Statistical Analysis Plan for Report of Moderate Subtypes of mpRCT of Therapeutic Anticoagulation in Covid-19

Version

Version 1, initialized January 18, 2021, finalized February 16, 2021

Background

This document is an ancillary document to the statistical analysis protocol (the 'core SAP,' Version 1.0, dated January 5, 2021 – amended February 16, 2021) for the multiplatform randomized controlled trial (mpRCT) of therapeutic anticoagulation in Covid-19. It outlines the planned analyses required for reporting of trial results in moderate patients, including by subtype. (A SAP for the preliminary analysis of the severe subtype was previously approved on January 12, 2021, after enrolment in this state was stopped on December 19, 2020, upon this subtype reaching a pre-specified statistical trigger.)

On January 21, 2021, the DSMBs informed the investigators that both reportable moderate subtypes (low and high D-dimer) had reached pre-specified stopping triggers. On January 22, 2021, enrollment of moderate subtypes into the therapeutic heparin randomization in all three mpRCT platforms was ceased. The current SAP is an ancillary document to the core SAP which details relevant analyses intended for the reporting of treatment effects in moderate patients, including by subtype. These analyses are listed and described in detail in the core mpRCT statistical analysis protocol, now included with a summary of amendments.

Moderate Reporting Populations

Participants in the moderate state are analyzed as an overall illness stratum, as well as stratified into subtypes which as pre-specified in the trial protocol. Specifically, the investigators had hypothesized that baseline D-dimer level may identify individuals who may have differential response to therapeutic heparin, and as such baseline D-dimer was used to separate the moderate state into three subtypes:

(1) moderate patients with baseline D-dimer <2 fold relative to local upper limit of normal/decision support limit ["low D-dimer"],

(2) moderate patients with baseline D-dimer ≥2 fold relative to local upper limit of normal/decision support limit ["high D-dimer"], and

(3) moderate patients with unknown baseline D-dimer ["unknown D-dimer"].

(Adaptive statistical stopping triggers were only specified for subtypes (1) and (2).)

Data

The reporting population defined in this SAP are all patients in the moderate subtypes. All patients will have completed 30 day as of February 22, 2021. Extended 90 day follow-up is available for a subset of participants.

Planned Analyses

All analyses below are performed and reported separately in the pre-specified D-dimer-categorized moderate subtypes and in the overall moderate population. As specified in the core SAP (with ammendments), the main models are performed on the modified intention to treat population ("mpRCT confirmed") comprised of patients who were confirmed to be positive for SARS-CoV-2. Sensitivity analyses are performed on the full intention to treat population among those with both confirmed and suspected (but not proven) infection. Per-protocol analyses are included. Secondary endpoints will Be analyzed, and include analyses deconstructing the primary endpoint components of mortality and organ support (including detailed type of organ support). Data on baseline characteristics, treatment patterns, and clinical course will be examined and presented both by D-dimer subtype and in moderate patients overall. The investigators will base reporting decisions on assuring adequate data completeness at the time of reporting.

Main analyses

#	Status	Population	Endpoint	Notes
14.1.1	Main	mpRCT confirmed; all moderate	OSFDs	Primary ordinal model; mpRCT primary endpoint
14.2.1	Main	mpRCT confirmed; all moderate	In-hospital mortality	Main dichotomous model; mpRCT secondary endpoint
14.1.2	Main	mpRCT confirmed; low D-dimer	OSFDs	Primary ordinal model; mpRCT primary endpoint
14.2.2	Main	mpRCT confirmed; low D-dimer	In-hospital mortality	Main dichotomous model; mpRCT secondary endpoint
14.1.3	Main	mpRCT confirmed; high D-dimer	OSFDs	Primary ordinal model; mpRCT primary endpoint
14.2.3	Main	mpRCT confirmed; high D-dimer	In-hospital mortality	Main dichotomous model; mpRCT secondary endpoint
14.1.4	Main	mpRCT confirmed; unknown D-dimer	OSFDs	Primary ordinal model; mpRCT primary endpoint
14.2.4	Main	mpRCT confirmed; unknown D-dimer	In-hospital mortality	Main dichotomous model; mpRCT secondary endpoint

Sensitivity analyses of the main models

All moderate

Tests for heterogeneity of treatment effect across moderate subtypes will be reported.

#	Status	Population	Endpoint	Notes
14.3.1	Sensitivity	mpRCT confirmed; all moderate	Dichotomized OSFD	Main dichotomous model for each dichotomization of OSFDs as a robustness check.
14.4.1	Sensitivity	mpRCT confirmed; all moderate	OSFDs	Main ordinal model
14.5.1	Sensitivity	mpRCT confirmed; all moderate	In-hospital mortality	Main dichotomous model
14.6.1	Sensitivity	mpRCT confirmed and suspected; all moderate	OSFDs	Include REMAP-CAP suspected but not proven COVID-19 patients
14.7.1	Sensitivity	mpRCT confirmed and suspected; all moderate	In-hospital mortality	Include REMAP-CAP suspected but not proven COVID-19 patients

14.8.1	Sensitivity	mpRCT confirmed; all moderate	OSFDs	Remove site and time effects
14.9.1	Sensitivity	mpRCT confirmed; all moderate	In-hospital mortality	Remove site and time effects
14.10.1	Sensitivity	mpRCT confirmed; all moderate	OSFDs	Excluding patients who received antiplatelet agents at baseline or who are randomized in the antiplatelet domain in REMAP-CAP (including those in the REMAP-CAP antiplatelet domain assigned to no antiplatelet)
14.11.1	Sensitivity	mpRCT confirmed; all moderate	In-hospital mortality	Dichotomous model excluding patients who received antiplatelet agents at baseline or who are randomized into the antiplatelet domain in REMAP-CAP (including those in the REMAP-CAP antiplatelet domain assigned to no antiplatelet)
14.59.1	Sensitivity	mpRCT confirmed; all moderate	3 component OSFDs	Testing the proportional odds assumption using a three-level OSFD (no organ support, organ support, death)
14.60.1	Sensitivity	mpRCT confirmed; all moderate	OSFDs	Remove moderate patients enrolled after January 7th, 2021

Key secondary efficacy and safety endpoints

All moderate

#	Status	Population	Endpoint	Notes
14.14.1	Secondary	mpRCT confirmed; all moderate	Major thrombotic events or death	Dichotomous model
14.15.1	Secondary	mpRCT confirmed; all moderate	All thrombotic events or death	Dichotomous model (major thrombotic events composite, adding DVT)
14.23.1	Secondary	mpRCT confirmed; all moderate	Hospital length of stay	Time to event analysis; truncated at 28 days
14.56.1	Secondary	mpRCT confirmed; low D-dime	Mortality 28 days	Time-to-event endpoint through 28 days
14.18.1	Secondary	mpRCT confirmed; low D-dime	Interim analysis of mortality 90 days	Time-to-event endpoint through 90 days (censoring patients with incomplete follow-up at the time of database lock; follow-up continues and full reporting to follow)
14.57.1	Secondary	mpRCT confirmed; all moderate	Intubation, death	Ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 28 following randomization: no invasive mechanical ventilation, invasive mechanical ventilation, or death by 28 days
14.58.1	Secondary	mpRCT confirmed; all moderate	Required OS	Dichotomous model based on proportion who progressed to require organ support through 28 days

14.20.1	Secondary	mpRCT confirmed; all moderate	Ventilator free days	Ordinal model days alive off a ventilator
14.21.1	Safety	mpRCT confirmed; all moderate	Major bleeding	Dichotomous model
14.19.1	Safety sensitivity analysis	mpRCT confirmed; all moderate	Major bleeding	Dichotomous model excluding patients who received antiplatelet agents at baseline or who are randomized into the antiplatelet domain in REMAP-CAP

Low D-dimer

#	Status	Population	Endpoint	Notes
14.14.2	Secondary	mpRCT confirmed; low D-dimer	Major thrombotic events or death	Dichotomous model
14.15.2	Secondary	mpRCT confirmed; low D-dimer	All thrombotic events or death	Dichotomous model (major thrombotic events composite, adding DVT)
14.23.2	Secondary	mpRCT confirmed; low D-dimer	Hospital length of stay	Time to event analysis; truncated at 28 days
14.57.2	Secondary	mpRCT confirmed; low D-dimer	Intubation, death	Ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 28 following randomization: no invasive mechanical ventilation, invasive mechanical ventilation, or death
14.58.2	Secondary	mpRCT confirmed; low D-dimer	Required OS	Dichotomous model based on proportion who progressed to require organ support through 28 days
14.20.2	Secondary	mpRCT confirmed; low D-dimer	Ventilator free days	Ordinal, days alive off a ventilator through 28 days
14.30.2	Safety	mpRCT confirmed; low D-dimer	Major bleeding	Dichotomous model

High D-dimer

#	Status	Population	Endpoint	Notes
14.14.3	Secondary	mpRCT confirmed; high D-dimer	All thrombotic events or death	Dichotomous model
14.15.3	Secondary	mpRCT confirmed; high D-dimer	All thrombotic events or death	Dichotomous model (major thrombotic events composite, adding DVT)
14.23.3	Secondary	mpRCT confirmed; low D-dimer	Hospital length of stay	Time to event analysis; truncated at 28 days
14.57.3	Secondary	mpRCT confirmed; low D-dimer	Intubation, death	Ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 28 following randomization: no invasive mechanical ventilation, invasive mechanical ventilation, or death
14.58.3	Secondary	mpRCT confirmed; high D-dimer	Required OS	Dichotomous model based on proportion who progressed to

				require organ support through 28 days
14.20.3	Secondary	mpRCT confirmed; low D-dimer	Ventilator free days	Days alive off a ventilator through 28 days
14.21.3	Safety	mpRCT confirmed; high D-dimer	Major bleeding	Dichotomous model

Unknown D-dimer

#	Status	Population	Endpoint	Notes
14.14.4	Secondary	mpRCT confirmed; unknown D-dimer	All thrombotic events or death	Dichotomous model
14.15.4	Secondary	mpRCT confirmed; unknown D-dimer	All thrombotic events or death	Dichotomous model (major thrombotic events composite, adding DVT)
14.23.4	Secondary	mpRCT confirmed; unknown D-dimer	Hospital length of stay	Time to event analysis; truncated at 28 days
14.57.4	Secondary	mpRCT confirmed; unknown D-dimer	Intubation, death	Ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 28 following randomization: no invasive mechanical ventilation, invasive mechanical ventilation, or death
14.58.4	Secondary	mpRCT confirmed; unknown D-dimer	Required OS	Dichotomous model based on proportion who progressed to require organ support through 28 days
14.20.4	Secondary	mpRCT confirmed; unknown D-dimer	Ventilator free days	Days alive off a ventilator through 28 days
14.21.4	Safety	mpRCT confirmed; unknown D-dimer	Major bleeding	Dichotomous model

- Secondary events with inadequate frequency to model will be examined as count data.
- Count for individual thrombotic events through 28 days will be reported by treatment arm.
- The occurrence of heparin-induced thrombocytopenia (HIT) will be examined by treatment arm, both overall in moderate and by subtype given low anticipated incidence rate.
- Count data will be examined for fatal bleeding and intracranial bleeding by treatment arm, both overall in moderate and by subtype given low anticipated incidence rate.

Per protocol analyses

TAC patients receiving a subtherapeutic or therapeutic heparin dose equivalent (a dose greater than intermediate – see SAP appendix dosing guide) will be included in the per-protocol analysis; VTP patients receiving a dose of low or intermediate intensity will be included in the per protocol analysis. Day 1 (on-treatment doses) are used for this analysis (note this is different from subgroup analyses below, which use pre-randomization dose equivalents).

All moderate

#	Status	Population	Endpoint	Notes
14.1.1	Secondary	mpRCT confirmed; all moderate	OSFDs	Primary ordinal model; mpRCT primary endpoint
14.2.1	Secondary	mpRCT confirmed; all moderate	In-hospital mortality	Main dichotomous model; mpRCT secondary endpoint
14.14.1	Secondary	mpRCT confirmed; all moderate	Major thrombotic events or death	Dichotomous model

14.15.1	Secondary	mpRCT confirmed; all moderate	All thrombotic events or death	Dichotomous model (major thrombotic events composite, adding DVT)
14.30.1	Secondary	mpRCT confirmed; all moderate	Major bleeding	Dichotomous model

Subgroup analyses

Reporting of 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. All subgroups are reported by reportable in overall moderate patients unless otherwise noted.

All moderate

Subgroup	**Specification of covariate**	OSFDs
Age	Categorical (<50 years, 50-70 years, and >70 years)	15.1.1
Sex	Dichotomous	15.2.1
Baseline respiratory support	Categorical (none, nasal cannula, facemask, NFNO/NIV/invasive MV)	17.1.1
Antiplatelet agent use at baseline in hospital at time of randomization	Dichotomous	15.4.1
Usual care VTP dose: low vs intermediate (patient classification strategy)*	Dichotomous	16.15.1
Usual care VTP practice: low vs intermediate (site classification strategy)	Dichotomous	16.16.1
Region	Categorical (North America, South America, Europe/UK, other)	17.1.1

*Based on pre-randomization dose equivalent (e.g., Day -1, or the pre-treatment dose equivalent) [note this is different from PPA above, which uses post—randomization, on-treatment dose equivalents).

Required Variables for Moderate 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 Protocol. Endpoints are defined in the core Statistical Analysis Protocol. 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 moderate state that has not removed consent for data.

Table 1. Patient-level variables required for analysis (categorical variables separated by "/")

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			
Moderate baseline D-dimer "low" or "high" subtype	D-dimer < 2x ULN/ D-dimer > or = 2X ULN/ Unknown			
Laboratory-confirmed Covid-19 status (proven vs. suspected)	Proven/suspected			
Organ support-free days to day 21	Ordinal			
Date of hospital discharge	Any date format			
In-hospital mortality	Dichotomous			
Mortality through 28 days	Dichotomous			
Mortality through 90 days	Dichotomous			
Intubation and death through 28 days	Ordinal (No intubation and survived to day 28 [best outcome]; intubated, survived to day 28; dead by day 28 [worst outcome])			
Ventilator free days (days alive off a ventilator, with any in hospital death as 0) through 28 days	Ordinal			
Required OS through 28 days	Dichotomous			
Major bleeding	Y/N			
If Major Bleeding, date of event	Date format			
Fatal bleeding	Dichotomous model			
Intracranial bleeding	Dichotomous			
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			
Heparin-induced thrombocytopenia (HIT)	Y/N			
If HIT, date of HIT	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 'initial anticoagulant dose equivalent' (post-randomization/on-treatment) as assessed by the platforms for all participants	Low/Intermediate/ Subtherapeutic/Therapeutic/ Unknown			
Classification of 'pre-randomization anticoagulant dose equivalent' (pre-randomization/pre-treatment) as assessed by the platforms for all participants	Low/Intermediate/ Subtherapeutic/Therapeutic/ Unknown			
Initial baseline anticoagulant administered if randomized to TAC	Enoxaparin/Dateparin/Tinzaparin/ Intravenous unfractionated heparin/ Other			
Race	Caucasian/Black/Asian/First Nations or aboriginal/Other			
Hispanic or Latino ethnicity	Yes/no/unknown			
Body mass index (BMI)	Continuous			
Heart failure	Yes/No	n/a		
Coronary artery disease (including prior myocardial infarction)	Yes/no	n/a		
Hypertension	Yes/no	n/a		
Peripheral arterial disease	Yes/no	n/a		
Cerebrovascular disease (stroke or TIA)	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			
Immunosuppressive disease	Yes/No			
Liver disease or cirrhosis	Yes/No			
Respiratory support at time of randomization	None/Nasal cannula/ Face mask/High flow nasal O2/ Non-invasive ventilation or invasive ventilation			
Region	North American/South America/ Europe-UK/Other			
Invasive mechanical ventilation at time of randomization (yes vs. no)	Y/N			
Baseline D-dimer as fold increase relative to local site upper limit of normal	Numeric			
Baseline D-dimer (absolute level)	Numeric			
Baseline INR	Numeric			
Baseline Neutrophils ($x10^9$/L)	Numeric			
Baseline Lymphocytes ($x10^9$/L)	Numeric			
Baseline Platelets ($x10^9$/L)	Numeric			
Baseline calculated creatinine clearance (ml/minL)	Numeric			
Bilirubin, mg/dL	Numeric			
Baseline use of anti-platelet agent (aspirin, clopidogrel, ticagrelor, prasugrel, dipyridamole)	Yes/No			
Randomized in REMAP-CAP antiplatelet domain	Yes/No		n/a	n/a
Remdesivir exposure at baseline	Yes/No			
Tocilizumab exposure at baseline	Yes/No			
Corticosteroid exposure at baseline	Yes/No			

Table 2. Site-level variables required for analysis

Frequency histograms will be examined to determine to what extent a site-level stratification of VTP dose practice is feasible in Moderate patients. Relevant cut-points will be chosen on reviewing the data if feasible.

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