - A dichotomous endpoint of ischemic cerebrovascular event (stroke).
    - Assessed during the index hospitalization, up to 28 days

21. **Hospital re-admission**
    - A dichotomous endpoint of readmission to hospital within 90 days from randomization
    - This endpoint will be reported descriptively using proportions, including for diagnoses of interest: bleeding, thrombotic event, MI, stroke, ventilatory support

22. **Renal replacement therapy**
    - A dichotomous endpoint of initiation of renal replacement therapy during the index hospitalization among patients not on renal replacement therapy at baseline.
    - Censored at day 90

23. **Acute kidney injury**
    - A dichotomous endpoint of acute kidney injury (as defined by KDIGO) or requirement of renal replacement therapy during the index hospitalization among patients not on renal replacement therapy at baseline.

    - Censored at day 90

24. **The World Health Organization (WHO) 8-point ordinal scale, value on day 14.**
    - A modified WHO ordinal scale will be used:
        0 + 1 + 2 = No longer hospitalized
        3 = Hospitalized, no oxygen therapy
        4 = Oxygen by mask or nasal prongs
        5 = Non-invasive ventilation or high-flow oxygen
        6 = Intubation and mechanical ventilation
        7 = Ventilation + additional organ support: vasopressors, renal replacement therapy (RRT), ECMO
        8 = Death

25. **28-Day Outcome of Ventilator or Death**
    - Binary variable to indicate whether the patient is on a ventilator on Day 28 or deceased by day 28.
    - Those discharged before day 28 who are not on a ventilator will considered to not be on a ventilator at day 28.

26. **Ventilator Support**
    - Dichotomous indicator of requiring all ventilator support (invasive and non-invasive) or death over the index hospital stay
    - Truncated at 90 days

27. **Any organ support**
    - Dichotomous indicator of requiring any organ support or death over the index hospital stay
    - Truncated at 90 days

28. **Critical major bleeding at 28 days**
    - At 28 days, a binary indicator of any major bleed (fatal or in critical area or organ) or death.

29. **Categorization of the primary endpoint - organ support free days**

- Three-level outcome: No organ support without death, some organ support without death, death

30. Four-level organ support

- Four-level outcome: No organ support without death, some organ support without invasive mechanical ventilation and without death, some invasive mechanical ventilation without death, death

31. Categorization of the endpoint–invasive mechanical ventilatory support free days

- Three-level outcome: No invasive mechanical ventilatory support without death, some invasive mechanical ventilatory support without death, death
- HFNO is not counted as ventilatory support

32. Major Thrombotic or Bleeding Composite Event by Day 28

- At 28 days, a binary indicator of
    - Death or
    - Major thrombotic event or
    - Critical major bleed (fatal, ICH, Bleeding in critical area or organ)

33. Composite Thrombotic or Bleeding Event by Day 28

- At 28 days, a binary indicator of
    - Death or
    - Any thrombotic event (major thrombotic event or DVT) or
    - Major ISTH bleed

34. EQ-5D

- At 90 days, continuous measure of function

35. Symptoms

- Binary indicator of any of the following symptoms: fatigue, cough, dyspnea, and chest pain.
- Repeat analysis for each individually
- At 90 days
- Among those that did not have the symptom prior to COVID-19 illness based on the appropriate eCRF

8. 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 or cumulative incidence 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.

9. Descriptive Statistics

1. Ordinal endpoints will be summarized by the cumulative frequency of each outcome. The 5th, 25th, 50th, 75th, and 95th 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 or cumulative incidence estimates, as available.

10. Baseline Characteristics and Co-interventions

The following demographics will be summarized across arms. More may be added as baseline summaries: Age, sex, BMI, race, ethnicity, illness severity at admission, pre-existing conditions, baseline use of oxygen (no, 2L or less, more than 2L but less than 20 L/min, high flow) non-invasive ventilation, invasive mechanical ventilation, ECMO, vasopressors/inotropes, renal replacement therapy, and miscellaneous physiological values and inflammatory biomarker laboratory values (see Appendix A). P2Y12 (specific agent used) by the first full day will be compared between groups. Additionally, exposure to relevant drugs (e.g., aspirin, steroids, immunomodulatory therapies, anticoagulation drug and dose) prior to hospitalization, at baseline, and during the treatment period will be compared between groups.

11. Adherence

Adherence will be assessed based on the proportion of patients receiving a P2Y12 agent consistent with their randomly assigned strategy by the end of the first full study day after randomization.

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. Events that occur at low frequency will be reported descriptively and not modelled.

12.1. Primary Analysis of Primary Endpoint

The **primary analysis model** is a Bayesian cumulative logistic model for the ordinal primary endpoint. The model is described below.

The primary endpoint has 23 possible ordered outcome values. Let the outcome for a patient labeled as Y_i, with possible values, –1 (death), 0, 1, …, 21. A cumulative logistic model is specified. The model is structured so that an OR >1 implies clinical benefit. The model has factors for:

1. Each level of the ordinal endpoint
2. Each global site, nested within country
3. Age; ≤39, 40-49, 50-59, 60-69, 70-79, 80+
4. Sex

5. Time: 2-week epoch bins of time working backwards from the last enrolled patient.
6. Hx cardiovascular disease, including HTN, and/or diabetes
7. Severe/Moderate cohort
8. For severe (type of organ support, invasive mechanical ventilation vs. not)
9. For moderate (the amount of O2 required, no O2, > 0 but <= 2, >2)
10. An effect for each intervention; the effects for P2Y12 are nested across cohorts
11. All sites within a country that have <5 patients randomized will be combined into a single site within that country.
12. For the primary outcome, if there is an outcome in the ordinal scale that did not occur in the data, then that outcome will be combined the next worse outcome. This is done for model stability. For example, if the outcome 11 never occurred, then a combined outcome of 10 & 11 will be modeled for the analysis.
13. If analyzing a single cohort that does not allow for the hierarchical structure in the model, the hierarchical structure of the treatment parameters will be replaced by a standard normal prior unless otherwise specified.

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.

12.2. 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 OR for each dichotomous break is presented. If the probabilities for the tails of the ordinal endpoint have small probabilities (<5%) they may not be conducted. No statistical test of proportional odds will be conducted.

12.3. 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 OR >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).

12.4. 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.

12.5. Analytical Approach for Cohort Analyses

The analyses for each cohort uses the same analysis for the primary models (ordinal, dichotomous, and time-to-event) with the following differences. For each model the treatment effect is modeled separately and independently in each defined cohort. A single group will be selected as the group to have a main effect treatment effect, modeled with a normal distribution with mean 0 and standard deviation 10 (for the log-odds or log-hazard ratio). This group is either the largest group or the first subgroup. Each additional group will have an additive effect on the log parametrization scale with independent normal distribution priors with mean 0 and standard deviation 10.

If multiple subtypes are reported in a single analysis, each group within each subtype will be modeled independently without Bayesian borrowing across subtypes for the treatment effect.

12.6. 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.

12.7. 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 2.5^{th} percentile to the 97.5^{th} percentile of the posterior distribution). For the ordinal endpoints, the odds ratios will be summarized. For the dichotomous endpoints, the odds ratios 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 or inferiority has been identified as statistically significant. For futility a threshold of 95% has been specified.

12.8. Exploratory Analyses

Exploratory analyses after unblinding will not be considered inferential and no p-values will be presented. Any post-hoc exploratory analyses 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.

12.9. Handling of missing data

For the primary endpoint of OSFDs missing primary outcomes will be ignored. A sensitivity analysis is conducted where last status carried forward is used for imputation. Patients with missing age, date of randomization, sex or treatment assignment will be ignored. For additional endpoints those patients missing the endpoint will be ignored (for time to event analyses censoring will be used and aren't considered missing). For the subgroup analyses patients with missing subgroup variables will be lumped into a single group of "missing" in addition to the subgroup classifications.

For time-to-event analyses patients that have a competing event that dictates they cannot achieve a positive outcome (like death for time to hospital discharge), the patient will be assigned a no positive event outcome at the maximum time for the analysis. Patients not achieving an absorbing event that become lost-to-follow up will be censored at the last known time (unless otherwise specified for the analysis).

12.10. Definition of times

Adherence and per protocol analyses will rely on assessment of drug administration by the end of the first full study day after randomization. Post-randomization day 1 is referred to as study day 1 and constitutes the 24-hour period commencing at midnight of the day after randomization.

12.11. Post-randomization analyses

Participants who are randomized to receive one strategy may in fact be treated with another strategy based on health status and provider discretion. Co-interventions during the treatment period (e.g., aspirin, corticosteroids, IL6 antagonists, anticoagulants and their dosing) may modify the benefit or harm of P2Y12. Exploratory analyses will estimate the causal effect of the treatment for these patients using marginal structural modelling techniques. These techniques use inverse probability weighting methods that are based on patient-level covariates to create comparable groups for the analysis.

Anticoagulant treatment will be classified as based on the following dosing equivalents categorization: (1) standard prophylactic, (2) intermediate prophylactic, (3) subtherapeutic, and (4) therapeutic. The criteria for each categorization for each anticoagulant are given in Appendix B. Based on sample size, may collapse groups for analyses

12.12. Heterogeniety of treatment effect

The heterogeneity of the treatment effect will be evaluated in the following a priori defined subgroups:

- Age (< 50 years, 50-70 years, > 70 years)
- Sex
- Invasive mechanical ventilation at baseline for severe cohort
- For moderate (the amount of O2 required, no O2, > 0 but <= 2, >2)
- Heparin dosing during day 1. Categorized as therapeutic if defined as therapeutic at any time during day 0 or 1.

Additional exploratory subgroup analyses will include the following:

- Race/Ethnicity
- D-dimer levels
- Markers of inflammation (CRP, ferritin)
- Baseline troponin
- BMI
- Shock (use of vasopressors or inotropes at baseline)
- Baseline chronic kidney disease
- Steroid administration for COVID-19 at baseline
- Il-6 inhibitor administration for COVID-19 at baseline
- If additional treatments are determined through other research to be beneficial before unblinding subgroups will be defined by those treatments.
- Sites with at least 80% ticagrelor use as assigned P2Y12 inhibitor vs. sites with less than 80% ticagrelor use
- Geographic (Europe, US+Canada, Central and South America)

12.13. Adaptive analyses

The goal for the P2Y12 arm is to determine if it is a safe and effective treatment for hospitalized patients with COVID-19.

Efficacy and Futility Monitoring Plan for P2Y12 Anti-Platelet treatment

The efficacy goal of the P2Y12 arm is to determine if it improves the clinical outcome for hospitalized patients with COVID-19 as measured by the primary outcome, organ-support free-days (OSFDs). There is also the key secondary efficacy goal which is to understand if P2Y12 reduces major thrombotic events and negatively increases bleeding rates.

The hypothesis that P2Y12 reduces organ dysfunction through inhibition of microthrombi in capillaries led to the selection of the primary OSFD outcome. The thrombotic endpoint is testing the hypothesis that the risk of arterial and venous (small, medium and large vessel) thrombosis is reduced with P2Y12.

Key Secondary Efficacy endpoint: a composite major thrombotic event (TE) endpoint of death, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke collected during hospitalization or at 28 days after enrollment.

Stopping Rules for Efficacy
The trial has been designed to separately test the efficacy of P2Y12 with respect to OSFD within two patient cohorts: patients with moderate or severe illness.

The P2Y12 arm will be declared superior to the usual care arm within a specific cohort if the posterior probability of superiority within the cohort is greater than 0.99.

There are no efficacy stopping boundaries for a cohort based on the key secondary endpoint of major thrombotic events or death. The key secondary endpoint is addressed only when futility has been declared for the organ-support free-day endpoint.

Stopping Rules for Futility
The P2Y12 arm would meet a stopping rule for futility for the primary OFSD endpoint only.

If, within a patient cohort, there is a 5% or less posterior probability that the OFSD odds-ratio for the P2Y12 arm compared to the usual care arm is greater than 1.2, favoring the P2Y12 arm, then P2Y12 would meet futility in the cohort.

Safety Monitoring Plan for P2Y12 Anti-Platelet treatment

A safety analysis for the two arms will be presented to the DSMB. The safety events of importance for the P2Y12 arm are a potential excess of major bleeding events, defined by the International Society on Thrombosis and Haemostasis (ISTH) criteria, including ICH and fatal bleeds.

ISTH Defined Major Bleeding
Bleeding that:
1. Resulted in death,
2. Intracranial hemorrhage
3. Occurred in a critical location (intraspinal, intraocular, retroperitoneal, intraarticular, intramuscular with compartment syndrome, or pericardial), or
4. Was associated with either a decrease in the hemoglobin level of at least 2 g per deciliter or transfusion of at least 2 units of packed red cells

A potential safety event for P2Y12 is excess thrombotic events and is a key secondary efficacy endpoint.

Major thrombotic events are defined as: A composite at day 28 or hospital discharge (whichever is first) of death, pulmonary embolism (PE), systemic arterial thromboembolism, myocardial infarction (MI), or ischemic stroke.

Pre-specified stopping guidelines for major bleeding events are not specified. Any decision on stopping the P2Y12 arm would need to balance the severe bleeding risk (e.g., fatal bleeding or intracranial bleeding) with any benefit on the primary endpoint, and reduction in TE and the need for organ support. We leave any decision on recommending stopping the P2Y12 arm for safety reasons to the DSMB given the risk/benefit profile. We have not provided a specific absolute or relative difference for the rates of severe bleeding between the groups as criteria for recommending stopping. Fatal bleeding or intracranial bleeding are the safety events of greatest importance.

It may be appropriate to assess risk factors associated with severe adverse events such as fatal bleeding or intracranial hemorrhage and recommend modification of eligibility criteria based on net clinical benefit. Therefore, recommendations might include changing the eligibility criteria to exclude patients at highest risks for these severe adverse events. Due to the uncertainty around rates in COVID-19 patients, it is possible that after seeing the rates in the current trial, the DSMB would request additional information from the unblinded statistician and/or the investigators before making a definitive recommendation about changing eligibility criteria or stopping an arm entirely.

There is a hierarchy of clinical importance of various TEs, with DVT in the absence of PE the least important and PE, stroke, systemic arterial embolism, and MI (all of which will be adjudicated) more clinically important. PE that impacts oxygenation or hemodynamics may impact the primary endpoint. The trial should not stop before a determination of a difference or not on the primary outcome has been reached, unless one of the two arms presents a clear safety risk, outweighing any potential efficacy benefit.

To aid the DSMB in the risk/benefit and safety determination the following analyses will be presented:

Safety Event	Quantity	P2Y12	Standard Care
ISTH Major Bleeding Events	Number of Events	X1	X2
	Number At 28-days	N1	N2
	Event Rates	X1/N1	X2/N2
	95% Confidence Interval (CI)	LB1, UB1	LB2, UB2
	Difference in Rates	Difference; 95% CI	
	Odds-Ratio	OR; 95% CI	
ICH and Fatal Bleeds	Number of Events	X1	X2
	Number At 28-days	N1	N2
	Event Rates	X1/N1	X2/N2
	95% Confidence Interval (CI)	LB1, UB1	LB2, UB2
	Difference in Rates	Difference; 95% CI	
	Odds-Ratio	OR; 95% CI	
Major Thrombotic Events (TE)*	Number of Events	X1	X2
	Number At 28-days	N1	N2
	Event Rates	X1/N1	X2/N2
	95% Confidence Interval (CI)	LB1, UB1	LB2, UB2
	Difference in Rates	Difference; 95% CI	
	Odds-Ratio	OR; 95% CI	
All-Cause Mortality	Number of Events	X1	X2
	Number At 28-days	N1	N2
	Event Rates	X1/N1	X2/N2
	95% Confidence Interval (CI)	LB1, UB1	LB2, UB2
	Difference in Rates	Difference; 95% CI	
	Odds-Ratio	OR; 95% CI	

*PE, stroke, systemic arterial embolism, and MI

These analyses are in addition to the efficacy and futility analyses that will be presented for the primary efficacy endpoint of organ-support free-days.

13. Models reporting outlines

13.1. Primary analysis of OSFDs

Population	

Endpoint	
Model	
Factors	

The following posterior probabilities will be reported for each subtype being reported:

Quantity of Interest	**Posterior Probability**
P2Y12 is superior to control	
P2Y12 is futile	
P2Y12 is inferior	

The following will be reported:

Odds Ratio Parameter	**Mean**	**SD**	**Median**	**95% Credible Interval**
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time epoch 1				
…				
Time epoch k-1				
Hx cardiovascular disease/diabetes				
Invasive medical ventilation (severe only)				
Oxygen >0 but <=2 (moderate only				
Oxygen > 2 (moderate only)				
Country				
P2Y12				

14. Appendix A: Baseline Characteristics to Report

15. Appendix B: Criteria for Classifying Anticoagulation Dosing