STATISTICAL ANALYSIS PLAN

Protocol Title: Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation versus Standard Care as a Rapid Response to the COVID-19 Pandemic

Short Title: RAPID COVID COAG

ClinicalTrials.gov Identifier: NCT04362085

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Last Revision Date: May 6, 2021
Version: 1.0
Final Sign-off Date:
Archive Date:

1. INTRODUCTION

This statistical analysis plan (SAP) outlines the planned statistical methods for the summary and analysis of data collected within the scope of the Coagulopathy of COVID-19 (RAPID COVID COAG) trial protocol version 1.4 dated October 13, 2020.

The SAP should be read in conjunction with the study protocol and the electronic Case Report Form (eCRF). This version of the SAP has been developed using the final version of the protocol mentioned above and eCRF version 1.3 dated September 17, 2020.

All statistical analyses will be performed using R version 3.6.2 and/or Stata version 15.1, or higher.

2. STUDY OBJECTIVES

2.1 Primary Objective

To determine the effect of therapeutic anticoagulation, with low molecular weight heparin (LMWH) or high dose nomogram of unfractionated heparin (UFH) compared to standard care in hospitalized patients admitted for coronavirus disease 2019 (COVID-19) with an elevated D-dimer on the composite outcome of intensive care unit (ICU) admission, non-invasive mechanical ventilation (positive pressure ventilation), invasive mechanical ventilation or death at 28 days.

Primary Outcome

The primary outcome of this trial is the difference in proportions of subjects with the composite of ICU admission, non-invasive or invasive mechanical ventilation or death between groups within the first 28 days post-randomization.

2.2 Secondary Objectives

To compare the following secondary outcomes between the experimental group receiving therapeutic doses of LMWH or high dose nomogram of UFH and the control group receiving standard care:

2.2.1 Secondary Outcomes

1) Proportion of all-cause death within the first 28 days post-randomization.

2) Proportion of subjects with the composite outcome of ICU admission or all-cause death within the first 28 days post-randomization.

3) Proportion of subjects with the composite outcome of invasive or non-invasive mechanical ventilation or all-cause death within the first 28 days post-randomization.

4) Proportion of subjects with major bleeding, as defined by the ISTH Scientific and Standardization Committee (ISTH-SSC), within the first 28 days post-randomization.

5) Proportion of subjects with red blood cell transfusion ≥ 1 unit within the first 28 days post-randomization.

6) Proportion of subjects who experienced the following: transfusion of platelets, frozen plasma, prothrombin complex concentrate, cryoprecipitate and/or fibrinogen concentrate within the first 28 days post-randomization.

7) Proportion of subjects who had renal replacement therapy defined as continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IHD) within the first 28 days post-randomization.

8) Hospital-free days alive up to day 28 post-randomization.

9) ICU-free days alive up to day 28 post-randomization.

10) Ventilator-free days alive up to day 28 post-randomization.

11) Organ support-free days alive up to day 28 post-randomization.

12) Proportion of subjects who had venous thromboembolism defined as symptomatic or incidental, suspected or confirmed via diagnostic imaging and/or electrocardiogram where appropriate, recognizing that access to diagnostic imaging may be limited in the midst of the COVID-19 pandemic. Confirmatory testing at a later date once exposure risk/personal protective utilization is not an issue is encouraged within the first 28 days post-randomization.

13) Proportion of subjects who had arterial thromboembolism defined as suspected or confirmed via diagnostic imaging and/or electrocardiogram where appropriate, recognizing that access to diagnostic imaging may be limited in the midst of the COVID-19 pandemic. Confirmatory testing at a later date once exposure risk/personal protective utilization is not an issue is encouraged within the first 28 days post-randomization.

14) Proportion of subjects with heparin induced thrombocytopenia within the first 28 days post-randomization.

15) D-dimer, a COVID-19 disease-related biomarker at day 2 +/- 24 hours post-randomization.

In addition, the following pre-specified components of the primary composite outcome will be analyzed (not pre-specified in the protocol):

16) Proportion of subjects with ICU admission.

17) Proportion of subjects with the composite of invasive or non-invasive mechanical ventilation.

18) Proportion of subjects with invasive mechanical ventilation.

3. STUDY DESIGN

3.1 Study Design

This is an open-label, parallel, two-arm randomized controlled trial (RCT) comparing therapeutic anticoagulation with LMWH or high dose nomogram of UFH (experimental group) to standard care (control group) to determine the effect of therapeutic anticoagulation on the composite outcome of ICU admission, mechanical ventilation (non-invasive or invasive) or death in hospitalized patients admitted for COVID-19.

3.2 Study Cohort

The study cohort consists of hospitalized adults admitted for COVID-19 prior to the development of critical illness. Individuals with the following characteristics are excluded: bleeding risk or risk of transfusion generally considered unacceptable, absolute indication for therapeutic anticoagulation, and already met components of the primary outcome.

3.2.1 Intent-to-Treat (ITT) Cohort

The Intent-to-Treat (ITT) cohort will consist of all randomized subjects. The primary analysis will be conducted on the ITT cohort according to the treatment group to which the subjects were randomized. In the rare event that a subject does not have a 28-day assessment and they were event-free and discharged alive prior to day 28, they will be assumed to still be event-free up to day 28.

3.2.2 Per-Protocol (PP) Cohort

The Per-Protocol (PP) cohort will consist of all eligible randomized subjects who received their intervention as allocated during the first 48 hours after randomization. The PP analysis will exclude subjects who did not receive their allocated treatment during the first 48 hours after randomization.

3.3 Treatment Definition

There are two treatment groups in the study. Subjects are randomized (1:1) within the age strata (≤65 and >65) to receive (i) therapeutic doses of LMWH or high dose nomogram of UFH (experimental group) or (ii) standard care with thromboprophylactic doses of LMWH or UFH (control group).

4. STATISTICAL ANALYSIS

Categorical data will be summarized by counts and percentages, and continuous variables by means and standard deviations, or medians and interquartile ranges. All outcome comparisons will include a treatment effect estimate along with a 95% confidence interval. All outcome comparisons will include a p-value calculated using an appropriate test.

4.2 Primary Outcome Analysis

The primary analysis will compare the proportions of subjects experiencing the composite outcome within 28 days after randomization between the 2 treatment arms (therapeutic doses of LMWH or high dose nomogram of UFH versus standard care). Difference in proportions and the 95% confidence interval will be reported. A Chi-squared test of independence will be conducted to obtain the p-value. Since randomization was stratified by age a logistic regression model will also be fit to obtain and test the treatment effect adjusting for age. These two complementary analyses are being performed since an adjusted analysis result in a different interpretation of the treatment effect (conditional) versus the unadjusted (marginal or population averaged). Although the protocol specifies binomial models with an identity link, these were found to not converge by the unblinded statistician while preparing DSMB reports. Therefore, the more stable logistic regression model will be used. Since two interim analyses were conducted, the level of significance at which the Chi-squared test of independence is conducted is 0.048 (two-sided).

4.3 Secondary Outcomes Analysis

For the secondary outcomes outlined in section 2.2.1, a chi-squared test of independence will be used to compare the proportions between groups where appropriate. Odds ratios with 95% confidence intervals, and p values will be reported.

Hospital-free days alive, ICU-free days alive, ventilator-free days and organ support-free days will be respectively analyzed as: the number of days out of hospital alive; the number of days out of ICU alive; the number of ventilator-free days alive (alive and free of invasive mechanical ventilation); and the number of organ support-free days alive (alive and free of invasive mechanical ventilation, non-invasive mechanical ventilation, high flow nasal cannula oxygen and vasopressor therapy) through day 28;

death up to 28 days will be assigned a value of –1. These outcomes will be analyzed using ordinal logistic regression.

The post-treatment D-dimer will be compared by means of linear regression (ANCOVA), adjusted for baseline. Since the D-dimer assay differed across sites, the raw values are not comparable. Therefore, the D-dimer will be analyzed as the logarithm of D-dimer x upper limit of normal (ULN) by taking the natural logarithm of the ratio of the actual d-dimer value divided by the ULN for the assay used.

4.4 Subgroup Analysis

Subgroup analyses for the following characteristics at baseline will be conducted, accompanied by tests of treatment by subgroup interaction, using a logistic regression model.

The subgroups pre-specified in the protocol are as follows:

- Age (≤65 years versus >65 years)
- Sex
- BMI (≤30 kg/m^2 versus >30 kg/m^2)
- Time from COVID-19 symptom onset (≤7 days versus >7 days since symptom onset)
- Diabetes mellitus
- Coronary artery disease
- Hypertension
- Race/ethnicity (Asian, Black or African American, Hispanic or Latino, White)

The following three pre-specified subgroups will also be analyzed (not pre-specified in the protocol):

- D-dimer levels at baseline (<2x upper limit of normal versus ≥2x upper limit of normal)
- Use of systemic corticosteroids at baseline
- Regions (North America, Brazil, Middle East, Ireland)

4.5 Sensitivity analysis

Sensitivity analyses will be performed (1) excluding those who did not have a follow-up until day 28, death, or other primary composite outcome component; (2) excluding those who did not satisfy all eligibility criteria; and (3) excluding both types of participants. Sensitivity analyses will be repeated in the PP subset, if different from the ITT population. If possible, the binomial model with identity link will be performed on the primary outcome as an additional sensitivity analysis.

To address changes in co-interventions over time due to emerging evidence from COVID-19 clinical trials, we will conduct a sensitivity analysis of the primary outcome using a logistic regression model with restricted cubic splines to model time by treatment interaction.

4.6 Missing data

The primary outcome will not have any missing data as per the definition of the ITT cohort above.

A multiple imputation approach may be applied to age as baseline characteristic for the adjusted analysis of the primary outcome in case of data missingness.

The secondary outcomes are also expected to be complete, or nearly complete since they are either components of the primary outcome or are measured in-hospital. Since secondary analyses are explorative, secondary outcomes will be analyzed as-is.

However, if a primary or secondary outcome is missing in more than 5% of randomized patients, a complete case analysis, an inverse probability weighted analysis and multiple imputation on outcome will also be conducted in addition to the primary strategies (see Sections 4.2 and 4.3).