Statistical Analysis Plan for Preliminary Report of Severe Subtype of mpRCT of Therapeutic Anticoagulation in Covid-19

Version

Version 1.0, initialized January 5, 2021, finalized January 12, 2021

Background

This document is an ancillary document to the statistical analysis protocol (Version 1.0, dated January 5, 2020) for the mpRCT of therapeutic anticoagulation in Covid-19. It outlines the planned analyses required for the urgent preliminary reporting of trial results in the severe Covid-19 subtype.

Enrolment in the mpRCT severe state was halted on December 19, 2020 following a recommendation from the data safety and monitoring boards of the three platforms based on a statistical trigger reached during interim analysis. The investigators aim to prepare a preliminary report that details key findings of the trial in the severe state for broad dissemination followed by a subsequent comprehensive report.

The statistical analysis protocol for the mpRCT stipulates that primary endpoints and key secondary endpoints (major thrombotic events, major bleeding) must be included in preliminary reports. Limited subgroup analyses may also be reported depending on the available data. This supplementary statistical analysis plan lists the planned analyses for this preliminary report; all of these analyses are listed and described in detail in the mpRCT SAP.

Unblinded Population

mpRCT Covid-19 severe subtype will be reported in this sub-SAP report. The unblinded population defined in the SAP is the severe subtype.

Data

Data used for this preliminary report will be available for the set of patients analyzed by the unblinded SAC for interim analysis of the primary mpRCT statistical model on January 4, 2021. This analysis will only include patients randomized through the stop of randomization to the TAC arm in the severe state (on December 19, 2020) for whom the primary endpoint was available on January 4, 2021. Information on baseline characteristics, secondary endpoints, and subgroup classification for this set of patients becoming available after January 4, 2021 will be included in the preliminary report where possible.

Planned Analyses

Primary

#	Status	Population	Endpoint	Notes
14.1	Primary	mpRCT confirmed	OSFDs	Primary ordinal model
14.2	Primary	mpRCT confirmed	In-hospital mortality	Primary dichotomous model

Sensitivity analyses of the primary models

#	Status	Population	Endpoint	Notes
14.3	Sensitivity	mpRCT confirmed	Dichotomized OSFD	Primary dichotomous model for each dichotomization of OSFDs as a robustness check.
14.4	Sensitivity	mpRCT confirmed unblinded	OSFDs	Primary ordinal model
14.5	Sensitivity	mpRCT confirmed unblinded	In-hospital mortality	Primary dichotomous model
14.6	Sensitivity	mpRCT confirmed and suspected unblinded	OSFDs	Include REMAP-CAP suspected but not proven COVID-19 patients
14.7	Sensitivity	mpRCT confirmed and suspected unblinded	In-hospital mortality	Include REMAP-CAP suspected but not proven COVID-19 patients
14.8	Sensitivity	mpRCT confirmed unblinded	OSFDs	Remove site and time effects
14.9	Sensitivity	mpRCT confirmed unblinded	In-hospital mortality	Remove site and time effects
14.10	Sensitivity	mpRCT confirmed unblinded	OSFDs	Excluding patients who received antiplatelet agents at baseline or who are randomized in the antiplatelet domain in REMAP-CAP
14.11	Sensitivity	mpRCT confirmed unblinded	In-hospital mortality	Excluding patients who received antiplatelet agents at baseline or who are randomized in the antiplatelet domain in REMAP-CAP
14.12	Exploratory sensitivity analysis: Severe State only	mpRCT confirmed unblinded	OSFDs	Specifies prior for TAC for enthusiasm [N(0.56,0.44)] and prior for skepticism [N(0, 0.44)]

Key secondary and safety endpoints

#	Status	Population	Endpoint	Notes
14.14	Secondary	mpRCT confirmed unblinded	Major thrombotic events or death	Primary dichotomous model
14.30	Safety	mpRCT confirmed unblinded	Major bleeding	Primary dichotomous model
14.31	Safety sensitivity analysis	mpRCT confirmed unblinded	Major bleeding	Primary dichotomous model Excluding patients who received antiplatelet agents at baseline or who are randomized into the antiplatelet domain

- Will report type of major thrombotic event descriptively

Per protocol analyses

#	Status	Population	Endpoint	Notes
14.38	Sensitivity	mpRCT per protocol	OSFDs	Primary ordinal model
14.39	Sensitivity	mpRCT per protocol	In-hospital mortality	Primary dichotomous model
14.40	Sensitivity	mpRCT per protocol	Major thrombotic events or death	Primary dichotomous model

Subgroup analyses

Reporting of these subgroup analyses will be contingent on the completeness of data on the subgroup variable. This decision will be at the discretion of the investigators and contingent on the completeness of data on the subgroup variable.

Subgroup	**Specification of covariate**	**Endpoint – Model #**			
		OSFDs (efficacy)	Hospital mortality (efficacy)	Major thrombotic event or death (efficacy)	Major bleeding (safety)
Age	Categorical (<50 years, 50-70 years, and >70 years)	15.1.1	15.1.2	15.1.3	15.1.4
Sex	Dichotomous	15.2.1	15.2.2	15.2.3	15.2.4
Invasive mechanical ventilation at baseline*	Dichotomous	15.3.1	15.3.2	15.3.3	15.3.4
Antiplatelet agent use at baseline in hospital at time of randomization	Dichotomous	15.4.1	15.4.2	15.4.3	15.4.4
Usual care practice: low vs intermediate (site classification strategy)	Dichotomous	16.15.1	16.15.2	16.15.3	16.15.4
Usual care practice: low vs intermediate (day 1 patient classification strategy)	Dichotomous	16.16.1	16.16.2	16.16.3	16.16.4

Required Variables for Severe State Patients

The following list of required variables is derived from the endpoints and subgroup variables listed above and the covariates listed in the Statistical Analysis Plan. Endpoints are defined in the Statistical Analysis Plan. Further work is required to define how these variables are defined in each platform. The following is the list of data needed for completing this sub-SAP.

The following data would be provided to Berry Consultants blinded Analysis Team for all analyses except 14.1, 14.2, and 14.3, which will be conducted by the Statistical Analysis Committee (SAC).

The following outcomes would be provided for every patient randomized to either VTP or TAC in the severe state that has not removed consent for data.

Table 1. Patient-level variables required for analysis

Variable	**Format**	**Variable Name by Platform**		
		REMAP-CAP	ACTIV-4a	ATTACC
Age	Numeric			
Sex	M/F			
Site	Label/number			
Date of randomization	Any date format			

Randomization arm (TAC vs. VTP)	Any code for TAC/VTP			
Laboratory-confirmed Covid-19 status (proven vs. suspected)	1 = proven; 0 = suspected			
Organ support-free days to day 21	Ordinal			
Major Pulmonary Embolism	Y/N			
If Major Pulmonary Embolism, date of event	Date format			
Major ischemic cerebrovascular event	Y/N			
If Major ischemic cerebrovascular, date of event	Date format			
Major myocardial infarction event	Y/N			
If Major myocardial infarction, date of event	Date format			
Major systemic arterial thromboembolism event	Y/N			
If Major systemic arterial thromboembolism, date of event	Date format			
Major bleeding event	Y/N			
If Major Bleed, date of bleeding event	Date format			
Randomized in REMAP-CAP antiplatelet domain?	Y/N			
Antiplatelet agent administration in hospital prior to or at the time of randomization	Y/N			
Classification of anticoagulant dosing administered on each of first two full study days following randomization for each patient randomized to VTP arm (low vs. intermediate) (See statistical analysis Table 3 footnotes for definitions of classification)	NA/low/Inter			
Invasive mechanical ventilation at time of randomization (yes vs. no)	Y/N			
Race	Hispanic or latino/Caucasian/black/Asian/First Nations			

Heart failure	Yes/No	n/a		
Severe cardiovascular disease	Yes/No		n/a	n/a
Diabetes mellitus (Type 1 or Type 2)	Yes/No			
Chronic kidney disease or end-stage renal disease	Yes/No			
Chronic respiratory disease	Yes/No			
Current tobacco use	Yes/No			
Immunosuppressive treatment	Yes/No			
Liver disease or cirrhosis	Yes/No			
Acute respiratory support at time of randomization	None/supplemental O2/high flow nasal O2/non-invasive ventilation/invasive ventilation/ECMO			
PaO2/FiO2 in ventilated patients only	Numeric		n/a	n/a
D-dimer	Numeric (fold increase relative to upper limit of normal)			
Fibrinogen	Numeric			
INR	Numeric			
Neutrophils ($x10^9$/L)	Numeric			
Lymphocytes ($x10^9$/L)	Numeric			
Platelets ($x10^9$/L)	Numeric			
Creatinine (mg/dL)	Numeric			
Troponin (units?)	Numeric			
Pre-hospital use of anti-platelet agent	Yes/No	n/a		
Dexamethasone exposure at baseline	Yes/No			
Remdesivir exposure at baseline	Yes/No			
Anti-platelet agent (aspirin, clopidogrel, ticagrelor, dipyridamole)	Yes/No			

Table 2. Site-level variables required for analysis

Variable	**Format**	**Variable Name by Platform**		
		REMAP-CAP	ACTIV-4a	ATTACC
Country	Numeric			
Standard VTP strategy	Intermediate/low			