Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: The ATTACC, ACTIV-4a, and REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2105911

Appendix 1

Multi-Platform Randomized Controlled Trial (mpRCT) Protocols and Statistical Analysis Plan

This appendix contains the following items:

1. The original protocol documents, the final protocol documents, and summary of changes

2. The original / final statistical analysis plans for the overall multi-platform RCT and both moderate and severe state specific analyses.

Relevant protocol documents included in this supplement are:

Protocol 1: Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP)

REMAP-CAP Core Protocol

Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP): CORE PROTOCOL

REMAP-CAP Core Protocol Version 3 dated 10 July 2019

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1. ABBREVIATIONS AND GLOSSARY

1.1. Abbreviations

ANZ	Australia and New Zealand
APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	Acute Respiratory Distress Syndrome
BHM	Bayesian Hierarchical Model
CAP	Community-Acquired Pneumonia
CIHR	Canadian Institutes of Health Research
CIHR-SPOR	Canadian Institutes of Health Research Strategy for Patient-Oriented Research
CRF	Case Report Form
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
eCIS	Electronic Clinical Information System
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EU	European
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
HDU	High Dependency Unit
HRC	Health Research Council
HRQoL	Health Related Quality of Life
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IEIG	International Embedding Interest Group
IIG	International Interest Group
ILTOHEIG	International Long-term Outcomes and Health Economics Interest Group
IPWG	International Pandemic Working Group
ISIG	International Statistics Interest Group

ITSC	International Trial Steering Committee
ITT	Intention-To-Treat
LOS	Length of Stay
NHMRC	National Health and Medical Research Council
OFFD	Organ Failure Free Days
P:F Ratio	Ratio of Partial Pressure of Oxygen in Arterial Blood and Fraction of Inspired Oxygen Concentration
PEEP	Positive End-Expiratory Pressure
PREPARE	Platform for European Preparedness Against (Re-)emerging Epidemics
RAR	Response Adaptive Randomization
REMAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RCC	Regional Coordinating Center
RCT	Randomized Controlled Trial
RMC	Regional Management Committee
RSA	Region-Specific Appendix
SAC	Statistical Analysis Committee
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SOPs	Standard Operating Procedures
VFD	Ventilator Free Days
WG	Working Group
WHODAS	World Health Organization Disability Assessment Schedule

1.2. Glossary

Borrowing is the process within the statistical model, whereby, when the treatment effect is similar in different strata, evidence relating to the effectiveness of an intervention in one stratum contributes to the estimation of the posterior probability in another stratum.

Core Protocol is a module of the protocol that contains all information that is generic to the Randomized, Embedded, Multifactorial, Adaptive Platform trial (REMAP), irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested.

Domain-Specific Appendix is an appendix to the Core Protocol. These appendices are modules of the protocol that contain all information about the interventions, which are nested within a domain that will be a subject of this REMAP. Each domain will have its own Domain-Specific Appendix (DSA). The information contained in each DSA includes criteria that determine eligibility of patients to that domain, the features of the interventions and how they are delivered, and any additional endpoints and data collection that are not covered in the Core Protocol.

Domain-Specific Working Group is a sub-committee involved in trial management, the members of which take responsibility for the development and management of a current or proposed new domain.

Domain consists of a specific set of competing alternative interventions within a common clinical mode, which, for the purposes of the platform, are mutually exclusive and exhaustive. Where there is only a single intervention option within a domain the comparator is all other usual care in the absence of the intervention. Where multiple interventions exist within a domain, comparators are the range of interventions either with or without a no intervention option, depending on whether an intervention, within the domain, is provided to all patients as part of standard care. Within the REMAP every patient will be assigned to receive one and only one of the available interventions within every domain for which they are eligible.

International Trial Steering Committee is the committee that takes overall responsibility for the management and conduct of the REMAP with oversight over all regions and all domains.

Intervention is a treatment option that is subject to variation in clinical practice (comparative effectiveness intervention) or has been proposed for introduction into clinical practice (experimental intervention) and also is being subjected to experimental manipulation within the design of a

REMAP. For the purposes of the REMAP an intervention can include an option in which no treatment is provided.

Monte-Carlo Simulations are computational algorithms that employ repeated random sampling to obtain a probability distribution. They are used in the design of the study to anticipate trial performance under a variety of potential states of 'truth' (e.g., to test the way in which a particular trial design feature will help or hinder the ability to determine whether a 'true' treatment effect will be discovered by the trial). Monte Carlo methods are also used to provide updated posterior probability distributions for the ongoing analyses of the trial.

Pandemic Appendix describes an appendix to the Core Protocol that includes the modifications to the Core Protocol that will occur during a pandemic of respiratory infection that results in severe CAP.

Platform Conclusion describes when a Statistical Trigger has been reached and, following evaluation by the Data Safety and Monitoring Board (DSMB) +/- the International Trial Steering Committee (ITSC), there is a *decision* to conclude that superiority, inferiority or equivalence has been demonstrated. Under all circumstances a Platform Conclusion leads to implementation of the result within the REMAP and under almost all circumstances a Platform Conclusion leads, immediately, to Public Disclosure of the result by presentation and publication. Where the Statistical Trigger is for superiority or inferiority, so long as the DSMB is satisfied that the Statistical Trigger has truly been met a Platform Conclusion will be automatic in almost all circumstances. Where the Statistical Trigger is for equivalence the DSMB, in conjunction with the ITSC, may decide to not reach a Platform Conclusion at that time but, rather, to continue recruitment, for example, to allow a conclusion to be reached regarding clinically important secondary endpoints. There are situations in which the need to evaluate interactions may also result in a Statistical Trigger not leading, immediately, to a Platform Conclusion, although if superiority or inferiority has been demonstrated all patients in the REMAP will receive the superior intervention or no longer be exposed to inferior intervention(s), respectively.

Platform Trial is a type of clinical trial that studies multiple interventions simultaneously. Common features of a platform trial include frequent adaptive analyses using Bayesian statistical analysis, Response Adaptive Randomization (RAR), evaluation of treatment effect in pre-specified strata, and evaluation of multiple research questions simultaneously that can be perpetual with substitution of answered research questions with new questions as the trial evolves.

Public Disclosure is the communication of a Platform Conclusion to the broad medical community by means of presentation, publication or both.

Regimen consists of the unique combination of interventions, within multiple domains, (including no treatment options) that a patient receives within a REMAP.

Region-Specific Appendix is an appendix to the Core Protocol. These appendices are modules of the protocol that contain all information about the trial specific to the conduct of the trial in that region. Each region will have its own Regional-Specific Appendix (RSA). A region is defined as a country or collection of countries with study sites for which a Regional Management Committee (RMC) is responsible.

Regional Management Committee is a sub-committee involved in trial management. The members of the RMC take responsibility for the management of trial activities in a specified region. The role, responsibilities, and composition of each RMC are specified in each region's RSA.

REMAP is a variant of a platform trial that targets questions that are relevant to routine care and relies heavily on embedding the trial in clinical practice. Like other platform trials, the focus is on a particular disease or condition, rather than a particular intervention, and it is capable of running perpetually, adding new questions sequentially.

Response Adaptive Randomization is a dynamic process in which the analysis of accrued trial data is used to determine the proportion of future patients who are randomized to each intervention within a domain.

State a state is a set of mutually exclusive and exhaustive categories, defined by characteristics of a patient within the REMAP, that are capable of changing over time for a single patient at different time-points during the patient's participation in the REMAP (i.e. they can be dynamic). States are used to define eligibility for domains and this can include defining eligibility that occurs after the time of enrollment. State is used as an additive covariate within the Bayesian statistical model.

Statistical Analysis Committee takes responsibility for the conduct of the preplanned adaptations in the trial. This task generally consists of running predetermined statistical models at each adaptive analysis and providing this output to the DSMB. It is not a trial sub-committee. Rather, it will usually comprise individuals who are employed by the organization that undertakes statistical analysis, and from a trial governance perspective is under the supervision of the DSMB.

Statistical Model is a computational algorithm that is used to estimate the posterior probability of the superiority, inferiority or equivalence of the regimens and interventions that are being evaluated within the REMAP.

Statistical Trigger within the REMAP two or more interventions within a domain are evaluated and statistical models are used to determine if one or more interventions are superior, inferior or equivalent. A Statistical Trigger occurs when the statistical models used to analyze the REMAP indicate that the *threshold* for declaring superiority, inferiority, or equivalence for one or more interventions within a domain has been crossed. A Statistical Trigger applies to a stratum but may be reached in more than one stratum for the same intervention at the same adaptive analysis.

Strata comprise a set of mutually exclusive and exhaustive categories (stratum), defined by baseline characteristics of a patient within the REMAP, in which the relative effects of interventions may be differential. These possibly differential effects of interventions are reflected in the statistical model, the randomization probabilities, and the Platform Conclusions. The criteria that define a stratum must be present at or before the time of enrollment.

Unit-of-analysis is the group of patients who are analyzed together within the model for a particular domain. The unit-of-analysis can be all patients who have received an allocation status in that domain or a sub-group of patients who received an allocation status determined by their status with respect to one or more strata. Within a domain, the RAR is applied to the unit-of-analysis.

2. INTRODUCTION

2.1. Synopsis

Background: Community-acquired pneumonia (CAP) that is of sufficient severity to require admission to an Intensive Care Unit (ICU) is associated with substantial mortality. All patients with severe pneumonia who are treated in an ICU will receive therapy that consists of a combination of multiple different treatments. For many of these treatments, different options are available currently. For example, several antibiotics exist that are active against the microorganisms that cause pneumonia commonly but it is not known if one antibiotic strategy is best or whether all suitable antibiotic strategies have similar levels of effectiveness. Of all the treatments that clinicians use for patients with severe CAP, only a small minority have been tested in randomized controlled trials to determine their comparative effectiveness. As a consequence, the standard treatments that are administered vary between and within countries. Current conventional clinical trials methods to assess the efficacy of treatments for pneumonia generally compare two treatment options (either two options for the same treatment modality, where both are in common use; or a new treatment against no treatment or placebo where the effectiveness of the new treatment is not known). Using this approach, in a series of separate and sequential trials, it will take an inordinate length of time to study all the treatment options. Additionally, with conventional trial designs it is not possible to evaluate interactions between treatment options.

Aim: The primary objective of this REMAP is, for patients with severe CAP who are admitted to an ICU, to identify the effect of a range of interventions to improve outcome as defined by all-cause mortality at 90 days.

Methods: The study will enroll adult patients with severe CAP who are admitted to ICUs using a design known as a REMAP, which is a type of platform trial. Within this REMAP, eligible participants will be randomized to receive one intervention in each of one or more domains (a domain is a category of treatment that contains one or more options, termed interventions, with each intervention option being mutually exclusive). The primary outcome is all-cause mortality at 90 days. There will also be both general and domain-specific secondary outcome measures.

In a conventional trial, enrollment continues until a pre-specified sample size is obtained, at which time enrollment ceases, and the trial data are analyzed to obtain a result. The possible results are

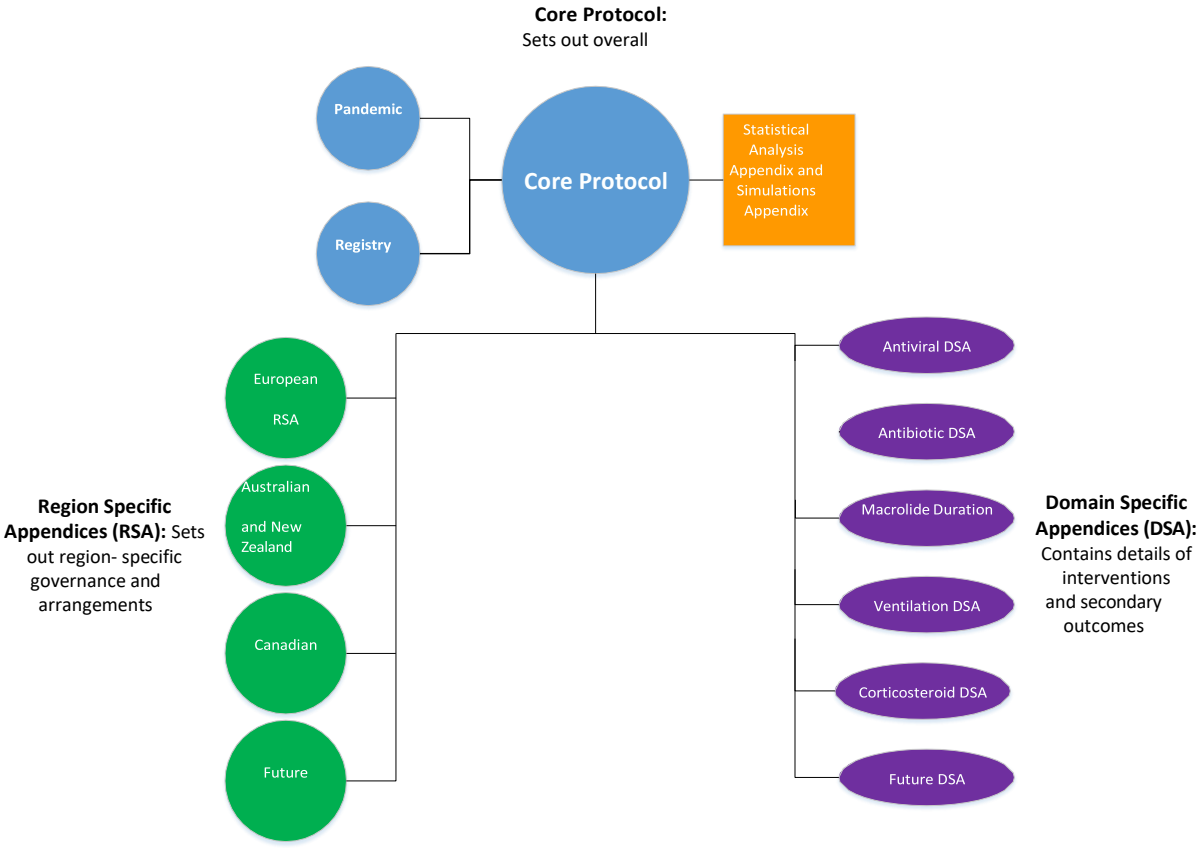
that a difference is detected or no that no difference is detected. However, when the conclusion of the statistical test is “no difference”, this could be that there truly is no meaningful difference, or that the result is indeterminate (i.e. it is possible that if more patients had been enrolled a clinically relevant difference may have been detected).

In comparison to a conventional trial, this REMAP uses an adaptive design, relying on pre-specified criteria for adaptation, that: avoids indeterminate results; concludes an answer to a question when sufficient data have accrued (not when a pre-specified sample is reached); evaluates the effect of treatment options in pre-defined subgroups of patients (termed strata); utilizes already accrued data to increase the likelihood that patients within the trial are randomized to treatments that are more likely to be beneficial; is multifactorial, evaluating multiple questions simultaneously; is intended to be perpetual (or at least open-ended), substituting new questions in series as initial questions are answered; and can evaluate the interaction between interventions in different domains. Bayesian statistical methods will be used to establish the superiority, inferiority, or equivalence of interventions within a domain. Interventions determined to be superior will be incorporated into standard care within the ongoing REMAP. Interventions determined to be inferior will be discontinued. While a limited number of initial treatments and treatment domains have been specified at initiation, it is planned that this REMAP will continue to evaluate other treatments in the future. Furthermore, in the event of a future epidemic of a novel or re-emerging respiratory pathogen (which typically present as severe CAP), this REMAP would be adapted to evaluate the most relevant treatment options. Each new treatment that is proposed to be evaluated within the REMAP will be submitted for prospective ethical review.

2.2. Protocol Structure

The structure of this protocol is different to that used for a conventional trial because this trial is highly adaptive and the description of these adaptations is better understood and specified using a ‘modular’ protocol design. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see glossary for definitions of these terms), by changing aspects of the trial during a pandemic, and commencement of the trial in new regions. The structure of the protocol is outlined in Figure 1.

Figure 1: Protocol Structure



The protocol has multiple modules, comprising a Core Protocol, Pandemic Appendix to the Core Protocol, multiple DSAs, multiple RSAs, and a Statistical Analysis Appendix. A Pandemic Appendix to the Core Protocol is intended to be added subsequently. A Simulations Appendix is updated periodically as an operational document.

2.2.1. Core Protocol

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent. The Core Protocol has the following structure:

- The background and rationale for studying severe CAP
- The background and rationale for the research approach
- The trial design including study setting, the criteria that define eligibility for the REMAP, treatment allocation, strata (see glossary for a definition of this term), principles of application of trial interventions, trial endpoints, methods to control bias, principles of statistical analysis, and criteria for termination of the trial

- The trial conduct including recruitment methods, time-lines for sites, delivery of trial interventions, data collection, data management, and management of participant safety
- The overall / international trial governance structures and ethical considerations

2.2.2. Domain-Specific Appendices

DSAs contain all information about the interventions that will be the subject of the REMAP, which are nested within domains. As such, the Core Protocol does not include information about the intervention(s) that will be evaluated within the REMAP, but rather provides the framework on which multiple different interventions, within domains, can exist within this trial. Each new DSA or addition of one or more interventions to an existing DSA will be submitted for ethical approval prior to commencement. It is anticipated that the DSAs will change over time with removal and addition of interventions within an existing domain, as well as removal and addition of entire domains. Each DSA has the following structure:

- background on the interventions within that domain
- criteria that determine eligibility of patients to that domain
- the features of the interventions and how they are delivered
- any endpoints and data collection that are specific to the domain and additional to those specified in the Core Protocol
- any ethical issues specific to the domain
- the organization of management of the domain

2.2.3. Region-Specific Appendices

This REMAP is intended to be a global trial, conducted in multiple different geographical regions. The RSAs contain all information about the REMAP that is specific to the conduct of the trial in a particular region. This allows additional regions to be added or changes to each region to be made without needing to make major amendments to the Core Protocol in other regions. It is planned that, within each region, the documents submitted for ethical review will comprise the Core Protocol, DSAs, and the RSA for that region (but not other regions). Each RSA has the following structure:

- the definition of the region
- the organization of trial management and administration within the region
- information about availability of domains and interventions
- data management and randomization procedures

- ethical issues that are specific to a region.

If there is information that applies to one or more sub-areas of a region (e.g. a country within Europe or a state or territory within a country) and it is necessary to incorporate this information in the protocol, this information will be included within the RSA. Unless otherwise specified, the RSA will apply to all locations within that region.

2.2.4. Statistical Analysis Appendix and Simulations Appendix

The Statistical Analysis Appendix contains a detailed description of how the statistical analysis will be conducted for reporting treatment effects and reporting interaction between treatments, as well as the RAR. The Statistical Analysis Appendix will be amended when new interventions are added to a domain or when a new domain is added, but will not be updated when interventions are removed from a domain because of inferiority.

The Simulations Appendix is an operational document that contains the results of Monte Carlo simulations that are conducted to describe and understand the operating characteristics of the REMAP across a range of plausible assumptions regarding outcomes, treatment effects, and interactions between interventions in different domains. The statistical power of the study (likelihood of type II error) and the likelihood of type I error are evaluated using these simulations. As the trial adapts, with, for example, the introduction of new interventions, the trial simulations are updated and the Simulations Appendix is amended. The Simulations Appendix is not part of the formal protocol but the conclusions from the Simulations Appendix will be included in protocol documents which will be updated as required. The Simulations Appendix will be maintained as a publicly accessible document on the study website.

2.2.5. Pandemic Appendix

The Pandemic Appendix (to the Core Protocol) contains information about how the core elements of the REMAP will be modified during a pandemic of severe acute respiratory infection that results in CAP. The Pandemic Appendix has the following structure:

- The background and rationale for studying severe CAP caused by a pandemic
- The procedure that will determine activation of the Pandemic Appendix
- How the trial design adapts during a pandemic, including changes to one or more of study setting, treatment allocation, strata, trial endpoints, and principles of statistical analysis that

will operate during a pandemic, as well as how the platform resets following a resolution of a pandemic

2.2.6. Version History

Version 1: Approved by the ITSC on 20 November 2016

Version 1.1: Approved by the ITSC on 10 April 2017

Version 2: Approved by the ITSC on 12 December 2017

Version 2.1: Approved by the ITSC on 26 March 2019

Version 3: Approved by the ITSC on 10 July 2019

2.3. Lay Description

Pneumonia, or infection involving the lungs, is a common reason for admission to an ICU. Severe pneumonia is associated not only with failure of lungs supplying oxygen to the body, but also failure of other organ systems that is due to an uncontrolled immune response to infection.

Patients with severe pneumonia routinely receive multiple treatments at the same time – medications to treat the infection (antibiotics), medications that may modify the immune system (immunomodulators) and supportive treatments to support failing organs, such as mechanical ventilation (organ support) and prevention of complications of critical illness or its treatment. For many categories of treatment there are many treatment options that are in widespread use, are believed or known to be safe and effective, but it is not known which option is best. This REMAP aims to determine the best treatment in each category of treatment, for example, the best antibiotic, the best immunomodulation strategy, and the best method to support each failing organ system.

In a conventional clinical trial, selected patients are allocated to receive one treatment from a short list of alternatives, typically one or two. This trial differs from conventional clinical trials by being randomized, embedded, multifactorial, adaptive, and a platform (a "REMAP"). (Angus, 2015) In this type of trial, we will test many alternative treatments ("multifactorial") by replacing *ad hoc* treatment decisions with "randomized" treatment allocation ("embedded"). Although treatments will be allocated randomly, patients will preferentially be allocated to treatments that statistical models derived from trial data indicate are more likely to be the most effective treatments. The trial will "adapt" in multiple ways including answering questions as soon as sufficient data have accrued

to answer the question of the effectiveness of each treatment and by changing the treatments that are being tested over-time so as to progressively determine the best package of treatments for pre-defined categories of patients with severe pneumonia. Once a treatment is identified as being optimal it is subsequently routinely provided to all eligible patients within the REMAP. The REMAP is also designed to adapt to test relevant interventions during a pandemic caused by lung infection that results in severe pneumonia.

2.4. Trial registration

This is a single trial conducted in multiple regions, but will, as a minimum, be registered with ClinicalTrials.gov. The trial registration number is: NCT02735707.

The Universal Trial Number is: U1111-1189-1653.

2.5. Funding of the trial

At initiation, the trial had funding from the following sources.

The Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE) consortium is funded by the European Union (FP7-HEALTH-2013-INNOVATION-1, grant number 602525). Within the PREPARE consortium, the trial has funding for the recruitment of approximately 4000 patients.

In Australia, the trial has been funded by the National Health and Medical Research Council (NHMRC) (APP1101719) for AUD $4,413,145, for the recruitment of 2000 patients.

In New Zealand, the trial has been funded by the Health Research Council (HRC) (16/631) for NZD $4,814,924, for the recruitment of 800 patients.

In Canada, the trial has been funded by the Canadian Institute of Health Research, Strategy for Patient-Oriented Research (CIHR-SPOR) Innovative Clinical Trials Program Grant (no. 158584) for CAD $1,497,200, for the recruitment of 300 patients.

Funding is being sought for other regions and countries.

3. STUDY ADMINISTRATION STRUCTURE

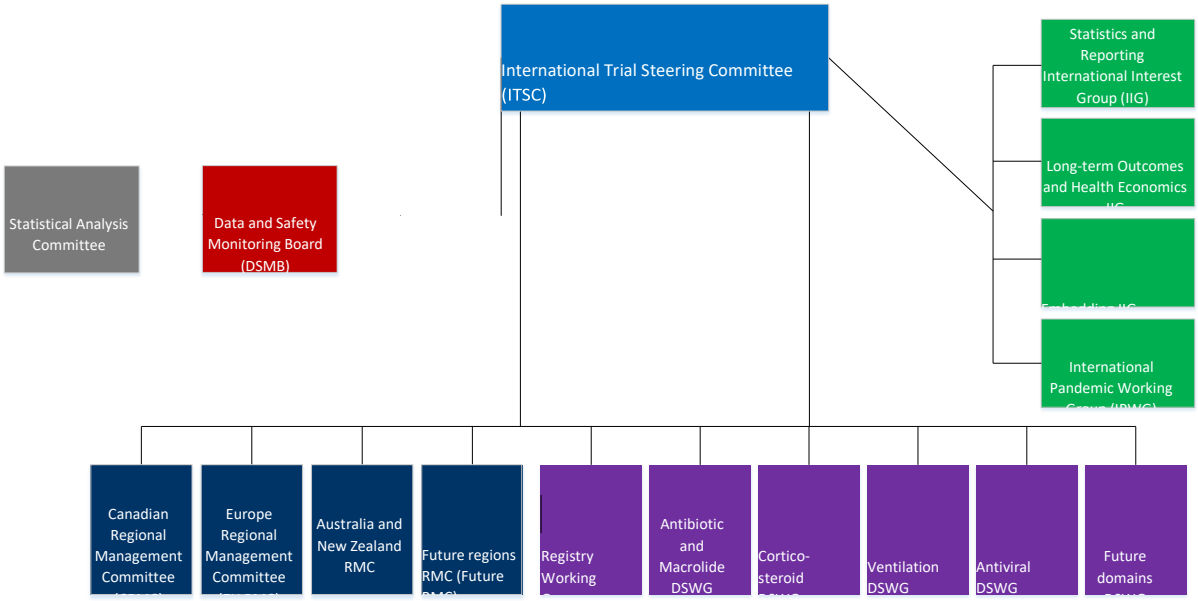
The study administration structure is designed to provide appropriate management of all aspects of the study, taking into account multiple factors including representation from regions that are participating in the trial, availability of skills and expertise related to trial conduct and statistical

analysis, and content knowledge regarding pneumonia and the interventions that are being evaluated. The administration model is designed to provide effective operational and strategic management of the REMAP that operates in multiple regions, is supported by multiple funding bodies and sponsors, and will evolve with addition of further regions and funding bodies as well as changes in the domains and interventions that are being evaluated.

The ITSC takes overall responsibility for the trial design and conduct. Each participating region has a RMC that takes primary responsibility for trial execution in that region. An internationally based Domain-Specific Working Group (DSWG) exists for each domain (or for several domains that are closely related) and has responsibility for design and oversight of each domain. Internationally based Interest Groups exist to allow discussion and development of particular aspects of the REMAP related to statistical analysis, embedding, and health economic analysis of results from the trial.

The organizational chart for REMAP-CAP is outlined in Figure 2.

Figure 2: REMAP-CAP Organization Chart



3.1. International Trial Steering Committee

The ITSC comprises the investigators who initially conceived and designed the trial (Foundation members) and representatives from each (funded and active) region. The intent of the ITSC is to have both theoretical and practical experience and knowledge regarding overall design, domain-specific expertise, and regional-specific expertise. As such, the ITSC will include clinical trialists, biostatisticians, regional lead investigators, domain lead investigators, and regional project managers, and must include one individual who is a Research Coordinator.

3.1.1. Responsibilities

The responsibilities of the ITSC are:

- development and amendment of the Core Protocol
- recruitment and approval of new regions to the REMAP
- liaison with the DSMB including, where appropriate, decisions regarding Platform Conclusions
- consideration of requests and approval of the addition of domains and their nested interventions to the REMAP including prioritization of new domains, new interventions within a domain or both
- liaison with the academic community including the International Committee of Medical Journal Editors (ICMJE) regarding issues such as data sharing and reporting of platform trials including REMAPs
- in conjunction with DSWGs, the analysis and reporting of results from domains
- approval of manuscripts reporting results that are submitted by DSWGs
- coordination of the REMAP during a pandemic
- obtaining funding for the REMAP
- determine the strategic direction of the REMAP

3.1.2. Members

Membership of the ITSC comprises at least 3 investigators from each funded location, the project manager or trial physician in each funded location, at least 1 investigator from Berry Consultants, at least one individual who is a research coordinator, and the chairs of active DSWGs. The operation of the ITSC will be specified by Terms of Reference that will be developed and modified, as required, by the ITSC. The members of the ITSC are:

Professor Derek Angus, Chair Corticosteroid DSWG and Foundation member Ms.

Wilma van Bentum-Puijk, European (EU) Project Manager

Dr. Scott Berry, President and Senior Statistical Scientist of Berry Consultants, and Foundation member

Ms. Zahra Bhimani, Canadian Project Manager

Professor Marc Bonten, European Executive Director, Chair European RMC, and PREPARE Work Package 5 co-lead (specific issues)

Professor Frank Brunkhorst, member EU RMC

Professor Allen Cheng, Chair Antibiotic Domain and Macrolide Duration DSWG Professor

Menno De Jong, member Antiviral DSWG

Dr. Lennie Derde, European Coordinating Investigator, PREPARE Work Package 5 co-lead (specific issues)

Professor Herman Goossens, Principal Investigator for PREPARE Professor

Anthony Gordon, member EU RMC

Mr. Cameron Green, Global Project Manager

Professor Roger Lewis, Foundation member (will step down when SAC is convened) Dr. Ed

Litton, member Australian and New Zealand (ANZ) RMC

Professor John Marshall, Canadian Executive Director

Dr. Colin McArthur, ANZ Deputy Executive Director and Chair Registry WG Dr. Shay

McGuinness, Chair ANZ RMC

Associate Professor Srinivas Murthy, Canadian Deputy Executive Director and Chair Antiviral DSWG

Professor Alistair Nichol, Chair Ventilation DSWG Associate

Professor Rachael Parke, member ANZ RMC Ms. Jane Parker,

Australian Project Manager Professor Kathy Rowan, member EU

RMC

Ms. Anne Turner, New Zealand Project Manager

Professor Steve Webb, ANZ Executive Director and Foundation member

3.1.3. Contact Details

The secretariat functions of the ITSC will rotate among the Regional Coordinating Centers (RCC).

3.2. Regional Management Committees

The operation of the REMAP in each region is undertaken by that region's RMC, the composition of which is be determined by investigators in each region with membership listed in each RSA. Cross-representation between RMCs is strongly encouraged.

3.2.1. Responsibilities

The responsibilities of each RMC are:

- development and amendment of the RSA for that region
- identification and management of sites in that region
- obtaining funding for that region
- liaison with regional funding bodies
- consideration of the feasibility and suitability of interventions (and domains) for that region
- liaison with the sponsor(s) for that region
- management of systems for randomization and data management for that region

3.3. Domain-Specific Working Groups

Each active and future planned domain (or closely related set of domains) will be administered by a DSWG.

3.3.1. Responsibilities

The responsibilities of each DSWG are:

- development and amendment of the DSA
- proposal and development of new interventions within a domain
- in conjunction with the ITSC, analyzing and reporting results from the domain
- obtaining funding to support the domain, with a requirement that, if such funds are obtained, that an appropriate contribution to the conduct of the REMAP is also made.

3.3.2. Members

Membership of each DSWG is set out in the corresponding DSA but should comprise individuals that provide broad international representation, content knowledge of the domain, and expertise of trial conduct and design.

3.4. International Interest Groups

The following International Interest Groups (IIG) contribute to the trial:

- REMAP-CAP International Statistics Interest Group (ISIG)
- REMAP-CAP International Embedding Interest Group (IEIG)

- REMAP-CAP International Long-term Outcomes and Health Economics Interest Group (ILTOHEIG)
- REMAP-CAP International Pandemic Working Group (IPWG)

3.4.1. Role

The role of the interest groups is to provide advice to the ITSC and DSWGs about trial design and conduct as well as advance academic aspects of the conduct, analysis, and reporting of platform trials including REMAPs.

3.5. Sponsors

In relation to recruitment that occurs in:

- countries in Europe the sponsor is University Medical Center Utrecht.
- Australia the sponsor is Monash University.
- New Zealand the sponsor is the Medical Research Institute of New Zealand.
- Canada the sponsor is Unity Health Toronto.

3.5.1. Role of sponsor

The role of the sponsor in each region is specified in each RSA.

3.5.2. Insurance

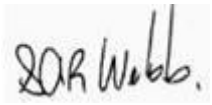
The provision of insurance is specified in each RSA.

4. INTERNATIONAL TRIAL STEERING COMMITTEE AUTHORIZATION

The ITSC have read the appendix and authorize it as the official Core Protocol for the study entitled REMAP-CAP. Signed by the ITSC,

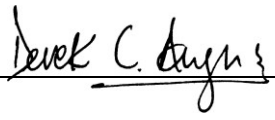
EU Executive Director
Marc Bonten

ANZ Executive Director
Steve Webb



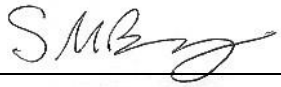
ANZ Deputy Director
Colin McArthur

ITSC Member
Derek Angus

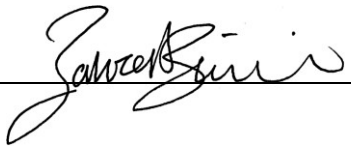


ITSC Member
Wilma van Bentum-Puijk

ITSC Member
Scott Berry



ITSC Member
Zahra Bhimani



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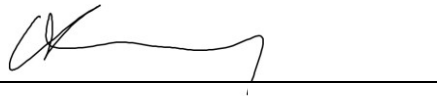

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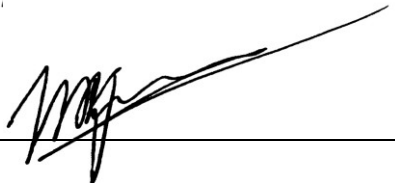

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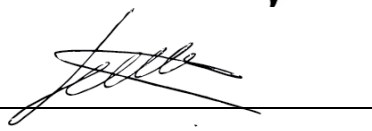

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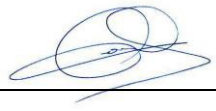

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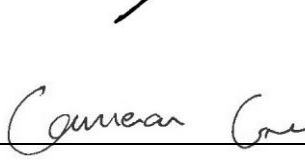

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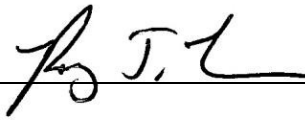

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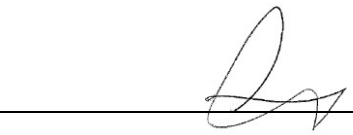

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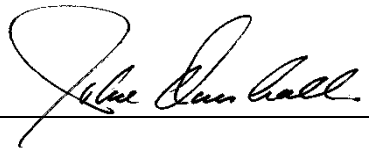

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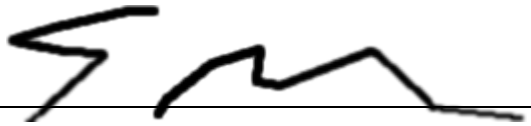
Shay McGuinness

ITSC Member
Srinivas Murthy



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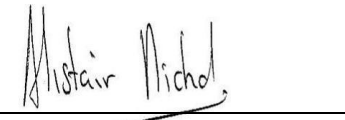
Alistair Nichol



ITSC Member
Rachael Parke

ITSC Member
Jane Parker

ITSC Member
Kathy Rowan

ITSC Member
Anne Turner

5. BACKGROUND & RATIONALE

5.1. Severe Community-Acquired Pneumonia

5.1.1. Introduction

This section, within the Core Protocol, provides background on the epidemiology, causes, treatment categories, and evidence base for the management of patients with severe community pneumonia. Detailed information regarding the rationale for specific interventions to which patients will be

randomized within the REMAP can be found in a corresponding DSA. As the trial is intended to be perpetual, if background information changes, appropriate amendments to the protocol documents will occur periodically, but it is anticipated that this will occur predominantly by amendment of DSAs.

5.1.2. Epidemiology

CAP is a syndrome in which acute infection of the lungs develops in persons who have neither been hospitalized recently nor had regular exposure to the healthcare system. (Musher and Thorner, 2014) A wide range of micro-organisms are capable of causing pneumonia but bacteria and viruses are responsible for the vast majority of cases where a cause is identified. Severe CAP is defined as pneumonia of sufficient severity to be an immediate threat to life. In developed countries, patients with severe CAP are often admitted to an ICU or a High Dependency Unit (HDU). Throughout the remainder of this protocol, we will use the term ICU for units that provide specialized care for critically ill patients, including HDU, Critical Care Units, and Intensive Treatment Units. Although admission criteria may vary, the occurrence of admission to an ICU or a HDU can be used as an operational definition of severe CAP.

CAP is an important health problem and a common cause of death from infection globally, with lower respiratory tract infection, implicated in 3.1 million deaths in 2012, ranked as the 4th most common cause of death, although most of these deaths occur in low and middle-income countries. (Bjerre et al., 2009, Musher et al., 2013, Singanayagam et al., 2009) In developed countries, around half of patients with CAP are treated successfully without admission to hospital. (Almirall et al., 2000) Among patients who are admitted to hospital around 10 to 20% are admitted to an ICU. (Alvarez-Lerma and Torres, 2004, Ewig et al., 2011) The population incidence of CAP that involves admission to an ICU is about 0.4 cases per 1000 per year. (Finfer et al., 2004) Among patients admitted to an ICU with CAP, case-fatality is reported to be in the range from 20 to 50%. (Alvarez- Lerma and Torres, 2004, Leroy et al., 1995, Sligl and Marrie, 2013) In low and middle-income countries, the overlapping syndromes of CAP, bronchiolitis, and bronchitis are a major public health problem and represent the world's most important cause of disability-adjusted life years lost and the third most important cause of death. (World Health Organization, 2008)

5.1.3. Standard care for patients with severe CAP

All patients admitted to an ICU with severe CAP will receive multiple different component therapies and many of these therapies will be administered concurrently. These therapies can be grouped into the following categories: treatment of the underlying infection (including antibacterial and antiviral

agents); the optional use of agents, such as corticosteroids, that modulate the host immune response to infection; and multiple supportive therapies that are used to manage organ systems that have failed or prevent complications of critical illness and its treatment (Table 1).

The choice of empiric antimicrobial therapy is generally made before a microbiologic etiology is established, both because of the lag between collection of specimens and the availability of results from microbiological tests, and because microbiological tests lack sensitivity, particularly when samples are collected after initiation of antimicrobial therapy. It is recommended that antimicrobial treatment be initiated promptly and at the point of care where the diagnosis of pneumonia is first made. (Musher and Thorner, 2014)

Examples of commonly used therapies that support failed organ systems or prevent the complications of critical illness and its treatment include oxygen therapy, invasive and non-invasive mechanical ventilation, intravenous fluid resuscitation, vasoactive drugs, dialysis, provision of nutrition, sedation, physiotherapy including mobilization, diuretic medications, suppression of gastric acid production, and mechanical or pharmacological interventions to prevent venous thromboembolism. The exact combination of supportive therapies is influenced by the spectrum of organ failures that occurs in any individual patient. (Dellinger et al., 2013)

Table 1: Potential targets of interventions to reduce mortality in patients with CAP

Target of intervention	**Examples**
Eradication of pathogens	Antibiotics (agents, route, dose) Antivirals (agents, route, dose) Microbiological diagnostic strategies
Modulation of the host immune response	Corticosteroid Macrolides
Methods to support failing organ systems and prevention of complications	Lung ventilation strategies and respiratory salvage modalities (e.g. extra-corporeal membrane oxygen, prone positioning) Renal replacement therapy Inotropic/vasopressor support Fluid resuscitation strategies

	Nutrition Mobilization Sedation Venous thromboembolism prophylaxis Stress ulcer prophylaxis

5.1.4. Treatment guidelines

A range of different guidelines have been published that are relevant to the care of critically ill patients with CAP. (Eccles et al., 2014, Lim et al., 2009, Mandell et al., 2007, Wiersinga et al., 2012, Wilkinson and Woodhead, 2004, Woodhead et al., 2011) These guidelines generally focus on recommendations related to assessment of severity, diagnostic evaluation, and empiric and guided antimicrobial therapy. Guidelines from the Surviving Sepsis Campaign are relevant to many aspects of the supportive care of the critically ill patients with CAP. (Dellinger et al., 2013)

There is a stark contrast between the substantial public health impact of severe CAP and the low quality of evidence that guides therapy. The number of treatment recommendations in guidelines that are supported by high quality randomized controlled trial (RCT) evidence is 4 of 44 for treatment recommendations in the European guidelines (Eccles et al., 2014, Lim et al., 2009, Woodhead et al., 2011), 11 of 43 in the United States guidelines (Mandell et al., 2007), and 7 of 93 in the Surviving Sepsis Campaign Guidelines. (Rhodes et al., 2017) As a consequence of the limited evidence-base there are a number of inconsistencies and even complete contradictions among international guidelines.

5.1.5. Variation in care and compliance with guidelines

Several observational studies report substantial variation in care with, for example, compliance with administration of antibiotics recommended by guidelines occurring in between 40% and 75% of patients. (Bodi et al., 2005, Frei et al., 2010, Lee et al., 2014, Shorr et al., 2006) These and other studies also report better clinical outcomes for patients who received antibiotics that were recommended by guidelines. (McCabe et al., 2009, Mortensen et al., 2004, Mortensen et al., 2005) However, it remains unclear if adherence to guideline recommendations is due to a direct causal link, or whether it is a surrogate for better quality care generally. There is also widely reported variation in compliance with many supportive therapies for patients with severe CAP, such as use of

low tidal volume ventilation, type of resuscitation fluid, and thresholds for the administration of transfusion for anemia. (Bellani et al., 2016, Finfer et al., 2010, Blood Observational Study Investigators of Anzics-Clinical Trials Group et al., 2010, Cecconi et al., 2015)

5.1.6. An unmet need for better evidence

Many factors contribute to the substantial unmet need for better evidence to determine the optimal treatment for patients with severe CAP. Severe CAP is common, case-fatality is high, the strength of current evidence is limited, and there is evidence of substantial variation in existing standard care. The combination of these factors provides a strong rationale for the need for better quality evidence about the impact of the different treatment options that are in existing practice, the impact of different combinations of treatment options, and the timely and effective evaluation of new candidate interventions to improve outcomes.

5.2. Influenza pandemics and emerging pathogens

A pandemic of severe CAP caused by a known (e.g., influenza) or unknown virus, as occurred during the Severe Acute Respiratory Syndrome (SARS) outbreak, can rapidly change the etiological spectrum of severe CAP in patients who require admission to an ICU. This necessitates adaptation of empiric treatment protocols or diagnostic procedures or both. Naturally, there will be no evidence base for the medical management of such a disease at the time of its emergence, and medical decisions will be mostly based on expert opinion with extrapolation from evidence derived from the treatment of analogous clinical syndromes. There is substantial unmet need to generate evidence about the most effective treatment approaches during a pandemic or regional outbreak.
Furthermore, to have impact on patient outcomes during an outbreak, evidence must be available during the pandemic. As a consequence, such evidence must be capable of being generated, disseminated, and implemented rapidly. More detailed background information about pandemics of respiratory infection, together with challenges associated with the clinical research response are outlined in the Pandemic Appendix.

5.3. Randomized Embedded Multifactorial Adaptive Platform Trials

5.3.1. Generating clinical evidence

Angus has noted several problems encountered when generating robust clinical evidence, including barriers to conducting clinical trials, the generalizability of data from populations that are too broad or too narrow, the issue of equipoise especially when comparing different types of existing care, and

the delay in translating results into clinical practice. (Angus, 2015) A REMAP provides a strategy to address many of these problems by gaining economies of scale from a common platform, which allows for broad enrollment but retaining the ability to examine for heterogeneity of treatment effects between defined subgroups. A REMAP focuses predominantly on the evaluation of treatment options for the disease of interest that are variations within the spectrum of standard care (although testing of novel or experimental therapies is not precluded) and does so by embedding the trial within routine healthcare delivery. In this regard the REMAP seeks to replace random variation in treatment with randomized variation in treatment allowing causal inference to be generated about the comparative effectiveness of different existing treatment options. The use of RAR, which allows the allocation ratios to change over time based on accruing outcomes data, maximizes the chance of good outcomes for trial participants. The embedding of such a platform within the day-to-day activities of ICUs facilitates the translation of outcomes to clinical practice as a "self-learning" system. As such, it also functions as an embedded and automated continuous quality-improvement program. A final advantage of a REMAP for pneumonia is the ability to rapidly adapt to generate evidence if new respiratory pathogens emerge, avoiding the inevitable delays associated with conventional trials in an outbreak of a new infectious diseases. (Burns et al., 2011)

5.3.2. Underlying Principles of the Study Design

A REMAP applies novel and innovative trial adaptive design and statistical methods to evaluate a range of treatment options as efficiently as possible. The broad objective of a REMAP is, over time, to determine and continuously update the optimal set of treatments for the disease of interest. The set of treatments that may be tested within a REMAP comprise the set of all treatments that are used currently or may be developed in the future and used or considered for use in the disease of interest. The design maximizes the efficiency with which available sample size is applied to evaluate treatment options as rapidly as possible. A REMAP has the capacity to identify differential treatment effects in defined sub-groups (termed strata), address multiple questions simultaneously, and can evaluate interactions among selected treatment options. Throughout the platform, patients who are enrolled in the trial are treated as effectively as possible. (Angus, 2015, Berry et al., 2015, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016)

A conventional RCT (i.e. a non-platform trial) makes a wide range of assumptions at the time of design. These assumptions include the plausible size of the treatment effect, the incidence of the primary outcome, the planned sample size, the (typically, small number of) treatments to be tested, and that treatment effects are not influenced by concomitant treatment options. These assumptions are held constant until the trial completes recruitment and is analyzed. (Barker et al., 2009, Berry,

2012, Connor et al., 2013) Participants who are enrolled in a conventional RCT are not able to benefit from knowledge accrued by the trial because no results are made available until the trial completes. A REMAP uses five approaches to minimize the impact of assumptions on trial efficiency and also maximizes the benefit of participation for individuals who are enrolled in the trial. (Angus, 2015, Berry et al., 2015, Aikman et al., 2013, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016)

These design features are:

- frequent adaptive analyses using Bayesian statistical methods
- RAR
- evaluation of differential treatment effects in pre-specified sub-groups (strata)
- evaluation of specified intervention-intervention interactions
- testing of multiple interventions in parallel and, subsequently, in series

This creates a 'perpetual trial' with no pre-defined sample size, the objective of which is to define and continuously update best treatment over the life-time of the REMAP. The design aspects, including the risk of type I and type II error, are optimized prior to the commencement of the trial by the conduct of extensive pre-trial Monte Carlo simulations, modification of the trial design, and re- simulation in an iterative manner. The methods related to the application of the design features and the statistical analysis of this trial are outlined in the methods section of the protocol (Section 7).
The following sections describe the background, rationale, and potential advantages of each of the design features of a REMAP (Section 5.3.4).

5.3.3. Nomenclature

A specific set of nomenclature is used to categorize potential treatments evaluated and populations within a REMAP as well as other aspects of the trial design and statistical analysis. A detailed glossary can be found in Section 1.2. Please see the glossary for the definition and explanations for the following terms: domain, intervention, regimen, stratum, state, Statistical Trigger, Platform Conclusion, and Public Disclosure.

5.3.4. Randomization and Response Adaptive Randomization

The study will randomly allocate participants to one or more interventions, with each intervention nested within a domain. In this regard, a platform trial is no different to other forms of RCT in that randomization provides the basis for causal inference. However, unlike a conventional RCT, the proportion of participants who are randomized to each available intervention within a domain will

not be fixed. Rather, the trial will incorporate RAR. RAR utilizes random allocation with a weighted probability for each intervention, with the weighted probability being proportional to the extent to which similar participants recruited earlier in the trial benefited or not from each particular intervention. (Angus, 2015, Berry, 2012, Connor et al., 2013, Aikman et al., 2013, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016) RAR will result in participants in each particular stratum being randomized with greater probability to interventions that are performing better within that stratum. At the initiation of a new domain or when a new intervention is added to a domain the randomization proportion of all new interventions is balanced and only changes, with the application of RAR, that takes into account uncertainty about treatment effect so as to avoid excessive variability in proportions generated by RAR until sufficient sample size has accrued.

The major consequence of RAR is that better therapies move through the evaluation process faster, resulting in trial efficiency gains. (Berry, 2012, Connor et al., 2013) The platform "learns" more quickly about the treatments we ultimately care about, i.e. those that work best. Moreover, as data accrues, newly randomized participants are more likely to receive interventions from which they benefit. (Berry, 2012, Connor et al., 2013, Meurer et al., 2012, Angus, 2015, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016) This is a highly ethical fusion of trial science with continuous quality improvement and a learning healthcare system. (Institute of Medicine, 2013) Assuming at least some interventions are better than others, the total mortality within the trial population will be lower than would have occurred with a fixed randomization proportion. It is also particularly relevant to the ethical conduct of trials that enroll critically ill patients where unanticipated increases in mortality have been seen (Dellinger et al., 2013) and to the conduct of trials during a pandemic in which there is in-built implementation of the therapies that are more likely to be beneficial during the trial. The simulations underpinning REMAP-CAP demonstrate that, in instances where particular interventions are indeed superior to others, the use of RAR will, on average, increase the odds of discovering the superiority not only with lower sample size, but with fewer participants exposed to the less efficacious therapies and, thus, fewer deaths.

There are potential disadvantages associated with RAR. It is intended that participating sites and trial investigators will be blind to the RAR proportions. One disadvantage is that, for interventions that are provided without blinding, the treating clinicians may be able to draw inference about the RAR proportions and, as a consequence, draw inference about the interim standing of interventions that are being tested in the REMAP. This could have adverse consequences including that clinicians are influenced to not enroll participants within a domain but rather directly prescribe the treatment that

they believe to be doing better outside the trial. However, a number of factors mitigate this potential concern. First, it can be difficult to distinguish between patterns of sequential allocation status that are derived from fixed versus RAR. Second, extreme proportions will not be used (except where a Statistical Trigger but not a Platform Conclusion has been reached, see later). Finally, for many conditions, team-based management means that an individual clinician will directly observe only a small proportion of all participants enrolled within the trial at each participating site. Another disadvantage of RAR is that, under certain allocation rules, statistical power can be reduced. This concern is mitigated via pre-trial simulation to test the effects of different allocation rules. Furthermore, a REMAP that comprises multiple domains with multiple interventions within each domain will generally have higher, rather than lower, power as a consequence of the use of RAR. Finally, by deploying RAR rules to minimize the odds of exposure to inferior interventions, the design is intended to motivate embedding in clinical practice, thereby resulting in more rapid recruitment.

Within each domain, RAR will be implemented for participants who are eligible to receive two or more interventions within a domain. Where a participant is eligible for only one option within a domain, this will be the treatment allocation for such a participant. In these circumstances, the provision of a treatment allocation status is made, predominantly, so as to provide a process that enhances the effectiveness of embedding, i.e. wherever possible the platform provides the treatment allocation.

5.3.5. Embedding

A trial is most efficient when all eligible participants are recognized and enrolled. Achieving universal enrollment of eligible participants increases the speed with which new knowledge is generated, maximizes internal and external validity, and minimizes operational complexity at the bedside (there is no need to distinguish between trial and non-trial patients, because all patients are trial patients). A number of strategies will be utilized to very tightly “nest” or embed trial processes in daily clinical care operations. The effectiveness of strategies to achieve embedding will be evaluated, updated, and shared with sites, taking into account different clinical processes at different sites. Wherever possible trial treatment allocations will be integrated with electronic customized order sets, produced at the point of delivery of care that also includes each site’s local care standards for concomitant therapies. This allows clinical staff to follow their typical workflow using protocolized order sheets to govern many aspects of patient care and serves to enhance compliance with the interventions allocated by the trial. The intention of embedding is that recruitment occurs 24/7 and is dependent on the usual medical staff who are responsible for patient care. Where possible electronic health records will be utilized to enhance screening and recruitment and specify the

'order set' for participants, including those orders that are determined by allocation status within the REMAP. While screening and recruitment for a REMAP can be conducted by research staff, it is not intended that recruitment should be dependent on research staff, particularly as such staff are typically only present during office hours. In addition to the facilitation of recruitment and high-fidelity delivery of the intervention, a further advantage is that the results of the trial can be translated rapidly within the ongoing REMAP so that all appropriate participants receive a treatment declared to be superior with continued allocation to that treatment option within the REMAP used to ensure implementation.

5.3.6. Multifactorial

If the trial randomizes in more than one domain of care it is multifactorial. The number of domains, at any time, is determined by a combination of the interventions that are appropriate and amenable for evaluation within the REMAP and the available statistical power, as determined by the conduct of simulations. It is intended that this REMAP will increase the number of domains, progressively, as the number of sites and rate of recruitment increases over time. The Bayesian models evaluate treatment effects (superiority, inferiority, equivalence) within each regimen but then, by isolating the effect of each intervention across all regimens in which that intervention is included, the independent effect of each intervention is estimated. The capacity to evaluate interventions within multiple domains, in parallel, increases trial efficiency substantially.

An additional advantage of the trial being multifactorial is the capacity to evaluate interactions between selected interventions in different domains. Where pre-specified, on the basis of clinical plausibility, statistical models will evaluate whether there is interaction between interventions in different domains. Where no interaction is suspected, interactions will not be evaluated as part of the *a priori* statistical model.

Although participants within a REMAP will, typically, receive treatment allocations for multiple domains the decision-making regarding concomitant therapies will be made by the treating clinician in other domains of care. Treatment decisions in other domains of care will be recorded and may be analyzed, using observational methods, to evaluate candidate interventions for evaluation by randomization within the REMAP.

5.3.7. Adaptive

Frequent adaptive analyses 5.3.7.1.

Frequent adaptive analyses using Bayesian statistical methods will be undertaken using Markov Chain Monte Carlo (MCMC) estimates of the Bayesian posterior probability distributions. The trial will utilize a set of pre-specified rules to reach conclusions regarding the effectiveness of interventions that are being evaluated. It is these pre-specified rules that determines how the trial "adapts" to the information contained in accumulating participant data. An analogy is that the 'routes' that a trial can take are pre-specified, within the protocol, but the exact route that the trial takes is determined by the data that accrues. Such adaptation improves statistical efficiency substantially.

Analysis of data to reach conclusions 5.3.7.2.

The following structure and sequence of events will be used to reach conclusions from data as it accrues and is analyzed. This document, the Core Protocol, sets out the pre-specified rules for interpreting the results of analyses. These rules include pre-specified threshold levels of probability for achieving superiority, inferiority or equivalence of interventions within a domain. At each adaptive analysis the Statistical Analysis Committee (SAC) evaluates whether one or more probability thresholds that are derived from the trial's statistical model have been exceeded. When the model indicates one or more of superiority, inferiority, or equivalence has occurred this is termed a Statistical Trigger. A Statistical Trigger may be reached for one or more strata at any given adaptive analysis.

The occurrence of a Statistical Trigger is communicated immediately to the trial DSMB by the SAC. The DSMB has primary responsibility for determining if a Statistical Trigger should lead to a Platform Conclusion. The declaration of a Platform Conclusion results in the removal of inferior intervention from randomization options or removal of all other interventions if an intervention is declared as superior. A Platform Conclusion will be communicated to the ITSC who have responsibility for immediate dissemination of the result by presentation and publication of the result.

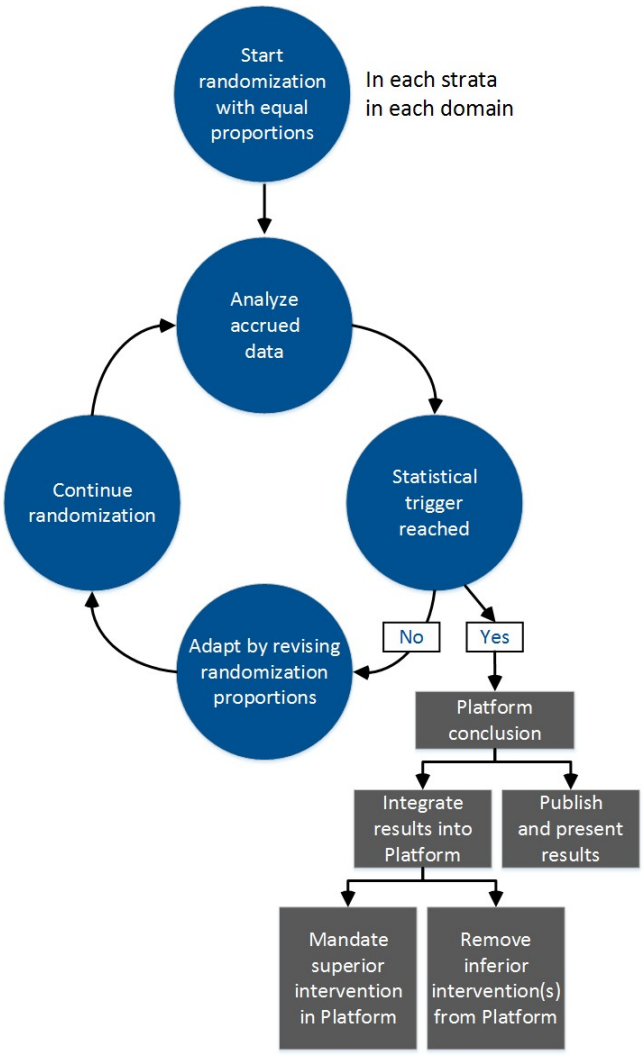
The algorithm by which a Platform Conclusion is reached is different for Statistical Triggers of superiority or inferiority, compared to those triggers that arise because of equivalence. Where the Statistical Trigger is for superiority or inferiority, so long as the DSMB is satisfied that the Statistical Trigger has been met validly, the default position is that the DSMB will declare this result as a Platform Conclusion. The only exception to this situation is if there is a need to evaluate potential interactions between treatments in different domains. In this circumstance the randomization

schedule will be adapted (all participants receive the superior intervention or randomization to one or more inferior interventions is removed) but Public Disclosure may be delayed until evaluation of the interaction is completed.

Where the Statistical Trigger is for equivalence the DSMB will evaluate clinically relevant secondary endpoints. The results, in relation to both primary and secondary endpoints, will be communicated to the ITSC. The DSMB, in conjunction with the ITSC, may declare a Platform Conclusion (for equivalence) or may opt to continue recruitment and randomization to the 'equivalent' interventions, for example, to allow a conclusion to be reached regarding clinically important secondary endpoints, to allow additional accrual to narrow the margin of equivalence (for example where health economic issues are relevant), or to allow evaluation of an interaction).

The pathway for and potential outcomes from each adaptive analysis is displayed in Figure 3.

Figure 3: Adaptive Analyses



5.3.7.3. *Probability thresholds*

In this REMAP the pre-specified rules are that, at any adaptive analysis, an intervention will be declared "superior," if it is has at least a 0.99 posterior probability of being the best intervention within its domain. An intervention will be declared "inferior" if it has a less than 0.01 probability of being the best intervention within its domain. Intervention equivalence is declared between two factors when there is at least a 0.90 posterior probability of the rate of the primary endpoint falls within a pre-specified delta.

Analysis within and between strata

The frequent adaptive analyses will evaluate the primary endpoint, *within one or more stratum*. Where specified, the statistical models for each strata will be able to 'borrow' information from adjacent strata leading to the declaration of a Statistical Trigger in one, more, or all strata. The

extent to which borrowing occurs is dependent on the pre-specified structure of the model and the degree of statistical congruence of treatment effect between stratum. Where treatment effects are divergent between stratum there is less 'borrowing'. The capacity to evaluate strata is particularly important for interventions that might plausibly have differential, including opposite, treatment effects in different strata. (Dellinger et al., 2013, Finfer et al., 2004, The Acute Respiratory Distress Syndrome Network, 2000) In traditional trial designs, divergent treatment effects among sub-groups may cancel each other out and this is one plausible explanation for the trials that report no overall difference in outcome. It should be noted that strata can be different for different domains and that strata can be changed over time (in conjunction with amendment of the protocol).

If a Platform Conclusion is reached just within a single stratum, this leads to cessation of randomization within that stratum, while continuing to randomize in other strata. It is acknowledged that a Platform Conclusion in one strata may rely on 'borrowing' from adjacent strata and that analysis just within a strata may yield a result that is different. Nevertheless, a Platform Conclusion is still regarded as valid if it relies upon borrowing from adjacent strata and will be reported and published including the extent to which it relies on borrowing.

Frequency of adaptive analyses 5.3.7.5

Adaptive analyses will occur frequently, with the frequency being approximately proportional to the rate of recruitment, and will be a largely automatic process; the frequency is chosen to balance logistical demands with the goal of learning rapidly from accumulating data. While this process will be overseen by an independent DSMB, the DSMB will not make design decisions unless the trial's algorithms are no longer acceptable from an ethical, safety, or scientific point of view. The DSMB, in conjunction with the ITSC, having reached a Platform Conclusion, and in deciding to terminate an intervention or domain (in conjunction with a Public Disclosure), may take into account one or more issues such as the value of continuing randomization so as to evaluate additional clinically relevant endpoints or to evaluate potential interactions, as well as take into account the opportunity cost associated with not moving to introduce new domains or interventions.

Advantages of adaptive analysis 5.3.7.6

The major advantage of this type of analysis approach is that a conclusion is reached when there is sufficient information to support the conclusion, rather than when enrollment reaches a predetermined sample size. This approach allows a result to be obtained as quickly as possible with appropriate sample size. It also avoids indeterminate results by continuing randomization until either superiority, inferiority, or equivalence is concluded. (Barker et al., 2009, Berry, 2012, Connor

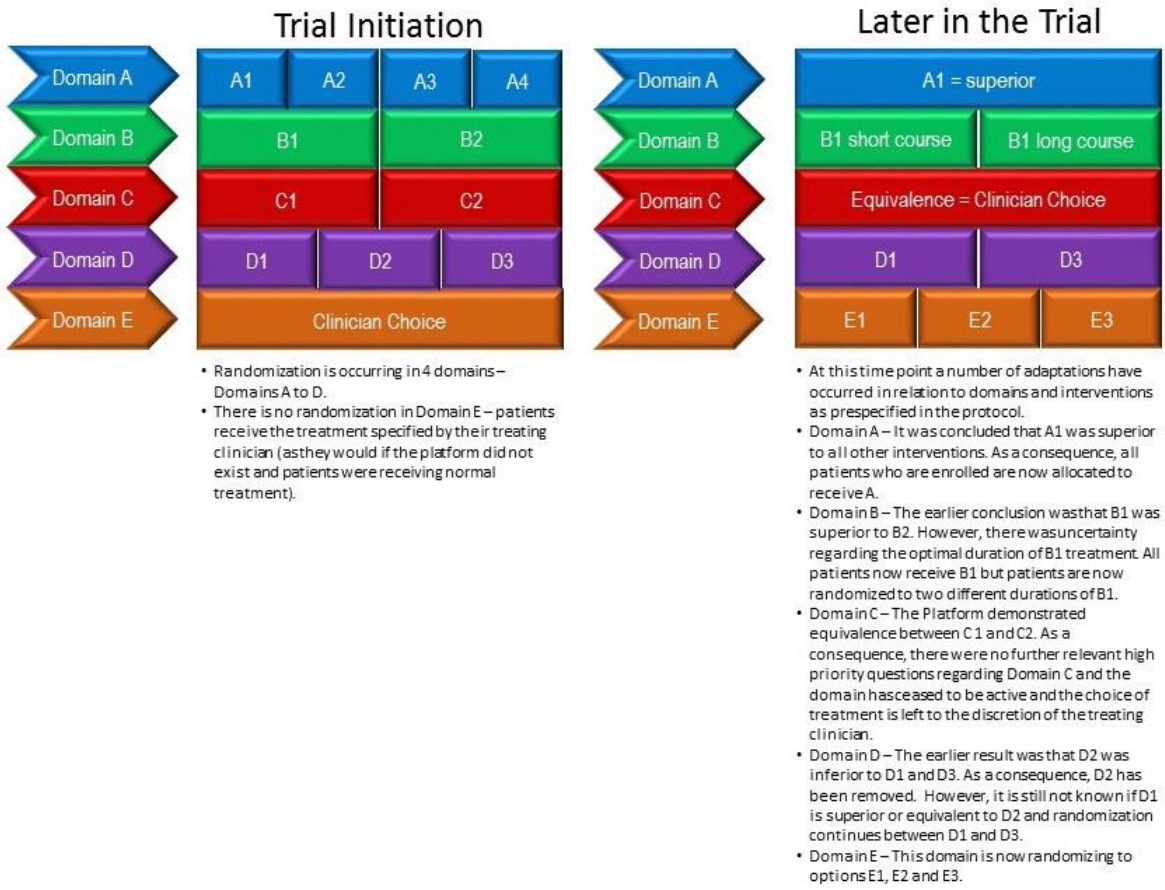
et al., 2013, Meurer et al., 2012, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016) An additional advantage is that dissemination of such results does not interrupt the conduct of the platform. In a single REMAP, there is no need for the "start-and-stop" periods that would typically occur under the alternative approach of multiple separate trials. These "downtime" periods can be quite extensive and carry a number of disadvantages. First, there is a lot of duplicative effort every time a near-identical treatment protocol goes through the appropriate development and approval processes. Second, clinical investigation units must maintain a certain infrastructure, and that infrastructure can be expensive to maintain during periods when participants are not being enrolled or expensive to recreate if the infrastructure degrades. Third, downtime is simply one more contributor to delay in the production of scientific knowledge.
Participants at large benefit from earlier production of knowledge regardless of whether new information demonstrates a therapy is effective or ineffective. Finally, the inevitable start up delay before a trial can "go live" can wipe out any possibility of conducting effective research during time-critical situations such as a pandemic.

5.2.7 Substitution of new domains and interventions within the REMAP

It is intended that the REMAP will be 'perpetual'. In conjunction with a Platform Conclusion being reached, the ITSC takes responsibility for determining what new questions will be introduced to the REMAP including adding one or more new interventions to a domain or adding one or more new domains. In a REMAP, the sample size is not fixed, rather maximum use is made of the available sample and more questions may be asked for the same monetary investment. (Barker et al., 2009, Berry, 2012, Connor et al., 2013, Meurer et al., 2012, Aikman et al., 2013, Bhatt and Mehta, 2016, Park et al., 2016) The only limit on the duration of a platform trial is the availability of ongoing funding, the availability of new interventions to evaluate, and that the disease continues to be a public health problem. The ITSC responsible for the REMAP will develop appropriate processes for identifying and prioritizing the selection of new interventions and domains that are introduced progressively into the REMAP over time.

How the domains and interventions within a REMAP might evolve over time is depicted in Figure 4.

Figure 4: REMAP Evolution Over Time



5.3.8. Nesting of the REMAP within a Registry

The REMAP can also be nested within a registry, with the registry recording information (typically a subset of the trial Case Report Form (CRF)) in all participants who met the REMAP entry criteria, or an expanded set of entry criteria, but who, for any reason, were not randomized. Information obtained from eligible but not randomized participants can be useful for evaluating the external validity of results and optimizing recruitment. Evaluation of non-randomized treatments received by all participants, both randomized and non-randomized, can be used to identify the consequences of natural variation in care so as to identify interventions that should be prioritized for evaluation by randomization within the REMAP. (Byrne and Kastrati, 2013) The design features of the trial and the conceptual advantages associated with each design feature are summarized in Table 2.

If a registry component is included the operation of the registry will be specified in a DSA that applies only to the registry aspects of the study.

5.3.9. Platform

Platform trials simultaneously evaluate multiple potential therapies, where the focus is on finding the best treatment for the disease, rather than precisely characterizing the effect of each intervention in isolation. (Angus, 2015, Berry et al., 2015, Bhatt and Mehta, 2016, Carey and Winer, 2016, Park et al., 2016, Rugo et al., 2016, Harrington and Parmigiani, 2016) Thus the goals of a platform trial are much more aligned with the goals of clinical care than a traditional, narrowly focused phase III RCT of a single agent. All of the component design features of a REMAP have been used previously and have accepted validity. What is innovative and novel, for a REMAP, is the combination of all of these design features within a single platform combined with their use for phase III evaluations and by using embedding to integrate the trial within routine clinical care.

Table 2: Features of a REMAP that contribute to advantages of the design

	Efficient use of information	Safety of trial participants	Avoiding trial down-time	Fusing research with care	Determining optimal disease management	Self-learning healthcare system
Multifactorial	✓		✓	✓	✓	
Response Adaptive Randomization	✓	✓		✓		✓
Embedding				✓		✓
Frequent adaptive analyses	✓	✓			✓	✓
Analysis of strata	✓	✓			✓	
Evaluation of interaction		✓			✓	
Substitution of new interventions	✓		✓		✓	

6. OBJECTIVES

6.1. Primary objective

The primary objective of this REMAP is, for adult patients with severe CAP who are admitted to an ICU, to identify the effect of a range of interventions to improve outcome as defined by all-cause mortality at 90 days.

6.2. Secondary objectives

The secondary objectives are to determine, for adult patients with severe CAP who are admitted to an ICU, the effect of interventions on ICU mortality, ICU length of stay (LOS), hospital LOS, ventilator free days (VFDs) censored at 28 days, organ failure free days (OFFDs) censored at 28 days, other endpoints as indicated for specific domains, and, where feasible or specified in a DSA, survival at 6 months, health related quality of life (HRQoL) assessed after 6 months using the EQ5D and disability assessed after 6 months using the World Health Organization Disability Assessment Schedule (WHODAS).

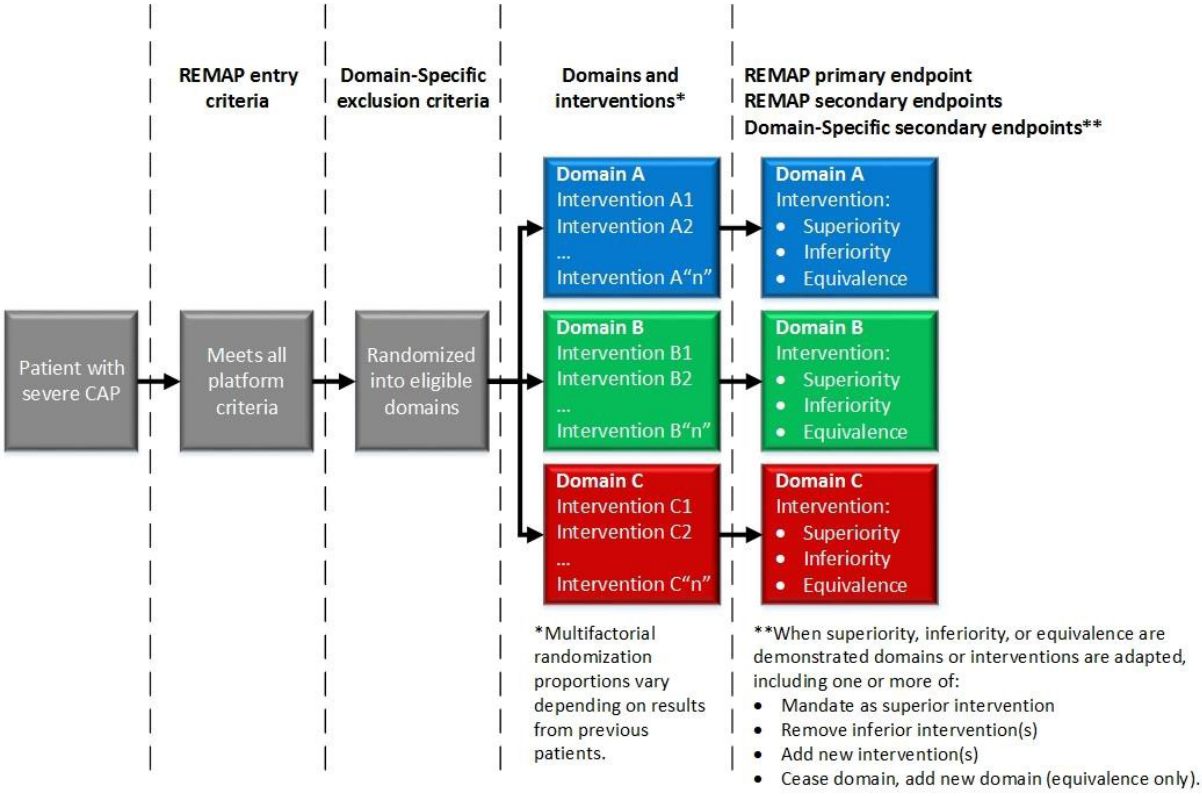
7. SUMMARY OF TRIAL DESIGN

7.1. Introduction

This is a REMAP that aims to test many interventions in a number of domains with the primary outcome being the all-cause mortality at 90 days. Frequent adaptive analyses will be performed to determine if an intervention is superior, inferior, or equivalent to one or more other interventions to which it is being compared, within a domain. A Bayesian analysis method will be used to evaluate superiority, inferiority, or equivalence, as well as to inform the adaptive randomization strategy within each domain. Where it is anticipated that interactions between interventions in different domains may be likely the statistical models will allow evaluation of such interactions. Where the statistical models evaluate such an interaction the models can incorporate the relative likelihood of such interactions, but with possibly low prior probability in cases where it is biologically implausible for interactions to occur. Each intervention within each domain will be evaluated within prospectively defined and mutually exclusive strata (sub-groups) of participants but information from one stratum may be used (via 'borrowing') to contribute to the analysis of the effect of that intervention in other strata. Interventions that are found to be inferior, for a specific stratum, are removed from use in that stratum, and will, typically, be removed from the REMAP allowing new interventions or domains or both to be introduced. An RAR algorithm will be used to preferentially randomize participants to interventions that appear to be performing better. Extensive simulation studies have been performed to define the type I error, power to detect specified differences, and demonstration of equivalence as well as a broad range of operating characteristics. It is planned that further simulation studies will be conducted in conjunction with consideration of the introduction of new interventions or domains or both into the REMAP. The intention-to-treat (ITT) principle will be used for all primary analyses.

The key structure of the REMAP is outlined in Figure 5.

Figure 5: REMAP Structure



7.2. Nomenclature

A specific set of nomenclature is used to categorize potential treatments evaluated and populations within a platform trial as well as other aspects of the trial design and statistical analysis. A detailed glossary can be found in Section 1.2. Please see the glossary for the definition and explanations for the following terms: domain, intervention, regimen, stratum, state, Statistical Trigger, Platform Conclusion, and Public Disclosure. The following section can only be understood in the context of an understanding of the definition and meaning of these specific terms.

7.3. Study setting and participating regions

The trial will recruit only participants who are admitted to an ICU. An ICU is defined as a location that identifies itself as an ICU (or HDU) and is able to provide at least non-invasive ventilation and continuous administration of vasoactive medications. By agreement with the RMC, the definition of an ICU may include a general ward in which a patient is under the care of an Intensive Care Specialist (Intensivist), but resource limitations prevent the immediate delivery of care occurring in the ICU. It is intended that the trial will be conducted in multiple regions. A region is defined as a country or

collection of countries with study sites for which a RMC is responsible. The country or countries for which a RMC are responsible, as well as all aspects of trial conduct that are specific to each region, are described in the RSAs.

Participating ICUs will be selected by a RMC based on response to an expression of interest and fulfilling pre-specified criteria including number of beds in the ICU, annual admissions for severe CAP, resources available to support research activities, and track record in conducting investigator-initiated multicenter trials.

The current regions are:

- Europe, with funding from a European Union FP7 grant (FP7-HEALTH-2013-INNOVATION-1, grant number 602525), to support the enrollment of 4000 participants. This funding terminates in 2021.
- Australia and New Zealand. In Australia the project has received funding from a NHMRC Project Grant (APP1101719), to support the enrollment of 2000 participants. This funding terminates in December 2021, although some extension may be feasible. In New Zealand the project has received funding from a HRC Programme Grant (16/631), to support the enrollment of 800 participants. This funding terminates in November 2021.
- Canada. In Canada the project has received funding for a CIHR grant (158584), to support the enrollment of 300 participants. This funding terminates in 2022.

It is intended that additional regions will be added if funding can be secured in other locations. It is desirable that the REMAP is active in as many locations as possible. There is no upper limit to the number of regions and the number of participating sites.

7.4. Eligibility criteria

The eligibility criteria for the REMAP are applied at two levels. One level is that there are inclusion and exclusion criteria that determine eligibility for randomization within the REMAP. The other level is that, once eligible for inclusion within the REMAP, additional criteria, typically exclusion criteria, are applied that are specific to the level of the domain. A patient is eligible for inclusion within a domain when:

- all REMAP inclusion criteria are present
- none of the REMAP exclusion criteria are present
- Domain-Specific criteria are met

As such, the key “inclusion criteria” for being eligible for a domain are that the patient is eligible for the REMAP. Criteria for inclusion in the registry, in which patients do not receive any randomized intervention, may be broader than the entry criteria for the REMAP (i.e. it is only a subset of registry eligible patients who are eligible for randomization within the REMAP).

7.4.1. REMAP Inclusion Criteria

In order to be eligible to participate in this trial, a patient must meet both of the following criteria:

1. Adult patient admitted to an ICU for acute severe CAP within 48 hours of hospital admission with
    a. symptoms or signs or both that are consistent with lower respiratory tract infection (for example, acute onset of dyspnea, cough, pleuritic chest pain) AND
    b. Radiological evidence of new onset infiltrate of infective origin (in patients with pre-existing radiological changes, evidence of new infiltrate)
2. Up to 48 hours after ICU admission, receiving organ support with one or more of:
    a. Non-invasive or invasive ventilatory support;
    b. Receiving infusion of vasopressor or inotropes or both

7.4.2. REMAP Exclusion Criteria

A potentially eligible patient who meets any of the following criteria will be excluded from participation in this trial:

1. Healthcare-associated pneumonia:
    a. Prior to this illness, is known to have been an inpatient in any healthcare facility within the last 30 days
    b. Resident of a nursing home or long-term care facility.
2. Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment.
3. Previous participation in this REMAP within the last 90 days

7.4.3. Domain-Specific Entry criteria

Each domain may have additional, domain-specific eligibility criteria, typically just exclusion criteria, although a combination of inclusion and exclusion criteria can be specified. Patients who fulfill the Overall REMAP Eligibility Criteria will be assessed for enrollment into all domains that are active at a

site. A participant enrolled in the trial will receive the number of REMAP-specific interventions equivalent to the number of Domains to which they are enrolled. The additional eligibility criteria that are specific to a domain are provided in each DSA.

Where a participant has an exclusion criterion to one or more interventions within a domain, but there are at least two interventions within that domain to which the participant is eligible the patient will be randomized to receive one of the interventions to which the participant is eligible.

7.5. Interventions

7.5.1. Domain-Specific Information

All information related to the background, rationale, and specification of interventions that will be administered within the trial are located in the DSAs. The minimum number of interventions within a domain is two and the maximum number is limited only by statistical power. Each RMC will select the interventions that will be available within a domain that will be offered to participating sites in that region but the default position is that all interventions that are available and feasible in that region or country should be offered to sites. Individual participating sites will select the interventions within a domain that will be available at their site with the default position being all available interventions. The randomization program will only provide treatment allocations that are permitted at each participating site. This allows interventions that are not necessarily available in all regions, for example because of licensing reasons, to be included within the REMAP. Within the context of comparative effectiveness research, this also allows sites to determine the interventions that are within their usual or reasonable spectrum of care. However, the viability of a domain is dependent on at least one intervention being available in all regions and being available at a substantial
majority of participating sites. This level of 'connectedness' is necessary for the validity of the statistical models that are used to analyze trial results.

7.5.2. Treatment allocation and Response Adaptive Randomization

Random allocation of treatment status forms the basis of all evaluations of causal inference. RAR will be used to vary the proportion of participants who are allocated randomly to each available intervention. Randomization is done at the regimen level, where a regimen is a selection of one intervention from each domain. The proportion of participants who receive a specified regimen will be determined by a weighted probability, with that probability being determined by the probability, taking into account all accrued data, of that regimen being the optimal regimen. RAR will result in participants being randomized with higher probability to interventions that are performing better.

The proportions that are specified by RAR are determined only by analysis of the primary outcome measure in participants who have completed 90 days of follow-up from the time of enrollment. Although outcome may be known before 90 days (death in hospital) the time at which these alternate events occur may be different. By only including participants in the analysis models that determine the RAR proportions potential bias that arises from different events occurring with different patterns of timing within the 90 day follow up period is avoided. The same statistical model will be used to both analyze the results of the REMAP as well as specify the randomization proportions.

RAR weights reflect the probability each particular regimen is the most effective over all possible regimens within each stratum. The probability a regimen is optimal reflects not just the point estimate of difference in outcomes, but also the uncertainty around that estimate. At initiation of a new domain, the proportion of participants allocated to each intervention is balanced (i.e. all interventions have equal proportions). The RAR proportions are then updated at the first adaptive analysis and at all subsequent adaptive analyses. When sample sizes are small, such as at the initiation of a domain, credible (probability) intervals are wide, and therefore randomization proportions remain close to being balanced among all regimens (i.e. randomization weights are weak and allocation remains close to balanced). When a new intervention is added to an existing domain it will commence with balanced randomization and the randomization weights will be updated with each adaptive analysis but will remain weak until sample size for the new intervention accrues.

As the data accrues and sample sizes increase, if the probability an intervention is part of the optimal regimen becomes large, but not large enough to claim superiority, the randomization proportions will be capped. This is done because interventions are provided on an open-label basis and extreme ratios would be at risk of allowing clinicians who recruit participants to draw inference about the effectiveness of individual interventions or regimens.

Some domains may have more than two interventions and it is possible that participant- or site-level characteristics may result in one or more interventions within a domain not being appropriate for an individual participant (for example, known intolerance to one of the interventions or a machine that is necessary to deliver an intervention not being available). Where a participant is unable to receive one or more interventions, but there are still two or more available interventions, random allocation will still be performed using RAR. However, interventions that are not available will be ‘blocked’ and the remaining RAR proportions will be divided by one minus the sum of the unavailable proportions and applied to the available interventions.

A detailed description of the statistical models and the application of RAR is outlined in the Statistical Analysis Appendix.

7.5.3. Adaptation of Domains and Interventions

Over the lifetime of this REMAP, it is anticipated that new interventions will be added to the starting domains and new domains initiated, including domains that are planned for activation in the event of a pandemic. The addition of interventions within existing domains, and the creation of new domains, will be considered according to a set of priorities and contingencies developed by the ITSC and are dependent on existing or new clinical need and there being sufficient statistical power available within the REMAP. All new interventions and domains will be subject to ethics and regulatory approval prior to initiation.

A domain in which an intervention is identified as being superior and for which there are no new interventions that are appropriate to be introduced will continue as a domain within the REMAP but with all participants allocated to receive the superior intervention. Interventions that are identified as being inferior will be removed from a domain, with or without replacement, as appropriate. If all interventions are identified to have equivalence the ITSC will consider options that include cessation of the domain or continuation of the domain with a smaller delta.

The implementation of adaptations that occurs as a consequence of declaration of a Platform Conclusion may be limited by availability of an intervention in some locations. For example, if a superior intervention was not available (for licensing or site-specific reasons) all inferior options would be removed only at the sites where the superior option is available. Randomization to remaining interventions would likely continue at those sites until the superior intervention is available at those sites.

7.6. Endpoints

The primary outcome for this REMAP will apply to all domains. Secondary outcomes generic to all Domains are provided in this Core Protocol below. Secondary outcomes specific to individual domains are provided in the relevant DSAs. The Primary Endpoint (or the end-point that is used for RAR) may be modified during a pandemic and will be outlined in the Pandemic Appendix.

7.6.1. Primary Endpoint

The primary endpoint for all domains will be all-cause mortality at 90 days.

7.6.2. Secondary Endpoints

A set of generic secondary endpoints will be evaluated in all domains. Additional secondary endpoints may be specified for a domain within the DSA. Some domain-specific secondary endpoints may be specified as Key Domain-Specific Endpoints and will be interpreted in conjunction with the primary endpoint in determining the overall effectiveness of interventions.

The generic secondary endpoints for the trial are:

ICU outcomes:

- ICU mortality censored at 90 days;
- ICU LOS censored at 90 days;
- VFDs censored at 28 days;
- OFFDs censored at 28 days;
- Proportion of intubated participants who receive a tracheostomy censored at 28 days;

Ventilator- and organ failure-free days will be calculated by counting the number of days that the participant is not ventilated or has no organ failure. If a participant dies during the hospitalization during which enrollment occurred, the number of VFDs or OFFDs will be set to zero. If the participant is discharged alive from hospital, the remainder of days censored at 90 days are counted as ventilator- or organ failure-free days.

Hospital outcomes:

- Hospital LOS censored 90 days after enrollment;
- Destination at time of hospital discharge (characterized as home, rehabilitation hospital, nursing home or long-term care facility, or another acute hospital);
- Readmission to the index ICU during the index hospitalization in the 90 days following enrollment;

The index hospital admission is defined as continuing while the participant is admitted to any healthcare facility or level of residence that provides a higher level of care than that corresponding to where the participant was residing prior to the hospital admission. (Huang et al., 2016) This definition is used commonly in ICU trials. Participants who have been and still are admitted to a healthcare facility 90 days after enrollment are coded as being alive.

Day 90 all-cause mortality will be collected in all regions. Additional outcomes will be collected, where feasible, may be mandated in a DSA or a RSA, may be collected by central trial staff or site staff, and will comprise:

- Survival at 6 months after enrollment (where feasible, refer to relevant regional RSA)
- HRQoL at 6 months after enrollment using the EQ5D-5L (where feasible, refer to relevant regional RSA)
- Disability status measured at 6 months after enrollment using the WHODAS 2.0, 12-item instrument (where feasible, refer to relevant regional RSA)

7.7. Bias Control

7.7.1. Randomization

Randomization will be conducted through a password-protected, secure website using a central, computer-based randomization program. Randomization will be at the patient level and occur after data necessary to implement the inclusion and exclusion criteria have been entered into the secure randomization website. The RAR will occur centrally as part of the computerized randomization process. Sites will receive the allocation status and will not be informed of the randomization proportions. Each region will maintain its own computer-based randomization program that is accessed by sites in that region but the RAR proportions will be determined by a SAC and provided monthly to the administrator of each region's randomization program who will update the RAR proportions.

7.7.2. Allocation concealment

Allocation concealment will be maintained by using centralized randomization that is remote from study sites.

7.7.3. Blinding of treatment allocation

The default position within the REMAP is that treatments determined by randomization will be provided on an open-label basis. However, the blinding of treatment status is not precluded within the REMAP. If required, details related to blinding of interventions will be specified in the DSAs.

7.7.4. Blinding of outcome adjudication

The primary outcome of all-cause mortality censored at 90 days is not subject to ascertainment bias. Wherever possible, trial management personnel, who are blinded to allocation status, will conduct any follow up after discharge.

7.7.5. Follow up and missing data

Regional trial management personnel will perform timely validation of data, queries and corrections. Any common patterns of errors found during quality control checks will be fed back to all sites. Data management center study personnel performing site checks will be blind to the study allocation. Missing data will be minimized through a clear and comprehensive data dictionary with online data entry including logical consistency rules. If values necessary for the Bayesian modelling of the primary endpoint and the RAR are missing they may be imputed, using available data. For example, if strata or state is missing, it will be multiply imputed based on the available variables and a prior distribution on the relative prevalence of each strata or state. Values for the primary endpoint will not be imputed. Additional details are provided in the Statistical Analysis Appendix.

7.8. Principles of Statistical Analysis

7.8.1. Preface

The purpose of this section of the protocol is to introduce and summarize the statistical methods that will be used to analyze data within the REMAP. This section duplicates some of the information provided in the Statistical Analysis Appendix but this section is intended to be accessible to individuals with an understanding of common clinical trial designs and classical frequentist analytical methods but without necessarily having training in Bayesian statistics. Interpretation of this section also requires an understanding of the meaning of specific terms for which definitions are provided in the glossary (see Section 1.2).

A formal description of the adaptive Bayesian data analysis methods fundamental to the REMAP design, which assumes substantial familiarity with Bayesian calculation of posterior distributions conditioned on observed data, is located in the Statistical Analysis Appendix. There is some limited overlap between these two sections of the protocol so that each may serve an appropriate audience as a standalone description of the statistical methods.

7.8.2. Introduction

Within the REMAP, two or more interventions within a domain are evaluated and sequential Bayesian statistical analyses are used over time to incorporate new trial outcome information to determine if an intervention is superior, if one or more interventions are inferior in comparison to all other interventions, or if one or more pairs of interventions are equivalent, with respect to the primary endpoint. Every participant will be assigned a set of interventions, comprising one intervention from each domain for which the participant is eligible. The combination of interventions to which a participant is assigned comprises the regimen and the regimens are the available arms in the trial. Participants will be classified by membership in different populations defined by one or more strata. The unit-of-analysis for a domain is the most granular level, defined by one or more stratum, or a state, within which the treatment effect of interventions within that domain may vary in the statistical model. Participants are also classified by the criteria that determine eligibility for each domain.

Inference in this REMAP is determined by analyses using pre-specified statistical models that incorporate region, country, time periods, age, and disease severity to adjust for heterogeneity of enrolled participants that might influence risk of death. These models incorporate variables that represent each intervention assigned to participants and possible interactions between interventions in different domains. The efficacy of each intervention within a domain may be modeled as not varying in any of the strata, or possibly varying in one or more of the different strata in the REMAP. Where the efficacy of each intervention within a domain is modeled as possibly varying, borrowing between strata is permitted. The unit-of-analysis that will be modeled may comprise the entire population (i.e. no categorization by strata is applied) or may be defined by one or more stratum. The unit-of-analysis and whether borrowing can occur between strata is pre- specified for each domain. At each analysis the current active statistical model (or models) is (are) used, and may include patients who were enrolled when previous versions of the model were being used. The current model is described in an operational document, maintained by the SAC. Unless otherwise specified (see Section 8.12) modifications and implementation of modifications to the model require the approval of the ITSC and do not require a protocol amendment.

Whenever a model hits a predefined threshold for any of superiority, inferiority, or equivalence for an intervention with respect to the primary endpoint, this is termed a Statistical Trigger. At any given adaptive analysis, a Statistical Trigger may be reached for all participants or for one or more stratum and will be reviewed immediately by the DSMB. When a Statistical Trigger is confirmed by the DSMB, based on a thorough review of the data including an evaluation of the proportion of patients

for whom monitoring of variables that contribute to the model has been completed, and totality of evidence, and where no compelling reason exists not to reach a conclusion (see Section 7.8.9) regarding that question the result that has led to a Statistical Trigger will be specified to be a Platform Conclusion. The declaration of a Platform Conclusion will lead to appropriate modification of the interventions available within that domain and a Public Disclosure of the result. A Statistical Trigger can be considered as a mathematical threshold, whereas a Platform Conclusion is a decision regarding one or more interventions within a domain.

7.8.3. Target populations (strata and states) and implications for evaluation of treatment-by-treatment and treatment-by-strata interactions

Introduction 7.8.3.1.

In a clinical trial there are many different potential participant-level covariates. A covariate can be a demographic variable that remains unchanged throughout the trial (i.e. age or gender) or a variable representing the severity or course of the disease that can vary over time (i.e. it can be assessed at the time of enrollment and at other times after enrollment during the course of the illness). In this REMAP, there are two special roles for a subset of these potentially time-varying covariates.

First, covariates determined at the time of enrollment that are identified in the design as possibly having differential treatment effect (i.e. interventions may have differential efficacy for the different levels of the covariate) are referred to as strata. Strata are used to define the unit-of-analysis for a domain within a model. Strata are a recognized element in Platform Trials.

Second, within this REMAP, there is interest in studying domains that are relevant for a target population or defined disease state that, while it may be present at the time of enrollment for some participants, may only occur after enrollment for other participants and may never occur for another set of participants. This disease state could be identified by the same covariate that might also have been used to define a strata (but doesn't have to have been). In this regard, the concept of 'state' is used to define participants with characteristics that define a target population that will be evaluated by a domain, analyzed within the REMAP, and for which the characteristics can be present at the time of enrollment or may develop after the time of enrollment. State can also be used to define the unit-of-analysis for a domain within the model.

The appropriate statistical handling of the analysis of patients who become eligible for a domain as a consequence of entering a state, after the time of enrollment, requires the use of models that take into account that the likelihood of entering the state after enrollment may have been influenced by

the allocation status for other domains that specified the initiation of interventions that commenced at the time prior to entry into the state.

This evolution of Platform Trial design, to include 'state' is a new extension that has not been considered within Platform Trials conducted previously.

Stratum 7.8.3.2.

A covariate in the REMAP that can be used as a unit-of-analysis within a Bayesian statistical model that allows for the possibility of differential treatment effects for different levels of the variable is referred to as a strata. The covariate is classified into mutually exclusive and exhaustive sets for analysis of treatment effect, as well as for defining separate RAR. The criteria that define a stratum are based on a characteristic that is present at or before the time of enrollment.

The simplest structure for strata is a single dichotomous stratum variable, which divides participants in the REMAP into two stratum. More complex arrangements are possible, such as a single strata variable that is ordinal or two (or more) dichotomous or ordinal strata variables the combination of which defines a single stratum (i.e. there are 2^N stratum when there are N dichotomous stratum variables).

The number of strata variables and the number of strata within the REMAP may be varied, depending on the impact of such decisions on statistical power, as determined by simulations. The modeling of strata may assume no differential effect for some domains. This may occur in two ways. Firstly, when the strata structure defines the entry criteria for a domain. Secondly, when two or more stratum are combined within a single unit-of-analysis (i.e. the unit-of-analysis comprises two or more stratum). If the unit-of-analysis comprises less than all available strata the analysis that is performed assumes that treatment effect does not vary between stratum combined within a common unit-of-analysis. The RAR is applied according to the model. So, the RAR applies to the patients that comprise the unit-of-analysis, irrespective of whether the unit-of-analysis comprises a single stratum or two or more stratum.

A strata variable can be set that is maintained as a silent or 'sleeping' strata which becomes active under pre-defined circumstances, such as the occurrence of a pandemic. In this situation, during the inter-pandemic period, all participants are categorized as non-pandemic but, during a pandemic, a distinction is made between patient with proven or suspected pandemic infection and patients in whom pandemic infection is neither proven nor suspected.

The *a priori* defined strata that are used for determination of results and for RAR may be changed during the life of the REMAP as knowledge is accumulated and, if this occurs, will result in amendment of one or both of the Core Protocol and DSAs. Data from patients enrolled before the change in the strata can be used to determine priors that are incorporated into the model at the outset of the incorporation of the new strata into the model.

Treatment-by-Stratum interactions: borrowing between strata

Where specified in the statistical model, the treatment effect of an intervention is allowed to vary between different strata. A Bayesian Hierarchical Model (BHM) is used for all treatment-by-strata interactions. In the BHM a hyperprior is used for the differing treatment effects across strata. The standard deviation of the hyperprior, gamma, is a modeling starting estimate for the variation in the magnitude of the difference in treatment effects between strata. By default, the starting estimate of the difference is zero. The gamma parameter influences the extent to which the treatment effect of different interventions is permitted to vary between strata. At the commencement of a model, the gamma parameter must be set, for each domain-strata pair.

In this REMAP, only three options are permitted with respect to specifying the gamma parameter for each domain-strata pair. Firstly, gamma may be set to zero. The effect of this is that treatment effect of an intervention is not permitted to differ between specified strata. The unit-of-analysis is not sub-divided according to the stratum variable. If gamma is set to zero for all strata for a domain, the unit of analysis is all patients randomized in that domain. Secondly, and at the opposite extreme, gamma can be set to infinity. In this situation treatment effect is evaluated separately and independently in each stratum (with no borrowing between stratum). Thirdly, gamma may be set to a defined number between zero and infinity. This parameter value cannot be varied for different domain-strata pairs, a global REMAP value has been selected. This specified value for gamma places a constraint on the variance of the difference in treatment effect in different stratum but permits the model to estimate treatment effect in one stratum by borrowing from other stratum. Borrowing occurs to the extent that it is supported by the accumulated data, but the setting of gamma influences the amount of borrowing and how quickly borrowing is able to occur. The value of gamma that has been chosen has been determined by simulations to achieve a compromise between type I and type II error in baseline scenarios that assume either equivalence or superiority. Where a value for gamma is specified in the model, in this REMAP the value of gamma will be 0.15.

The specification of gamma determines the unit of analysis in the model and the extent of borrowing. For each domain-strata pair, the unit of analysis can be all patients (gamma = zero), each stratum with borrowing (gamma = 0.15), or each stratum separately (gamma = infinity).

The gamma that will be set, and hence the unit-of-analysis, for each domain-strata pair is specified in each DSA.

Analysis set for strata, timing of enrollment and timing of information regarding strata membership 7.8.3.4.

It has already been specified that the criteria that define a stratum must be present at or before the time of enrollment. In some situations, the information necessary to determine membership of a stratum may become available after the time of enrollment or may be acquired from information derived after enrollment where the understanding of biology of a disease makes it reasonable to assume that the criteria was met at the time of enrollment. This situation might apply to status with respect to a particular pathogen where results of microbiological testing are not available until after enrollment or when the sample that is tested is not collected until after enrollment.

In this situation randomization is permitted within patients where the criteria is suspected or proven at the time of randomization. With regards to possible infection with a specified pathogen, suspected or proven infection at the time of randomization is sufficient to allow an allocation status to be made. For a patient with suspected infection, membership within the strata is defined by the final test results, but a patient who is suspected but is never tested is analyzed as a positive. If a Platform Conclusion is reached for one or more stratum, analyses will also be done on patients with suspected infection who receive the intervention but who turn out to be negative. Whether borrowing between strata is permitted will be specified in the DSA.

State 7.8.3.5.

A state is a clinical condition of a participant that may change during the course of their treatment. The different states within the REMAP are used to define possible eligibility of the participant for different domains at different times in the trial. A state is a set of mutually exclusive categories, defined by characteristics of a participant, that are dynamic in that they can change for a single participant, at different time-points, during the participant's participation in the REMAP.

The number of state variables and the number of states within the REMAP may be varied, depending on the impact of such decisions on statistical power, as determined by simulations. The same state may be shared by one or more domains but may be different in different domains. The *a priori*

defined states that are used for determination of results and for RAR may be changed during the life of the REMAP as knowledge is accumulated or as domains change and, if this occurs, will result in amendment of one or both of the Core Protocol or DSAs. Data from patients enrolled before the change in the state can be used to determine priors that are incorporated into the model at the outset of the incorporation of the new state into the model.

Timing of randomization and revealing of allocation status

Several different scenarios are recognized that represent different combinations of randomization within a stratum or a state and by the options for the time (at enrollment or later) at which administration of the allocated intervention is commenced.

At the time of enrollment, all participants, are randomized to one intervention in every domain for which the participant is eligible for at enrollment or might become eligible for depending on the progression of the state of their illness (i.e. randomization occurs once and only once at the time of enrollment).

For participants, who at the time of enrollment are eligible for a domain and for which the intervention will be commenced immediately, the allocation status is revealed immediately and the participant then commences treatment according to their allocated intervention. This is referred to as **Randomization with Immediate Reveal and Initiation**.

In circumstances where the participant is eligible for inclusion in the REMAP but is not eligible for a domain at the time of enrollment but might become eligible if the participant's state changes, the participant's allocation status is revealed only if and when the patient enters the state that confers eligibility. This is referred to as **Randomization with Delayed Reveal**.

Another situation applies when eligibility is determined by information that relates to the condition of the patient at the time of initial assessment of eligibility and is relevant to determination of eligibility but is not known until later. In this circumstance, the participant's allocation status can be revealed when the additional information becomes available. Examples of this type of information include the results of microbiological tests and the outcome of a request for consent. Information related to the safety of an intervention in individuals that may change between the time of initial assessment of eligibility and initiation of an intervention may also be reassessed and be used to determine if an allocation status will be revealed. Where initiation of the intervention is deferred pending availability of this additional information, this is referred to as **Randomization with**

Deferred Reveal. It is noted that submission of information regarding microbiological results, consent, or safety information occurs without knowledge of allocation status.

Variation in relation to the timing of revealing and initiation of an intervention has implications to the treatment-by-treatment interactions that are potentially evaluable. Analysis of participants who are enrolled in one or more domains on the basis of Randomization with Immediate Reveal can be conducted within a state, for which membership occurs for at least some participants at the time of enrollment. However, the analysis within this state will also include participants who are enrolled in the same domain on the basis of Randomization with Delayed Reveal with their eligibility for the act of revealing allocation status being defined by progression to the same state at some time-point after enrollment. Participants who are randomized within such a domain, at time of enrollment, but never enter a state that corresponds to eligibility for a domain never have their allocation status revealed and do not contribute to the analysis of treatment effect for interventions in that domain. In this regard, the ITT principle is not violated as the allocation status of such participants is never revealed. The models that are used to provide statistical analysis of the effect of an intervention within a domain that is contained wholly within one state are not able to evaluate interactions with interventions in domains that are defined in different states.

The final scenario to consider involves participants who are enrolled in one or more domains on the basis of Randomization with Deferred Reveal within a stratum. For such participants, their allocation status is revealed at, or close to, the time of deferred initiation of the intervention, when additional information necessary to establish eligibility has become available but relates to information that applies at baseline. Participants in this category are analyzed within baseline stratum in an ITT fashion. As such, the model allows evaluation of interactions with treatments in other domains that share the same stratum. Within such a domain, it can be assumed that there will be some participants who are never eligible to commence receiving the intervention (for example, due to death, or never reaching the defined criteria for the intervention to be commenced) and do not receive the intervention. However, all participants who have an allocation status revealed, even if the intervention is never administered, are analyzed according to and in compliance with the ITT principle.

Treatment-by-Treatment interactions

Where specified in the statistical model, the treatment effect of an intervention is allowed to vary depending on treatment allocation in another domain (i.e. allow evaluation of treatment-by-treatment interaction). A BHM is used for all treatment-by-treatment interactions. In the BHM, a

hyperprior is used for the differing treatment-by-treatment interaction effects. The standard deviation of the hyperprior, lambda, is a modeling starting estimate for the variation in the magnitude of the difference in treatment effect dependent on an intervention assignment in another domain. By default, the starting estimate of the difference is zero (i.e. no interaction). The lambda parameter influences the extent to which the treatment effect of different interventions is permitted to vary dependent on intervention assignment in other domains. At the commencement of a model, the lambda parameter must be set, for each domain by domain pair.

In this REMAP, only three options are permitted with respect to specifying the lambda parameter for each domain-domain pair. Firstly, lambda may be set to zero. The effect of this is that there are no treatment-by-treatment interactions being evaluated between interventions in those two domains. Alternatively, lambda may be set to a defined number between zero and infinity. This parameter value cannot be varied for different domain-domain pairs; a global REMAP value has been selected. This specified value for lambda places a constraint on the variance of the difference in treatment-by-treatment interaction. Borrowing occurs to the extent that it is supported by the accumulated data, but the setting of lambda influences the initial amount of borrowing and the degree of borrowing as data accumulates. The value of lambda that has been chosen has been determined by simulations to achieve a compromise between type I and type II error in baseline scenarios that assume either no interactions or moderate interactions exist. Where a value for gamma is specified in the model, in this REMAP the value of gamma will be 0.075. The third choice is to allow no borrowing of the treatment-by-treatment interactions. This is equivalent to selecting a lambda of infinity. This choice would be the most aggressive choice in estimating treatment-by-treatment interactions.

The lambda that will be set for each domain-domain pair is specified in each DSA.

7.8.3.8. *Nested analysis of interventions within a domain*

Within domains in which there are three or more interventions, some interventions may be more likely to have a similar treatment effect. There are several examples of such similarity. For example, the interventions within a domain may comprise a no intervention option and two doses or strategy of administration of the same intervention, or two or more interventions within a domain may belong to the same class of drug than one or more other interventions in that domain.

In situations in which interventions may be more similar than others, the model may nest the more similar interventions within a higher-level intervention category that comprises all the interventions deemed similar. In this situation, and to evaluate the occurrence of a Statistical Trigger, there are two models for analysis. Firstly, all patients receiving the nested interventions, treated as a single

combined intervention, are compared with all other interventions in the domain. Secondly, all interventions are modeled individually. In this analysis, the interventions within a nest are modeled using a BHM incorporating the nesting structure. The BHM has a hyperprior specified for the shrinkage across interventions within the nest. This analysis will compare all interventions within a domain to all other interventions. This BHM analysis is used for the RAR assignments.

Whether nested analysis will be performed and, if so, the membership of category of more similar interventions will be specified in the DSA.

Current strata and states

The strata are defined, at the time of enrollment, by:

- Shock, defined in 2 categories, present or absent, with present defined as the patient is receiving continuous infusion of intravenous vasopressor or inotrope medications at the time of enrollment
- Influenza defined in two categories, present or absent, based on the results of microbiological tests for influenza. Any patient with suspected influenza who is not tested will be deemed positive. Any patient who is not suspected of having influenza and is not tested will be deemed negative. The availability and interpretation of microbiological tests are likely to change during the REMAP and an operational document will be used to specify how different tests are interpreted. Eligibility for a domain that tests antiviral medications active against influenza will be based on status with respect to influenza being proven or suspected at time of enrollment but it is noted that strata status is defined by the final results of influenza testing which may not be known at time of enrollment and may include analysis of samples collected after enrollment where it is reasonable to presume that the sample reflected influenza status at time of enrollment.
- Pandemic infection defined in two categories, proven or suspected pandemic infection or neither proven nor suspected pandemic infection. This is a 'sleeping strata' and will not be active before or after a pandemic but may be activated during a pandemic. The decision to activate a pandemic infection strata is specified in the Pandemic Appendix to the Core Protocol.

The default states are defined by the occurrence of:

- Hypoxemia, defined in 3 categories, comprising participants who are not receiving invasive mechanical ventilation; participants who are receiving invasive mechanical ventilation and

have a ratio of arterial partial pressure of oxygen to fractional inspired concentration of oxygen (P:F ratio) of ≥ 200 mmHg or are receiving invasive mechanical ventilation with the Positive End-Expiratory Pressure (PEEP) set to less than 5 cm of water (irrespective of the P:F ratio); and participants who are receiving invasive mechanical ventilation with a PEEP of 5 cm of water or more and have a P:F ratio of <200 mmHg.

The domains to which each strata or state applies, the unit-of-analysis (which determines which if any treatment-by-strata interactions are evaluated in the model), the relationship between the timing of domain eligibility and the revealing of allocation status, whether nested analysis will occur, and what treatment-by-treatment interactions will be evaluated are specified in each DSA.

7.8.3.10. Pre-specified subgroup analysis after achievement of a Platform Conclusion

Following the achievement of a Platform Conclusion it is permissible for additional sub-group analyses to be conducted. The variables that specify such sub-groups are outlined *a priori* in each DSA. These variables are different to those that define strata or states in the model and are not used in determination of a Statistical Trigger or RAR for that domain. In a domain in which the unit-of- analysis comprises two or more stratum, additional sub-group analyses can be conducted for variables that do specify stratum that have been combined to determine the unit-of-analysis.

All such analyses will only be conducted following the determination of a Platform Conclusion and, although reported, such analyses are always regarded as preliminary. Following a Platform Conclusion, the results of a pre-specified subgroup analysis may be used to make changes to the model and, where appropriate and to an appropriate degree, data derived from the REMAP can be used to set the prior distribution at the commencement of the new model.

7.8.4. Bayesian Statistical modeling

Inferences in this trial are based on a Bayesian statistical model, that will calculate the probability of superiority, inferiority, and equivalence of the interventions (known as a posterior probability distribution) within a unit-of-analysis that is defined by one or more stratum, taking into account the evidence accumulated during the trial (based on data on the outcomes of participants) and on assumed prior knowledge (known as a prior distribution). For the evaluation of the main effects of interventions within a domain (and evaluation of regimens) the default design assumes that parameters in the model have uninformative prior distributions at the first adaptive analysis. This means that any subsequent Platform Conclusion is not capable of being influenced by any discretionary choice regarding the pre-trial choice of prior distribution (i.e. it is the most

conservative approach, making no assumptions regarding the prior distribution). At each subsequent adaptive analysis, the prior distribution is determined by all accumulated data available at the time of the adaptive analysis. The Bayesian approach is seen as continually updating the distribution of the model parameters.

It is not precluded that, under certain circumstances, such as during a pandemic and where there was strong prior evidence along with an ethical imperative to evaluate a particular choice of therapy, that the design could allow an informative prior to be used for the analysis of results from the trial. It may also be permitted to use an informative prior when data that is incorporated in the informative prior is derived from patients already randomized within this REMAP. If informative priors are used this will be specified in the relevant DSA.

The study design can use informed priors to guide some elements of the design, such as for the evaluation of interaction terms, and will be described in the Statistical Analysis Appendix. As outlined above, gamma will be set to allow and influence the evaluation of treatment-by-strata interactions and lambda will be set to allow and influence the evaluation of treatment-by-treatment interactions.

This method of statistical analysis differs from conventional (frequentist) trials. Frequentist statistics calculate the probability of seeing patterns in the data from a trial if a hypothesis is true (including patterns not observed). This approach relies on assumptions about frequency distributions of trial results that would arise if the same trial were repeated *ad infinitum*. Thus, it requires specific sample sizes, which in turn requires pre-experiment assumptions regarding plausible effect sizes and outcome rates. Although many clinicians are comfortable with this approach, the pre-trial assumptions are frequently incorrect, and the design lacks the flexibility either to easily address the complex questions more reflective of clinical practice or to make mid-trial corrections when the pre- trial assumptions are wrong without concern that the integrity of the final analysis is violated. To allow increased flexibility and yet still generate robust statistical inferences, REMAP relies on an overarching Bayesian, rather than frequentist, framework for statistical inference.

A Bayesian approach calculates the probability a hypothesis is true, given the observed data and, optionally, prior information and beliefs. The advantage of this approach is that, as more data are accrued, the probability can be continually updated (the updated probability is called the posterior probability). In this trial, frequent adaptive analyses will be performed, creating a very complicated sample space, and hence the Bayesian approach is a very natural one for these adaptive designs. The characterization of the risk of false positive error, or power, are done through Monte Carlo trial

simulation. In contrast to frequentist confidence intervals which have awkward direct interpretation, Bayesian analyses return probability estimates that are directly interpretable as probabilities that statements are true (like the probability that one intervention is superior to another).

A number of variables are incorporated into the statistical model so as to provide 'adjustment'. The variables for which such adjustment will be made will be the country in which a participant is treated, changes in outcome that occur over time (era), stratum and state at enrollment (shock and hypoxemia as measures of severity of illness), and age.

The main effect in the model is the treatment effect of each intervention. Each stratum, combination of stratum, or state (where eligibility is defined by a state) is analyzed separately but the model captures the commonalities across such sub-groups. Additionally, and where specified, the statistical model allows evidence relating to the effectiveness of an intervention in one stratum to contribute (via 'borrowing') to the estimation of the posterior probability in other strata, but this only occurs to the extent that treatment effect is similar in different strata.

When a Platform Conclusion is achieved, the results derived from the model, including any contribution from borrowing, will be reported. It is acknowledged that the estimate of treatment effect for a stratum may be contributed to by borrowing from adjacent strata but the results from the strata that have contributed to borrowing will not be reported. The results of these analyses are used to achieve the primary objective of the trial which is to determine the effectiveness of interventions and, where specified, the extent to which that effectiveness varies between strata (intervention-stratum interaction). Additionally, but only where specified *a priori*, the model is able to estimate the effectiveness of an intervention in one domain contingent on the presence of an intervention in another domain (treatment-by-treatment interaction). Although the model can identify an optimal regimen this is not the primary objective of the trial.

Greater detail of the methods within the Bayesian model to be applied in this REMAP are provided in the Statistical Analysis Appendix. The adaptive analyses will use data submitted from participating sites to their regional database. Each provider of regional data management will provide regular updates of data to the SAC for utilization in the adaptive analyses. The frequency of adaptive analyses will occur approximately monthly, unless the amount of data in a month is deemed insufficient. The timely provision of outcome data from participating sites is critically important to the conduct of frequent adaptive analyses.

7.8.5. Statistical Handling of Ineligible Participants

The goal of this REMAP is to enroll as wide a participant population as possible. Because of this and the desire to explore multifactorial regimens it will not be uncommon that a participant will be ineligible for single interventions or entire domains, or interventions may be temporarily unavailable for use. In this section we present the details for how this REMAP deals with these possible circumstances.

If an intervention is unavailable at the time of randomization due to site restrictions (for example, exhausted supply or unavailable machinery) then the participant will be randomized to all remaining interventions and this participant will be included in the primary analysis set as though they were randomized unrestricted to their assigned intervention.

If a participant is ineligible for an entire domain then that participant will not be randomized to an intervention from that domain. The participant will be randomized to a regimen from all remaining domains. As long as the participant is randomized within at least one domain they will be included in the primary analysis. For the ineligible domain the participant will be assigned a covariate for that domain reflecting the ineligibility for the domain. This allows the model to learn about the relative efficacy of the remaining interventions in the domains in which the participant has been randomized. If there is a domain with only two interventions and participant is ineligible for one of the two then the participant will be treated as though they are ineligible for the domain. If there is a domain with more than two interventions but a participant is ineligible for all but one then the participant will be deemed ineligible for the domain. If a participant is only eligible for one intervention within a domain the allocation process may still provide a recommendation that the only available intervention should be provided to the participant (but this is so as to reinforce trial processes associated with successful embedding and such patients will not be included within any analysis of the relevant domain).

If there is a domain with more than two interventions and the participant is ineligible for at least one due to a patient-level factor (for example known intolerance to an intervention), but eligible for at least two, then the participant will be randomized among those interventions that the participant is eligible to receive. The participant will have their assignment included in the primary Bayesian model with an appropriate covariate identifying their ineligibility status that takes into account that a patient-level factor that determines partial eligibility could be associated independently with outcome. The impact of participants with partial eligibility will be taken into consideration by the

DSMB at the time of consideration of whether a Platform Decision is appropriate following a Statistical Trigger.

7.8.6. Intervention Superiority Statistical Trigger

At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being a member of the optimal regimen, for that unit-of-analysis, then that intervention will be deemed as being superior to all other interventions in that domain in that target population. This Statistical Trigger may also be applied for a state that defines the target population for a domain.

7.8.7. Intervention Inferiority Statistical Trigger

At any adaptive analysis, if a single intervention has less than a 0.01 posterior probability of being a member of the optimal regimen, for a unit-of-analysis, then that intervention will be deemed as being inferior for that target population. If superiority and inferiority were to be discovered simultaneously (for example when there are two interventions), the result will be interpreted as demonstrating superiority. This Statistical Trigger may also be applied for a state that defines the target population for a domain.

7.8.8. Intervention Equivalence Statistical Trigger

If two interventions within a domain, for a unit-of-analysis, have at least a 0.90 probability of being within a pre-specified delta for the primary endpoint then these interventions will be deemed as being equivalent. The size of the pre-specified odds ratio delta is 0.20, meaning equivalence is reached with at least a 90% probability of neither intervention increasing the odds ratio of mortality by more than 0.20. An odds ratio delta of 0.2 has been chosen on the basis that it is consistent with guidance from the Food and Drug Administration (FDA) (U.S. Department of Health and Human Services, 2016) and the European Medicines Agency (EMA) (European Medicines Agency, 2005), as well as discussed in academic literature, and the magnitude of treatment effect that has been specified in published superiority trials that enroll patients who are critically ill (Aberegg et al., 2010, Ware and Antman, 1997, European Medicines Agency, 2005, U.S. Department of Health and Human Services, 2016). A measure of relative treatment effect (odds ratio) is specified, rather than an absolute difference in treatment effect. This choice is made because it is reasonable to expect the mortality rates to vary between strata, and the relative effect is a more robust analysis method across these differences.

In a domain with two interventions equivalence is evaluated between the single pair of interventions. In a domain with more than two interventions, equivalence is evaluated for every possible pairwise comparison.

A DSA may define levels of delta for equivalence that are different from the default delta. This includes the possibilities of specifying a delta that may be asymmetrical for some or all pair-wise comparisons or both. The DSA will set out the rationale for any variation in delta and may include, but are not limited to, cost or burden.

This Statistical Trigger for equivalence may also be applied for a state that defines the target population for a domain.

7.8.9. Action when a Statistical Trigger is achieved

Introduction 7.8.9.1.

If a Statistical Trigger is achieved this will be communicated by the SAC to the DSMB. Subject to the DSMB confirming that a Statistical Trigger has been reached validly, the DSMB will oversee a range of actions, as follows.

7.8.9.2. *Actions following Statistical Trigger for superiority*

If an intervention triggers a threshold for superiority and the DSMB declares this as a Platform Conclusion, the intervention is deemed as being superior. At that point randomization to all other remaining interventions in the domain in that unit-of-analysis will be halted at sites at which the superior intervention is available (randomization to the non-superior interventions may continue at sites at which the superior intervention is not available pending its availability). The result will be communicated to the ITSC who will take responsibility to undertake Public Disclosure as soon as practicable with the dissemination of the research result via presentation or publication or both.

Within the REMAP and at sites with access to the superior intervention, all participants will be allocated to the superior intervention (while still being randomized to interventions from the other domains). In this regard the domain remains active with what can be considered as 100% RAR to the superior intervention, pending the addition of any new interventions to be evaluated against the current superior intervention. It is also possible that a superior intervention will be retained but subject to further evaluation, by randomization, to refine the optimal characteristics of the superior intervention (for example duration of therapy or optimal dose).

7.8.9.3. *Actions following Statistical Trigger for inferiority*

If the trial triggers a threshold for inferiority and the DSMB declares this as a Platform Conclusion, the intervention is deemed as being inferior. At that point the intervention will not be randomized to any more participants in that unit-of-analysis. The result will be communicated to the ITSC who will take responsibility to undertake Public Disclosure as soon as practicable with the dissemination of the research result via presentation or publication or both.

Where a Platform Conclusion is reached for superiority or inferiority, the DSMB may recommend that Public Disclosure should be delayed until additional results are available, so as to allow further recruitment to evaluate interactions between interventions in different domains or for other clinically or statistically valid reasons. However, declaration of a Platform Conclusion will always result in the removal of inferior interventions from a domain and that all eligible participants within the REMAP receive a superior intervention.

7.8.9.4. *Actions following Statistical Trigger for equivalence*

If a Statistical Trigger arises because one or more pairs of interventions are deemed as being equivalent within a unit-of-analysis, this will be communicated to the ITSC by the DSMB. The ITSC in conjunction with the DSMB may undertake additional analyses, for example, of clinically relevant secondary endpoints.

The approach to a Statistical Trigger for equivalence is different depending on the number of interventions within a domain.

For domains with only two interventions a valid Statistical Trigger for equivalence will be reported as a Platform Conclusion. With respect to the adaptation of the domain, the following actions are possible:

- Removal of the domain from the Platform
- Switching the allocation status to deterministically assign one of the Interventions, for example the less burdensome or less expensive intervention
- No change to the interventions within the domain with continuation of RAR. This could be to further evaluate secondary endpoints, a smaller delta of equivalence, or interest in interactions with other Interventions. Such changes would require amendment to the DSA.

Factors that should be taken into account by the DSMB and the ITSC include the results of the primary analysis, analysis of clinically relevant secondary end-points, the possibility of treatment-by- treatment interactions, the relative burden and cost of the two interventions, the clinical interpretation of the adequacy of the delta, and the possibility that ongoing randomization with a smaller delta might also allow a Statistical Trigger for superiority (with a small effect size).

The options following a Statistical Trigger for a pair of Interventions in a Domain with three or more Interventions are more complex. Within a domain with three or more interventions the information provided by the DSMB to the ITSC may include specification of the ordinal rank of the equivalent interventions within the domain. With respect to reporting of Platform Conclusions and adaptations of the domain the following actions are possible:

- A pair of equivalent interventions may be compressed into a single group for the purposes of ongoing analysis. Both interventions continue to be interventions that are available within the domain for allocation, but the primary analysis considers the effect of the two interventions as a single group, where a balanced randomization will be assigned to each of the intervention pair within this compressed group. Secondary analyses can continue to be conducted to determine if equivalence is maintained with the possibility of the intervention being restored as individual interventions if results no longer support equivalence. It is acknowledged that re-analysis of the domain immediately following compression of one (or more) pairs of equivalent interventions may result in the occurrence of other Statistical Triggers (e.g. a compressed pair may be superior or inferior to all remaining interventions). Any statistical Trigger that results from compression of one or more pairs will be responded to as outlined in this section with reporting of the cascade of Statistical Triggers. Compression of a pair of interventions can occur with or without reporting of a Platform Conclusion.
- Removal of one of the pair of equivalent interventions from the domain, for example the more burdensome or more expensive intervention, which will result in a reporting of a Platform Conclusion.
- No change to the interventions within the domain with continuation of RAR. This could be to further evaluate secondary endpoints, a smaller delta of equivalence, or interest in interactions with other interventions. Such changes would require amendment to the DSA. This could occur with or without reporting a Platform Conclusion.

Factors that should be taken into account by the DSMB and the ITSC include the results of the primary analysis, analysis of clinically relevant secondary end-points, the possibility of treatment-by- treatment interactions, the relative burden and cost of the two interventions, the clinical interpretation of the adequacy of the delta, the possibility that ongoing randomization with a smaller delta might also allow a Statistical Trigger for superiority (with a small effect size) and the ordinal position of the equivalent pair within the domain.

In a domain that comprises three or more interventions, but in which two or more interventions are analyzed in a nested manner, the nested group may be combined for analyses of equivalence. Where compression converts a domain with three or more interventions into a domain with two interventions (and data continues to support equivalence of the compressed interventions) such a domain will be regarded as a two-intervention domain for the purposes of evaluation of Statistical Triggers for superiority, inferiority, and equivalence.

If a Platform Conclusion is reached, the ITSC will take responsibility to undertake Public Disclosure as soon as practicable with the dissemination of the research result via presentation or publication or both. There is no automated adaptation when equivalence is deemed to have occurred. Where appropriate each DSWG will produce an operational document, that is publicly accessible, that considers a range of plausible scenarios and provides guidance as to the actions that should occur in the event of a Statistical Trigger for equivalence for different pairs of interventions. If any of these documents are updated, previous versions will be archived but continue to be publicly accessible.

7.8.10. Analysis set for reporting

The primary analysis set that will be used for reporting a Public Disclosure will comprise all participants who are analyzed at the time the adaptive analysis results in the occurrence of a Statistical Trigger. As such, there will be some participants who have been randomized but are not included within this analysis, either because participants have not yet completed 90 days of follow up or because data for a participant who has completed 90 days of follow up has not yet been submitted. At the time of Public Disclosure, a secondary analysis will also be reported that comprises all participants who are evaluable through to the point at which there was cessation of randomization to the relevant comparator arms.

7.8.11. Simulations and statistical power

The design of the trial, at initiation, and in conjunction with the planning of the introduction of new interventions within a domain or of new domains, will be informed by the conduct of extensive

simulations using standard Monte Carlo methods. Simulations will be updated whenever a new intervention is added within a domain or whenever a new domain is added to the REMAP. However, simulations will not be updated when an intervention is removed from a domain because of the declaration of a Platform Conclusion that the intervention is inferior. These simulations will evaluate the impact of a range of plausible scenarios on the statistical properties of the trial.

Existing simulations indicate that when a single intervention in a domain with two interventions is beneficial, with a constant benefit for all participants, the power to be determined superior to the complement intervention as a function of its odds-ratio benefit is greater than 90% when there is at least a 25% odds-ratio decrease in the probability of mortality for the funded sample size of 6800 participants. The timing of these conclusions of superiority have a median time of less than 2000 participants. The probability that an intervention will be deemed superior to a complementary intervention when in truth the two are equal (a type I error) is typically less than 2.5%.

The results of detailed simulations of current domains is located in the Simulations Appendix which is maintained as an operational document that is publicly accessible and updated as required.

7.8.12. Updating model after monitoring

If any variable that contributes to the model is identified to be inaccurate at a monitoring visit, the data will be corrected and utilized for the next interim analysis. Any change to a previous statistical trigger will be reviewed by the DSMB to determine the implications. The DSMB will advise the ITSC if there is any material change in a Platform Conclusion which, if published, will be reported to the journal as an erratum.

7.9. Co-enrollment with other trials

Co-enrollment of participants in other research studies, including interventional trials, is strongly encouraged. The principle is that co-enrollment should always occur and is only not permitted when there is a clear threat to the validity of either study or it would materially influence the risk to participants. Decisions regarding co-enrollment with other trials will be made on a trial-by-trial basis. Where a potentially co-enrolling trial is being conducted in more than one region in which the REMAP is being conducted the decision regarding co-enrollment will lie with the ITSC. Where a potentially co-enrolling trial is being conducted only in one region in which the REMAP is being conducted the decision regarding co-enrollment will lie with the RMC. In all circumstances the ITSC and RMCs should liaise regarding decisions about co-enrollment. Decisions regarding co-enrollment

with other trials will be distributed to participating sites as an operational document and will not require or involve amendment of this protocol.

7.10. Cooperation between the REMAP and other trials with overlapping populations or interventions

During the life-time of the REMAP it is likely that there will be many other clinical trials that will have inclusion and exclusion criteria which would include participants who are eligible for this REMAP. This would include, obviously, trials with a primary interest in patients with CAP, but could also include patients with the Acute Respiratory Distress Syndrome (ARDS) and patients with severe sepsis or septic shock. Such trials will likely test a range of interventions, some of which may also be intervention options within this REMAP. This REMAP seeks to cooperate and coordinate maximally with other trials. Examples of such cooperation and coordination would include, but not be limited to, utilization of REMAP infrastructure for screening and recruitment to other trials, sharing of data collected by the REMAP, and sharing of allocation status so as to allow incorporation of allocation status within analysis models.

Where another trial is evaluating an intervention that is also included within this REMAP each site (or region) would need to establish rules that determine circumstances in which each trial has preference for recruitment. Where another trial and this REMAP are evaluating different interventions the extent to which cooperation is possible will also be determined by the extent to which the interventions are compatible, i.e. capable of having their effect evaluated independently within each trial.

7.11. Registry of non-randomized patients

In some locations, the REMAP may be nested within a registry. Where this occurs the operation of the registry, including eligibility criteria, ethical issues, and variables that will be collected, will be described in a separate Registry Appendix.

7.12. Criteria for termination of the trial

This trial is designed as a platform, allowing for continued research in patients with CAP admitted to an ICU. The platform allows for the study to be perpetual, with multiple different domains that can be evaluated at any one time, and over time. Frequent adaptive analyses are performed to determine whether the interventions under evaluation are still eligible for further testing or randomization should be stopped due to demonstrated inferiority, superiority or equivalence.

It is anticipated that after inclusion of the initially planned sample size, the study would continue to include additional participants and test additional domains and/or interventions until one of the following occurs:

- CAP is no longer deemed to be a public health problem
- The effectiveness and/or cost-effectiveness of all interventions are known and there are no new plausible interventions to test

Should the whole study be stopped, the end of trial is the date of the last scheduled follow up for any participant.

8. TRIAL CONDUCT

8.1. Site time-lines

8.1.1. Initiation of participation at a site

A range of options are available for the sequence of activities by which a site commences participation. The following outlines the default sequence of participation. The first level of participation is termed 'observational only'. During this stage eligible participants will be identified, preferably using a process of embedding with recognition by clinical staff and registration on the study website as soon as eligibility is recognized. Treatment decisions will be made by that site's clinical staff, and observational data using the study CRF or a sub-set of the CRF will be collected. The next level of participation is termed 'single domain'. During this time period, eligible participants are identified and randomized, but only within a single domain. The next level of participation is termed 'multiple domains' although this would typically include only the addition of a single domain at any one time-point with staggered introduction of additional domains. Decisions about transition through levels would be made by the site, in conjunction with the RCC, and would be influenced by factors including speed and accuracy of identification of eligible participants, accuracy of information provided at time of randomization, compliance with allocated treatment status, and timeliness of reporting of outcome variables that are used to determine RAR algorithms. It is also permissible to commence the trial with multiple domains being active at initiation.

8.1.1. Vanguard sites

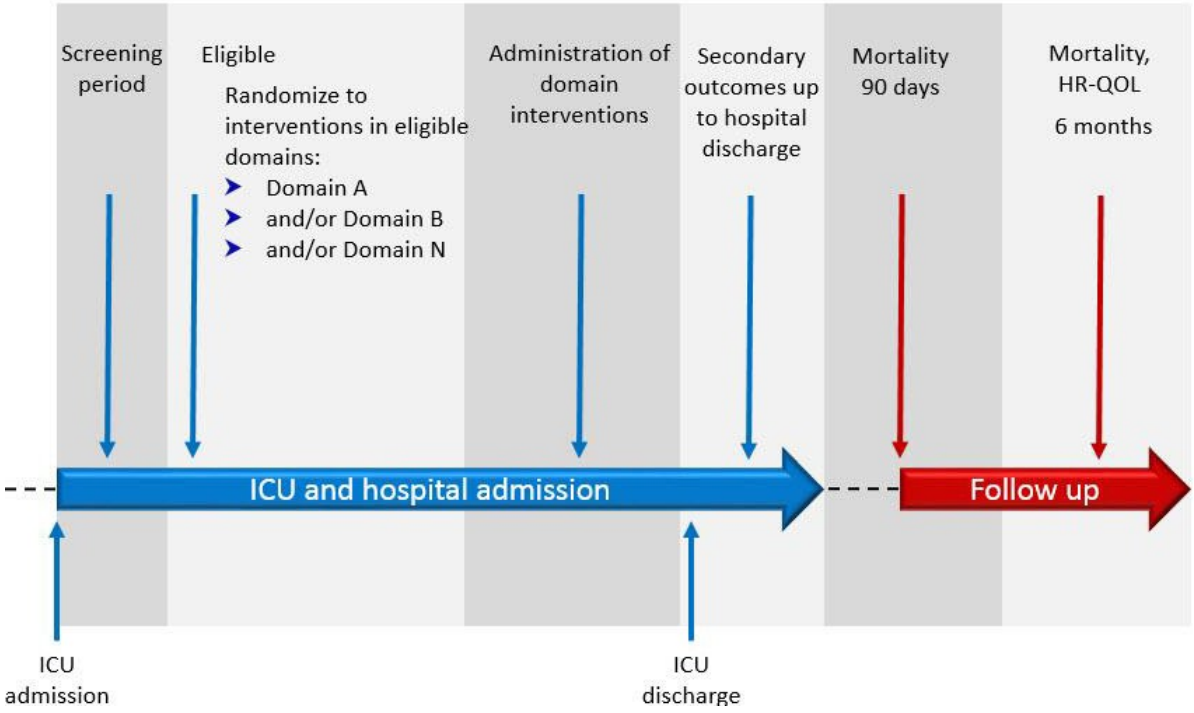
In each region or at the initiation of a new domain or both, the trial may consider commencing with only a small number of vanguard sites. The purpose of commencing the trial at vanguard sites is to learn about the effectiveness of different options for trial processes so that this information about

the most effective trial processes can be shared with subsequent non-vanguard sites. If a site is acting as a vanguard site this will be specified in any application for ethical approval at that site.

8.2. Summary of time-lines for recruited participants

A summary of the study and follow up schedule is outlined in Figure 6.

Figure 6: Study Procedures



8.3. Recruitment of participants including embedding

8.3.1. Embedding

The trial is designed to substitute allocation of treatment status by randomization where otherwise a treatment decision would have been made by clinical staff (where it is clinically and ethically appropriate to do so), and for this to occur at the time that the treatment decision would have otherwise been made. It is not essential that embedding is used to achieve recruitment and randomization but it is preferable and it is encouraged that participating sites work in conjunction with the trial team to achieve embedding wherever possible and as soon as possible.

The success of embedding can be evaluated by the proportion of eligible participants who are recruited and randomized, that recruitment and randomization occurs as soon as possible after

eligibility occurs, and that there is compliance with the allocated intervention. Successful embedding will enhance the internal and external validity of the results generated by the trial.

Each site, taking into account its own clinical work practices, will be asked to develop internal processes that will be used to achieve successful embedding. Wherever possible the RCC will advise and assist sites to achieve successful embedding. In brief, each participating site will identify their ICU admission procedures that occur with each new patient and then align these procedures to facilitate assessment of eligibility by clinical staff who provide routine care for each patient. This can be achieved through several methods including checklists on electronic Clinical Information Systems (eCIS).

8.3.2. Participant recruitment procedures at participating units

Once screened and identified as eligible the clinical staff (medical or nursing) or research staff will randomize the participant. Standard Operating Procedures (SOPs) will be developed to guide staff who undertake randomization. For example, in ICUs with an eCIS, an integrated website link may be used to allow direct access to the trial randomization webpage and, where possible, provide a summary (or direct population from the eCIS) of information that is required to be entered into the randomization web-site. To complement this system the research staff in each ICU will review patients admitted each day to assess the suitability of patients deemed not eligible out of hours, either because they were missed on screening or because the clinical situation has changed.

8.4. Treatment allocation

An eligible participant will receive a treatment allocation that is determined for all domains for which the participant is eligible to receive at least one of the available interventions. The management of the randomization process in each region is specified in each RSA. Information related to RAR is presented in the Interventions section of the Trial Design (Section 7.5.2) and in the Statistical Analysis Appendix. As noted elsewhere, all randomized allocation will be determined at the time of initial enrollment, but allocation status will not be made known for domains that operate using Randomization with Delayed Reveal (see Section 7.8.3.4). If the participants clinical condition changes and enters the state that confers eligibility this information will be provided to the randomization web-site and the allocation status will be revealed to the site.

8.5. Delivery of interventions

8.5.1. Treatment allocation and protocol adherence at participating units

In conjunction with participating sites, trial management staff will develop generic and site-specific documents that outline processes for implementation of and facilitate adherence with participant's allocated treatment status. Wherever possible these will seek to integrate trial processes with existing routine treatment processes to allow seamless adoption of the allocated treatments. For example, after randomization the clinical staff will be directed to use a pre-populated order sheet, necessary for the treating clinicians to authorize and for a bedside nursing staff to follow allocated treatment processes for that individual participant. It is intended that this process will not only reduce the complexity of ordering the study treatments but also reduce errors and increase adherence to the allocated protocol.

With respect to blinding, the default position within the REMAP is that treatments determined by randomization will be provided on an open-label basis. Where interventions are conducted on an open-label basis, all members of the ITSC and all other staff associated with a RCC of the trial will remain blinded until a Platform Conclusion is reported by the DSMB. Although the default is the provision of open-label treatments the blinding of treatment status is not precluded within the REMAP. Whether interventions are open-label or blinded will be specified in DSAs.

8.6. Unblinding of allocation status

Unblinding of any blinded treatment by site research staff or the treating clinician should only occur only in when it is deemed that knowledge of the actual treatment is essential for further management of the participant. A system for emergency unblinding will be provided in the DSA of any domain that includes interventions that are administered in a blinded fashion. Any unblinding process will ensure that the investigator can directly and rapidly unblind in an emergency situation. All unblindings and reasons as they occur will be documented in the CRF. Unblinding should not necessarily be a reason for study drug discontinuation.

8.7. Criteria for discontinuation of a participant in the trial

Trial participants may be discontinued from the trial entirely or from one or more domain-specific interventions according to predefined criteria for discontinuation. The criteria for discontinuation specific to each domain are specified in the relevant DSA.

Criteria for discontinuation from the REMAP interventions entirely include:

1. The treating clinician considers continued participation in the REMAP interventions are not deemed to be in the best interests of the patient
2. The participant or their Legal Representative requests withdrawal from ongoing participation in all REMAP interventions

In the case of discontinuation, the reasons for withdrawal will be documented. Consent to the use of study data, including data collected until the time of discontinuation and data to inform primary and secondary outcome data will be requested specifically from participants or their Legal Representative who request discontinuation. Following discontinuation of a REMAP intervention, participants will be treated according to standard ICU management. Participants who are withdrawn will not be replaced. All data will be analyzed using the ITT principle.

8.8. Concomitant care and co-interventions

All treatment decisions outside of those specified within the REMAP will be at the discretion of the treating clinician. Prespecified co-interventions related to specific domains will be recorded in the CRF and are outlined in the relevant DSAs.

8.9. Data collection

8.9.1. Principles of data collection

Streamlined data collection instruments and procedures will be used to minimize the workload in study sites. The CRF will be developed by the ITSC and made available to the participating sites as a paper and electronic CRF (eCRF) for ease of data collection. Data may be entered directly into the eCRF or first entered onto a paper copy of the CRF and entered subsequently into the eCRF. All data will be collected by trained staff who will have access to a comprehensive data dictionary. Information recorded in the CRF should accurately reflect the subject's medical/ hospital notes, must be completed as soon as it is made available, and must be collected from source data. The intent of this process is to improve the quality of the clinical study including being able to provide prompt feedback to the site staff on the progress, accuracy, and completeness of the data submitted. The eCRF will be web-based and accessible by a site or investigator specific password protected.

8.9.2. Variables to be collected

The generic variables to be collected for all domains in this REMAP are as detailed, indicatively, in the Core Protocol, below. Additional domain-specific variables are outlined in the relevant DSAs. Baseline variables are defined as at or before the time of randomization.

8.9.2.1. *Baseline and required for randomization*

- Overall REMAP Inclusion / exclusion check list
- Date and time of hospital admission
- Date and time of first ICU admission
- Domain-specific exclusion checklist
- Shock status
- Hypoxemia status
- Influenza status
- Pandemic status

8.9.2.2. *Baseline but not required for randomization*

- Demographic data (date of birth, age, sex, estimated body weight and height)
- Co-existing illnesses and risk factors for pneumonia
- Source of ICU admission
- Acute Physiology and Chronic Health Evaluation (APACHE) II variables
- Sequential Organ Failure Assessment (SOFA) variables
- Intervention allocation status within domains and randomization number
- Results of microbiological testing

8.9.2.3. *Daily from randomization until discharge from ICU or Day-28 whichever comes first*

- Hypotension and administration of vasopressors/inotropes
- Administration of dialysis
- Administration of invasive or non-invasive ventilation
- P:F ratio components

8.9.2.4. *ICU Outcome data*

- Date and time of ICU discharge
- Survival status at ICU discharge

- Dates of ICU readmission and discharge

Hospital outcome data 8.9.2.5.

- Date and time of hospital discharge
- Survival status at hospital discharge
- Discharge destination
- Results of microbiological testing

Antimicrobial Administration 8.9.2.6.

- Administration of antibiotic medications
- Administration of antiviral medications

Outcome data 8.9.2.7.

At the discretion of the site, unless specified otherwise in a RSA or DSA, and collected by phone:

- Survival status at 90 days
- Survival status at 6 months
- HRQoL measured by EQ-5D at 6 months
- Disability status measured by WHODAS at 6 months and baseline information to interpret disability
- Opinions and beliefs regarding participation in research (reported at 6 months)

Process-related outcomes 8.9.2.8.

- Time from index hospital admission to ICU admission
- Time from ICU admission to randomization
- Selected co-interventions
- Compliance with allocated intervention(s).

8.9.3. Data required to inform Response Adaptive Randomization

This REMAP will use frequent adaptive analyses and incorporate RAR. All variables used to inform RAR will be pre-specified. The key variables include:

1. Baseline and allocation status
    a. Unique trial-specific number
    b. Location (Country and Site code)

c. Date and time of randomization
d. Eligibility for each domain
e. Intervention allocation for each domain
f. Reveal status for each intervention allocation for each domain
g. Age category
h. Strata
    i. Shock or no shock
    ii. Influenza status
    iii. Pandemic strata
i. State
    i. Hypoxemia

2. Outcome
    a. All-cause mortality at 90 days
    b. Date of hospital discharge

Data fields required to inform the adaptive randomization process and Statistical Trigger will be pre-specified and will be required to be entered into the eCRF within 7 days of death and within 97 days of enrollment into the REMAP if the participant is alive at 90 days.

8.9.4. Blinding of outcome assessment

Wherever feasible outcome assessment will be undertaken by research staff who are blinded to allocation status. Such blinding will not be feasible for many outcomes, particularly those that occur while the participant is still admitted to an ICU or the hospital. However, the primary endpoint and key secondary endpoints are not variables that are open to interpretation and so accuracy will not be affected by outcome assessors not being blinded to allocation status.

8.10. Data management

8.10.1. Source Data

Source documents are where data are first recorded, and from which participants' eCRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarized into the eCRF), clinical and office charts, laboratory and pharmacy records, radiographs, and correspondence.

8.10.2. Confidentiality

All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by a unique trial-specific number and/or code in any database, not by name. Information linking the participant's medical data to database materials will be maintained in a secure location at the participating site. This information will not be transmitted to the members of the ITSC, any DSWG, or RMC. The key to code and recode participant identifiers will only be accessible to local site investigators (research nurse and principal investigator) but not to members of the central study team. ICU and coded individual subject data and records will be held in strictest confidence by the site investigator and healthcare staff and by all central research staff, as permitted by law.

8.11. Quality assurance and monitoring

The trial will be conducted in accordance with the current approved protocol, Good Clinical Practice (GCP), relevant regulations and SOPs.

8.11.1. Plans for improving protocol adherence and complete data

Data entry and data management will be coordinated by the Regional Project Manager and the RCC, including programming and data management support.

Several procedures to ensure data quality and protocol standardization will help to minimize bias. These include:

- Start-up meeting for all research coordinators and investigators will be held prior to study commencement to ensure consistency in procedures;
- A detailed dictionary will define the data to be collected on the CRF;
- The data management center will perform timely validation of data, queries and corrections if errors are found during quality control checks;
- Data monitoring will occur as described below.

8.11.2. Data Monitoring

The study will be monitored by a representative of the RCC. A site initiation teleconference or visit will be conducted before site activation. Routine monitoring visits will be conducted the frequency of which will be determined by each site's rate of recruitment. Email and telephone communication will supplement site visits.

A monitoring report will be prepared following each visit and reviewed by the RMC if appropriate. A follow up letter will be sent to the principal investigator and research coordinator at the site and will be filed in the site investigator file.

Medical records, any other relevant source documents and the site investigator files must be made available to the representative of the RCC for these monitoring visits during the course of the study and at the completion of the study as needed.

Domain-specific monitoring and protocol adherence issues are addressed in each DSA.

8.12. Data safety and monitoring board

A single DSMB will take responsibility for the trial in all regions in which it is conducted. The DSMB compiled for this study will consist of 5-7 members; the chair has been selected to have expertise in clinical trial methodology, and to have experience with adaptive clinical trial design. Additional medical, statistical, and other experts will be selected to ensure all necessary expertise to oversee a trial of this complexity and scope. The DSMB will conduct its activities in accordance with a separate Charter; the Charter must be approved by the DSMB, and ITSC prior to the initiation of the trial. The DSMB will be unblinded to ensure the highest quality oversight of the trial, in accordance with current recommendations of regulatory authorities.

The DSMB will review received frequent updates of the trial's adaptive analyses from the SAC. The role of the DSMB will be to ensure that the pre-specified trial algorithm is being implemented as designed, that the design remains appropriate from a scientific and ethical point of view, to confirm when a Statistical Trigger has been reached, and to either reach or recommend that a Platform Conclusion has been reached, as outlined in Section 7.8.9. Trial enrollment and conduct will be continuous.

The DSMB will not make design decisions. If the DSMB believes the trial's algorithms are no longer acceptable from an ethical, safety, or scientific point of view it will make recommendations to the ITSC which has ultimate decision-making authority regarding the trial design. Where the DSMB and the SAC agree on a temporary deviation from the study protocol for safety reasons, they are not required to inform the ITSC of this decision. If the DSMB and SAC agree that a permanent change is necessary, the chairs of the DSMB, SAC and ITSC will meet to discuss the best way to proceed to ensure patient safety and the scientific integrity of the trial. Where the SAC and DSMB disagree on the need to deviate from the pre-specified trial design, the DSMB must inform the ITSC of their recommendations and the rationale for these.

8.13. Safety monitoring and reporting

8.13.1. Principles

The principles used in the conduct of safety monitoring and reporting in this trial are those outlined by Cook *et al.* in the manuscript "Serious adverse events in academic critical care research". (Cook et al., 2008) A high proportion of critically ill patients who will be enrolled in this trial will experience mortality or substantial morbidity. The case-fatality proportion for critically ill patients with CAP is likely to be in the order of 20 to 30% and high proportions of patients will have one or both of laboratory abnormalities or complications of critical illness and its treatment. Patients who are critically ill, irrespective of whether or not they are enrolled in a trial, will typically experience multiple events that would meet the conventional definition of a Serious Adverse Event (SAE).

Trials involving vulnerable populations must have research oversight that protects patient safety and patient rights and also ensures that there can be public trust that the trial is conducted in a manner that safeguards the welfare of participants. The strategy outlined for the definition, attribution, and reporting of SAEs in this trial is designed to achieve these goals but does so in a way that seeks to avoid the reporting of events that are likely to be part of the course of the illness or events that are recognized as important by their incorporation as trial endpoints.

8.13.2. Definition

In accordance with accepted standards a SAE is defined as an event that is fatal, life-threatening, results in (or may result) in disability that is long-lasting and significant, or results in a birth defect or congenital anomaly.

8.13.3. Reporting Procedures for Serious Adverse Events

The trial endpoints, as outlined in the Core Protocol and as specified in DSAs, are designed to measure the vast majority of events that might otherwise constitute an SAE. In particular, SAEs that might be attributable to specific interventions are included as secondary endpoints in each DSA but are recorded only for participants who are enrolled in that domain. If required, additional clarification of issues related to the identification of SAEs that are relevant to a specific domain will be described in the DSA. Generally, only SAEs that are not trial-end points require reporting.
However, any SAE that is considered by the site-investigator to be attributable to a study intervention or study participation should be reported (Section 8.13.4). Where an SAE is not a trial end point it should be reported only where, in the opinion of the site-investigator, the event might

reasonably have occurred as consequence of a study intervention or study participation (Section 8.13.4).

Events that meet the definition of an SAE, require reporting in accordance with the criteria outlined above, and occur between trial enrollment but before hospital discharge will be reported to a RCC. These SAEs should be reported to a RCC within 72 hours of trial staff becoming aware of the event, unless otherwise specified in a RSA. The minimum information that will be reported will comprise:

- Unique trial-specific number
- Date(s) of the event
- Nature of the event, including its outcome, and the rationale for attribution to a trial intervention
- Whether treatment was required for the event and, if so, what treatment was administered

8.13.4. Attribution of serious events to study interventions

It is likely that many participants within the trial will experience events that could be attributed to one or more study interventions. However, it will often be difficult to distinguish, in real-time, between events that occur as a consequence of critical illness and treatments that are not specified by the trial, and interventions specified by the trial. Site investigators should exercise caution in attributing events to study interventions. However, the standard that should be applied to determine whether SAEs are attributable to study interventions in this trial is that it is possible, probable, or certain that there is a direct link between a trial intervention and the SAE or the SAE is not considered to be a normal feature of the evolution of critical illness and its treatment.

8.13.5. Attribution of a death to study interventions or study participation

Critically ill patients who will be enrolled in this trial are at high risk of death. The primary endpoint of the trial is mortality and the objective of the trial is to identify differences in the primary endpoint that can be attributed to treatment allocation which will often include treatments that are believed to be or known to be safe and effective but for which it is not known whether some treatments are more effective than others. Where the trial evaluates interactions that are novel and not part of usual standard care the threshold for considering attribution to the novel experimental intervention should be lower than if an intervention is already in widespread use and its safety profile has already been established.

9. GOVERNANCE AND ETHICAL CONSIDERATIONS

9.1. Management of participating sites and trial coordination

Each region will have a RCC. Each RCC will take primary responsibility for the management of participating sites, data management for those sites, and provide web-based randomization for sites in its region. The processes by which each RCC will provide trial management and coordination is set out in each RSA.

9.2. Ethics and regulatory issues

9.2.1. Guiding principles

The study will be conducted according to the principles of the latest version of the Declaration of Helsinki (version Fortaleza 2013) and in accordance with all relevant local ethical, regulatory, and legal requirements as specified in each RSA.

9.2.2. Ethical issues relevant to this study

Patients who will be eligible for this study are critically ill, and many eligible patients will be receiving sedative medications for comfort, safety and to facilitate standard life saving ICU procedures. In patients who are not necessarily receiving sedative medications, the presence of critical illness, itself, leads commonly to an altered mental state that will affect the patient's mental capacity. The presence of these factors will mean that most patients who are eligible for the study will not be able to provide prospective consent for participation. Additionally, many interventions within this trial must be initiated urgently, either because there is an immediate time critical imperative to initiate the intervention or because the most valid evaluation of the intervention occurs if the trial intervention is initiated at the same time-point as would occur in clinical practice.

The broad approach regarding consent that will be used in this study are as follows:

- Patients who, in the opinion of the treating clinician, are competent to consent will be provided with information about the trial and invited to participate
- The vast majority of patients who are eligible for the REMAP will not be competent to consent. For such patients, and as permitted by local laws and requirements for ethical approval:
    - For domains in which all interventions available at the participating site are regarded as being part of the spectrum of acceptable standard care by the

clinicians at that site, entry to the study is preferred to be via waiver-of- consent or some form of delayed consent. If required by local laws or ethical requirements and alternative to this pathway will be participation in conjunction with the agreement of an authorized representative of the participant.

- For domains in which at least one intervention available at the participating site is regarded as experimental or not part of the spectrum of acceptable standard care then prospective agreement by an authorized representative will be required. An exception to this principle is recognized when there is a time-imperative to commence the intervention which would routinely preclude obtaining the prospective agreement by an authorized representative.
- For domains in which eligibility may develop after initial enrollment in the trial it is permissible to obtain contingent consent from the participant or contingent agreement from an authorized representative, i.e. there is contingent approval to randomize the participant if the participant meets eligibility criteria for a domain subsequently.
- Where any participant is enrolled without having provided their own consent, the participant's authorized representative will be informed as soon as appropriate and informed of processes to cease trial participation. If required by local laws or processes for ethical approval, the authorized representative will be asked to provide agreement to on-going participation. In undertaking these trial processes research staff will be cognizant of the need to avoid unnecessary distress or create unnecessary confusion for authorized representatives and all other persons who have an interest in the participant's welfare.
- Where any participant is enrolled without having provided their own consent, the participant should be informed of their enrollment after regaining competency, in accordance with local practice and jurisdictional requirements. Where any participant is enrolled and does not regain competency (due to their death or neurological impairment) the default position, subject to local laws and ethical review processes, will be that the enrolled person will continue to be a participant in the trial.

It should be noted that once RAR is initiated, participants within the REMAP, on average, derive benefit from participation. As a consequence of RAR participants are more likely to be allocated to the interventions within each domain that are more likely to result in better outcomes.

9.2.3. Approvals

The protocol, consent form(s) and participant and/or authorized representative information sheet(s) will be submitted to an appropriate ethical review body at each participating institution and, as required, to any additional regulatory authorities. Written approval to commence the study is required for all relevant ethical and regulatory bodies.

9.3. Protocol modifications

9.3.1. Amendments

A "substantial amendment" is defined as an amendment to one or more of the Core Protocol, DSA, or RSA that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial;
- the quality or safety of any intervention used in the trial;
- cessation of any intervention or domain for any reason;
- the addition of any new intervention within a domain; or
- the addition of new interventions within a new domain

All substantial amendments to the original approved documents, including all modifications of interventions available within a domain and the addition of interventions within a new domain will be submitted for approval to all relevant ethical and regulatory review bodies that were required for original approvals. Non-substantial amendments will not be notified to such review bodies, but will be recorded and filed by the trial sponsors.

Where the cessation of any intervention or any domain occurs for any reason, this is an operational issue and randomization to that intervention or domain will no longer be available. Cessation of an intervention or domain, either entirely, or within a prespecified subgroup, will be reported to all relevant regulatory bodies.

9.4. Confidentiality

The principles of confidentiality that will apply to this trial, are that all trial staff will ensure that the confidentiality of all participants information will be maintained and preserved at all times. The participants will be identified only by a unique trial-specific number on all documents and electronic databases that contain any information specific to the participating individual. Each site will maintain a separate file that links each participant's unique trial-specific number to the participant's name and other identifying information such as date of birth, address, and other contact information. No other information will be maintained in the file that links the participant unique trial-specific number to participant identifying information.

9.5. Declarations of interest

All trial staff will be required to declare and update all interests that might or might be seen to influence one or both of the conduct of the trial or the interpretation of results. All investigators involved in REMAP-CAP maintain a registry of interests on the REMAP-CAP website. These are updated periodically and publicly accessible on the study website.

9.6. Post-trial care

The trial has no responsibility for the ongoing management or care of participants following the cessation of all trial specified interventions.

9.7. Communication

9.7.1. Reporting

Each participating site will comply with all local reporting requirements, as specified by that site's institution.

Should the entire trial be terminated, all relevant local ethical and regulatory bodies will be informed within 90 days after the end of the study. The end of the study is defined as the last participant's last follow-up.

9.7.2. Communication of trial results

Trial results will be communicated by presentation and publication.

9.8. Publication policy

Manuscript(s) and abstract(s) resulting from the data collected during this study will be prepared by the corresponding DSWG. Where results are influenced by interaction between domains, the DSWG for both domains will take responsibility for preparation of manuscripts and abstracts. All manuscripts and abstracts reporting trial results that are prepared by one or more DSWGs must be submitted to and approved by the ITSC before submission.

Site investigators will not publish or present interim or definite results, including but not restricted to oral presentations. The role of site investigators and research coordinators at participating sites will be acknowledged by their names being listed as collaborators. Where required publications will comply with the publication policies of clinical trials groups that have endorsed or supported the study.

9.9. Data access and ownership

9.9.1. Data ownership

All data are owned by the responsible sponsor under the custodianship of the ITSC. As the trial is intended to be perpetual, all data will be retained indefinitely.

9.9.2. Access to Data

Direct access will be granted to authorized representatives from ITSC, sponsors, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. The trial will comply with all relevant jurisdictional and academic requirements relating to access to data, as apply at the time that the data are generated. Ownership and access to data where a commercial organization is involved in the trial (for example by provision of goods or services that are tested within a domain) will be set out in a contract between trial sponsors and that commercial organization.

The trial will not enter into a contract with a commercial organization unless the contract specifies that:

- There is complete academic independence with regard to the design and conduct of all aspects of the trial including analysis and reporting of trial results

- May agree to provide a pre-publication version of presentations or manuscripts to a commercial organization but that the commercial organization has no authority to prevent or modify presentation or publication
- That all data are owned by the trial and the commercial organization has no authority to access data

9.10. Consent form

Template information and consent forms will be provided to participating sites as an operational document.

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Original Version of the REMAP Pandemic Appendix to the Core

PANDEMIC APPENDIX TO THE CORE PROTOCOL VERSION

The version of the Pandemic Appendix to the Core Protocol is in this document's header and on the cover page.

Version History

Version 1: Approved by the Pandemic Working Group on 31st January, 2020
Version 1.1: Approved by the Pandemic Working Group on 12th February, 2020

PANDEMIC APPENDIX TO THE CORE PROTOCOL GOVERNANCE

The study administration structure is outlined in the Core Protocol. As outlined in the Core Protocol, a Pandemic Working Group (PWG) is established and works in conjunction with the International Trial Steering Committee (ITSC), to take responsibility for the Pandemic Appendix to the Core Protocol (PAtC) and to advise on operational aspects following emergence of a pandemic.

Pandemic Working Group

The responsibility of the PWG is to maintain and update this PAtC and to advise the ITSC regarding application of the PAtC during a pandemic. The PWG will liaise with individuals and organizations that are external to REMAP-CAP as required. Membership of the PWG is flexible. The core membership is listed but additional members can be added at any time and as required.

Chair: The Chair of the ITSC will Chair the Pandemic Working Group

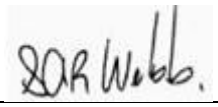
Members:
Prof. Derek Angus
Prof. Yaseen Arabi
Prof. Richard Beasley
A/Prof. Scott Berry
Prof. Frank Brunkhorst
Dr. Lennie Derde
Dr. Robert Fowler
Prof. Anthony Gordon
Mr. Cameron Green
Dr. Ed Litton
Prof. John Marshall
Dr. Colin McArthur
Dr. Srinivas Murthy
Prof. Alistair Nichol
Ms. Jane Parker
Prof. Kathy Rowan
Prof. Tim Uyeki
Prof. Steve Webb

Contact Details

Chair: Professor Steve Webb
Department of Epidemiology and Preventive Medicine
School of Public Health and Preventive Medicine, Monash University
Level 3, 533 St Kilda Road
Melbourne, Victoria, 3004
AUSTRALIA
Phone: +61 3 9903 0343
Email: steven.webb@monash.edu

PANDEMIC WORKING GROUP AUTHORISATION

The Pandemic Working Group have read the appendix and authorize it as the official Pandemic Appendix to the Core Protocol for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair  Date 12th February, 2020

Steve Webb

BACKGROUND AND RATIONALE

Introduction

It is reasonable to presume that any pandemic respiratory infection of major significance to public health will manifest as severe Community Acquired Pneumonia (CAP) with concomitant admission to an Intensive Care Unit (ICU). Previous pandemics and more localized outbreaks of respiratory emerging infections have resulted in severe CAP and ICU admission[1-3]. A pandemic of respiratory infection is much more likely to be caused by a virus than a bacterium and, among viruses a distinction should be drawn between influenza, which is known to result in periodic but unpredictable pandemics, and other viruses, such as Coronaviruses, that may have pandemic potential, as the features of trial design may be different.

Previous pandemics and outbreaks of emerging infectious diseases have outlined the urgent need for evidence, preferably from Randomized Controlled Trials (RCTs), to guide best treatment. However, there are substantial challenges associated with being able to organize such trials when the time of onset of a pandemic and its exact nature are unpredictable[4-6]. As an adaptive platform trial that enrolls patients during the interpandemic period, REMAP-CAP is ideally positioned to adapt, in the event of a respiratory pandemic, to evaluate existing treatments as well as novel approaches.

One of the challenges associated with planning clinical trials during a pandemic is that the precise nature of the infecting organism, clinical consequences, and suitable interventions (particularly those that are pathogen-specific) cannot be reliably known in advance.

Nevertheless, a range of scenarios can be anticipated and used to provide direction and guidance regarding the most appropriate research response.

The most likely organism responsible for a respiratory pandemic is a novel influenza virus that has undergone antigenic shift[7]; the most recent influenza pandemic occurred during 2009-2010. In recent years, there have been outbreaks of severe Community Acquired Pneumonia due to novel Coronaviruses which resulted in the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003 and the Middle-Eastern Respiratory Syndrome Coronavirus (MERS-CoV) outbreak that commenced in 2012. The pandemic potential of a novel Coronavirus that causes pneumonia is not known. The pre-specified adaptations to REMAP-CAP will need to be different for influenza in comparison to a non-influenza pandemic pathogen.

Pandemic research preparedness

Introduction

The conceptual approach to pandemic preparedness has been influenced substantially by the occurrence of the 2009 Influenza A H1N1(2009)pdm pandemic, outbreaks of SARS and MERS-CoV, the Zika pandemic, and Ebola virus disease outbreaks in West Africa[8]. A broad conclusion from these outbreaks is that it is likely that high quality research can change the incidence and consequences of the epidemic but that such research is extremely difficult because planning of research only commences after the discovery of the epidemic. As a consequence, researchers and organizations interested in developing improved processes for research have identified three key elements to facilitate time-critical research about an epidemic. These elements are that the research must be pre-planned, pre-approved, and practiced[9,10]. REMAP-CAP and, in particular, the PAtC, is an attempt to establish these pre-requisites and to guide treatment for patients who may be critically ill with pneumonia as a consequence of infection with a pandemic organism.

The World Health Organization (WHO) has recommended establishing and strengthening outbreak-ready, multi-center clinical research networks in geographically diverse regions to facilitate research during pandemics.[11] It has also recommended testing of protocols during interpandemic periods and stressed the value of such clinical research consortia in collecting and distributing information during a future pandemic.

Pre-planned

Pre-planned means that the trial protocol is written and that the trial processes related to project management, screening, recruitment, delivery of interventions, data collection, data management, analysis, and reporting are all in place. The PAtC, in conjunction with the existing REMAP-CAP protocol documents and trial processes, will mean that all aspects that can be pre-planned have been.

Pre-approved

The PAtC is a key component of the of the pre-approval strategy. The availability of this document allows ethics review boards, hospital research governance staff, existing and potential sites to understand and approve the study processes that would be implemented during a pandemic. Where different options need to exist, depending on the nature of the pandemic, these are pre-specified, as much as possible. Any unanticipated substantive deviation from this Appendix would be subject to an amendment, hopefully expedited, in the

event of a pandemic. The PAtC, like the Core Protocol, does not specify any interventions that are evaluated within the REMAP. It is highly likely that one or more research questions (in domains already approved during the interpandemic period) will be relevant specifically in patients with CAP caused by the pandemic infection. The PAtC allows these questions to continue to be answered specifically in patients with pandemic infection, where appropriate, using Bayesian prior probabilities derived from patients already enrolled during the interpandemic period. It is proposed to develop 'sleeping domains', which could be activated if appropriate during a pandemic, as well as retain the option of developing one or more completely new domains following the emergence of pandemic, which would require separate ethical approval and contracts with participating sites.

This strategy, as part of the study design, offers an ethically, clinically and legally acceptable mechanism for research in the context of a pandemic that can be initiated rapidly.

There are two further aspects relevant to ethical approval of the PAtC. The first is that existing or pandemic-specific domains of REMAP-CAP may include an intervention that specifies no treatment within that domain (noting that the Core Protocol specifies that all additional standard care is provided with treatment decisions being made by the treating clinician). This is clinically and ethically appropriate as the response of critically ill patients to a range of different treatments has proven to be unpredictable. There are many examples of treatments that have resulted in harm[12] and situations in which surrogate outcome measures were not reliable indicators of improvement in patient-centered outcomes. As such, there should not be any presumption that it is better for patients to receive active interventions.

The second is the capacity to apply Response Adaptive Randomization (RAR) within the REMAP. As outlined in the Core Protocol, RAR results in an increasing proportion of patients being allocated to any intervention within a domain that has a higher probability of being superior with that proportion increasing as statistical confidence accrues. Participants within REMAP-CAP during a pandemic may be able to benefit from information about the relative effectiveness of interventions that is not in the public domain and not available to patients who are not participants in REMAP-CAP. As outlined in the Core Protocol, any intervention confirmed to be superior within the REMAP is then implemented by application of a RAR proportion that is equal to 100%. RAR will be implemented for pandemic patients as soon as sufficient data have accrued and operational implementation is feasible.

Practiced

REMAP-CAP will be recruiting during the interpandemic period in multiple countries in both Southern and Northern Hemispheres with the support of several Regional Coordinating Centers. This research activity, during the interpandemic period, ensures that sites, site training, project management, data management, analysis processes, and trial governance are functional and practiced. Furthermore, the eligibility process and delivery of trial interventions are optimized for embedding which allows study processes to occur within minimal disruption to the delivery of clinical care, which may well be under substantial strain during a pandemic. There is already extensive experience with the Case Report Form (CRF) that is used and will continue to be used during a pandemic.

Implications of REMAP design during a pandemic

Time-critical generation of evidence

A pandemic will likely result in a large number of affected persons with cases occurring over a short period of time, perhaps as short as a few months. Conventional clinical trials that utilize frequentist statistical techniques require a fixed sample size with limited capacity to analyze the results of the trial until recruitment is completed. The setting of the sample size requires an estimate of the size of the treatment effect and it is known that the assumptions that are made in setting the size of the treatment effect are often incorrect[13,14]. A frequentist trial that over-estimates the size of the treatment effect may conclude without reaching a valid conclusion, whereas one that under-estimates the size of the treatment effect is delayed in providing time-critical information that the treatment is even more effective than estimated. REMAP-CAP utilizes Bayesian statistical methods which allow frequent adaptive analyses to occur. This will ensure that time-critical information about the effectiveness of treatment interventions is not delayed unnecessarily. The REMAP design is particularly suited to pandemics because it requires no pre-trial assumptions about the size of the treatment effect and will allow dissemination of evidence as soon as possible. Furthermore, as the trial progresses during a pandemic the Data Safety Monitoring Board (DSMB) has access to information from adaptive analyses that may not achieve thresholds to allow reporting as a Platform Conclusion but may be relevant to public health which, under appropriate circumstances, can be shared with public health authorities without threatening the scientific validity of the ongoing trial.

Multifactorial design and evaluation of interactions

If there are multiple interventions, each of which may have independent effects on outcome, the multi-factorial nature of a REMAP allows these to be evaluated simultaneously, rather than in series or in separate parallel trials (see *Figure 1*). This design feature contributes to efficiency and is also anticipated to result in more clinical evidence being generated more rapidly during a time-critical pandemic.

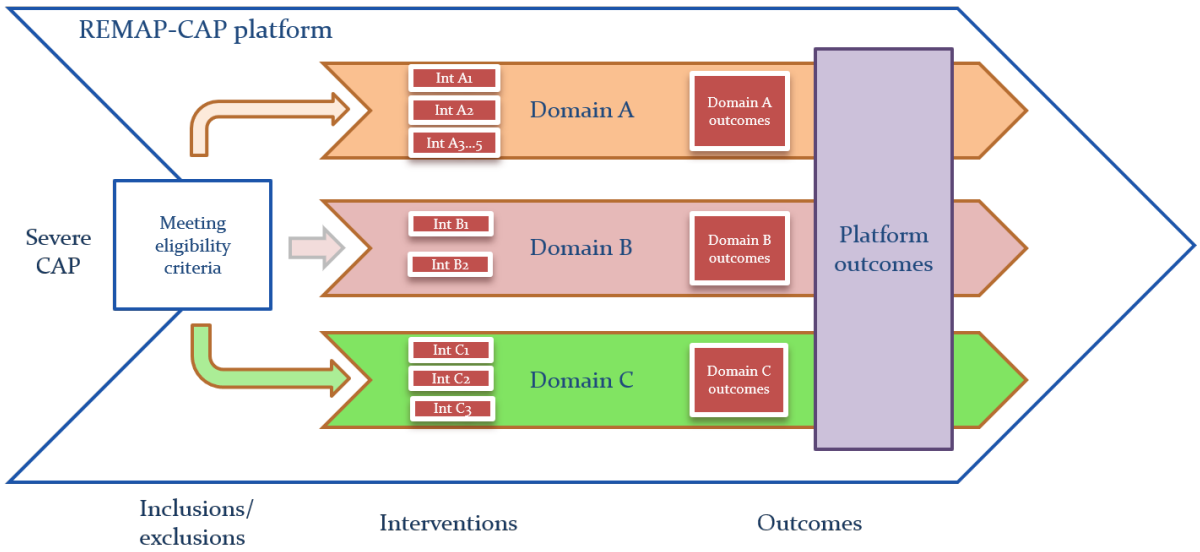


Figure 1. The multifactorial structure of REMAP-CAP

Furthermore, where pre-specified, the statistical model utilized in REMAP-CAP will allow estimation of treatment effect of interventions that may be contingent on other treatment

assignments within the pandemic component of the REMAP. For example, it is plausible that the effectiveness of an intervention for immune modulation is dependent on co-delivery of an agent that is effective at inhibiting growth or replication of the pathogen. Conventional trials, in which only a single domain of treatment is evaluated, are not capable of detecting this type of treatment-by-treatment interaction, and thereby unable to identify the best overall treatment strategy for these patients.

Setting of research priorities

In 2017, the WHO outlined the research priorities for a pandemic that was caused by a novel strain of influenza. These priorities were:

- Research on the effectiveness of empirical treatment with oseltamivir and other neuraminidase inhibitors (NAI) in critically ill patients, including placebo-controlled trials during seasonal as well as pandemic influenza.
- Investigating alternative strategies to NAI monotherapy to increase antiviral potency and improve clinical outcomes.
- Research on immune-modulatory strategies in severe influenza, including corticosteroids and macrolides.
- A need for high quality data on the effectiveness of most aspects of supportive care related to influenza.
- A need to assess the roles of virologic factors (e.g. replication sites, duration and viral load levels) in larger numbers of patients (including critically ill patients) in causing severe disease and associated complications, linking them to clinical outcomes.

REMAP-CAP is not able to meet all of these requirements but is well suited to evaluate the effectiveness of antiviral therapies active against influenza, immune modulatory strategies and different aspects of supportive care[15]. Identical or similar research questions would exist for any pandemic caused by an organism that was not influenza and REMAP-CAP has also similar capabilities in this scenario.

WHO endorsement

REMAP-CAP has been designated by the WHO as a Pandemic Special Study. Under this designation, it has been tasked with helping answer crucial questions during a declared pandemic, as listed above. This designation ensures that knowledge translation of clinical trial results can occur directly with policymakers and public health officials for rapid implementation around the globe. It ensures that results generated from REMAP-CAP during a declared pandemic can be translated in an efficient and transparent manner to benefit affected patients.

ADAPTATION OF REMAP-CAP DURING A PANDEMIC

This PAtC supplements the Core Protocol during a pandemic including deactivation at the conclusion of a pandemic. Decisions regarding the operationalization of the Pandemic Appendix to the Core Protocol are made by the ITSC with advice from the PWG (see Section 8.1). The Appendix sets out all potential adaptations of the Core Protocol and unless otherwise specified, all other aspects of the Core Protocol remain active. Activation of the PAtC will be advised to the DSMB with specification of the selected operational characteristics.

Study setting: definition of an ICU

During the interpandemic period, the REMAP recruits only participants who are admitted to an ICU. During a pandemic, there may be insufficient ICU beds available to care for all critically ill patients resulting in provision of advanced organ support occurring in locations other than an ICU.

For sites at which the pandemic stratum (see below) has been activated, an area within the hospital that is able to deliver one or more of the qualifying organ failure supports specified in the Core Protocol (non-invasive ventilation, invasive ventilation, and vasopressor therapy) will meet the definition of an Intensive Care Unit. It is preferred in such circumstances that the patient is under the care of a specialist who is trained in the provision of critical care, but this is not an essential requirement.

Eligibility criteria

Platform-level eligibility criteria may be modified if necessary to accommodate a published case definition, to align with criteria specified in guidelines, such as the ATS/IDSA guidelines on CAP[16], or to accommodate necessary modifications to the online eligibility system used for enrolment. In previous epidemics of community-based infection, nosocomial acquisition has been well described. Relaxation of the requirement for community acquisition or organ failure criteria or both may be appropriate. All changes to eligibility criteria would apply only to patients in the pandemic stratum (see section 7.3).

Pandemic stratum

Introduction

As outlined in the Core Protocol, a pre-specified stratum of the REMAP is the presence or absence of suspected or proven pandemic infection. This is maintained as a 'passive stratum' during the interpandemic period that can become active during a pandemic. It consists of two exclusive strata categories: pandemic infection is neither suspected nor proven (PINSNP) and pandemic infection is either suspected or proven (PISOP) at baseline. At times when the PAtC is not activated, i.e. during the interpandemic period, all participants are categorized as PINSNP.

Activation and deactivation of the PAtC and PISOP stratum

In response to a pandemic (see section 8.1), the PISOP stratum is activated using a two-step process. First there is a decision of the ITSC to open the PISOP stratum for the platform. The second step is site-by-site activation of the PISOP stratum, requiring agreement of both the site and the Regional Coordinating Centre (RCC). This allows variation in activity of the pandemic infection to be accommodated with sites only open for PISOP recruitment when there is active pandemic infection locally. Switching-on of the stratum can occur at any time and expected to always be available with less than 24 hours lead time. The capacity to enroll patients into the PISOP stratum can be switched-off on a site-by-site basis, but the ITSC can switch off the PISOP stratum for all sites if it is believed that a pandemic is no longer ongoing. The REMAP applies a new and separate statistical model for participants in the PISOP stratum

which can utilize, where appropriate, informative priors derived from pre-pandemic PINSNP participants.

It should be noted that for sites in which the pandemic stratum is open, that the REMAP allows for continued recruitment of patients into the REMAP who are in the PINSNP stratum. For example, during an influenza pandemic, PINSNP would include patients with infection that has been proven to be a non-pandemic strain of influenza. During a pandemic, patients who are in the PINSNP stratum continue to be analyzed using the interpandemic statistical model (see below). As such, there are two categories of PINSNP participants- those included during the interpandemic phase and those included during a pandemic. Both categories of patients contribute to the interpandemic model for all active domains.

The PAtC is activated and deactivated for a site at the same time as the PISOP stratum is opened and closed. If a pandemic commences prior to ethical and governance approval of the PAtC, the PISOP stratum can be activated using approvals for the Core Protocol, and the PAtC would be activated as soon as ethical approval is obtained.

The pandemic statistical model

Introduction

The model that is active during the pandemic and includes only PISOP patients (for some or all domains) is referred to as the ***pandemic model***. The model that is active before (and after) the pandemic, which includes PINSNP patients during the pandemic and may include some PISOP patients for some domains, is referred to as the ***interpandemic model*** (see *Figure 2*).

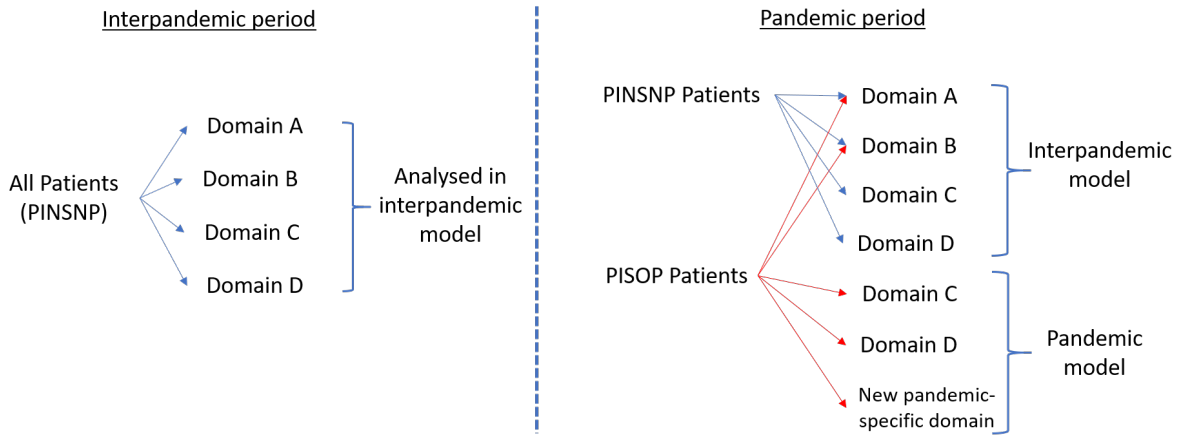


Figure 2. Diagram of the interpandemic and pandemic models

The pandemic model is only used for PISOP participants and only for those domains selected by the ITSC. A PISOP patient can contribute to both the pandemic and interpandemic model in different domains but each patient's contribution to a model is mutually exclusive with respect to each domain. The ITSC will select the domains to be included in the pandemic model where a differential treatment effect is postulated in the presence of pandemic infection or the need exists to learn about the outcome quickly, or both.

A consequence of the application of two separate statistical models is that treatment-by-treatment interactions can only be evaluated for those domains that are in the same model. The principal advantages of the use of two models are:

- that this is necessary where the pandemic model requires a different primary end-point

- the platform is able to continue recruitment of patients with CAP who are neither suspected nor proven to have pandemic infection
- where appropriate informative priors can be included at commencement of the pandemic model
- where appropriate thresholds for a Statistical Trigger can be modified
- only those domains that are relevant to the pandemic are included within the pandemic model.

During the interpandemic period, it is intended that there may be some domains, for example the Ventilation Domain, that will utilize a separate domain-specific statistical model. It should be noted that during the interpandemic period, such a domain is not part of the interpandemic statistical model. During a pandemic any such domain would continue to be evaluated with its own domain-specific statistical model. During a pandemic, the operating characteristics of the domain-specific statistical model may be modified in the same way that the pandemic model is modified from the interpandemic model. For example, PISOP patients may be analysed within a pandemic version of the domain specific statistical model utilising a modified primary end-point, with application of informative priors derived from the interpandemic time period.

Pre-specification of trial parameter options

There are many clinical features of a respiratory pandemic that cannot be predicted in advance. For several parameters related to trial design and statistical analysis, this Appendix pre-specifies a range of options from which the actual modifications will be chosen at the commencement of a pandemic. The appendix provides guidance regarding the principles that would guide selection from within the available options and often provides the planned default option. The provision of flexibility regarding limited aspects of trial design provides the capacity to tailor aspects of the trial to the characteristics of the pandemic. For these decisions, the ITSC has decision-making responsibility, with advice from the PWG. These decisions would be regarded as operational and, unless otherwise specified (5.3.4), will be made prior to the conduct of the first adaptive analysis using the pandemic model and would be made only from within the range of options pre-specified in this Appendix. It is not intended that the selected parameters would be modified in any way during the pandemic unless advised to do so by the DSMB. The selected trial parameters would be placed in the public domain, on the study website, and provided as an update to participating sites and relevant ethical review bodies prior to the first adaptive analysis of the PISOP stratum.

Application of other strata specified in the Core Protocol in the pandemic model

The shock strata may be applied to the PISOP stratum. The default position is that the shock strata will not be applied to the PISOP stratum.

If the pandemic is caused by a novel strain of influenza the pre-existing influenza strata is not applied in the pandemic model. For PINSNIP patients, the “influenza present” stratum would continue to apply and would be used to differentiate patients infected with a non-pandemic strain of influenza from patients in the “influenza not present” stratum. Membership of PISOP and influenza present stratum are mutually exclusive. It is anticipated that the influenza present stratum would apply only to patients with infection due to a proven non-pandemic strain of influenza at baseline. Patients in whom influenza was suspected, but the results of

strain-specific diagnostic tests were not available at the time of assessment of eligibility, will be allocated to the PISOP stratum at sites where the stratum is active.

Strata within the PISOP stratum

A strata applied within the PISOP stratum is the confirmation status of pandemic infection, defined in two categories, present or absent, based on the results of microbiological tests for the pandemic organism. Any patient with clinically suspected pandemic infection who is not tested or the result is not yet known will be deemed positive.

The availability and interpretation of microbiological tests are likely to change during the pandemic and an operational document will be used to specify how different tests are interpreted. It is noted that pandemic infection confirmed status is defined by the final results of testing for the pandemic organism which may include analysis of samples collected after enrollment where it is reasonable to presume that the sample reflected pandemic infection status at time of enrollment.

The sensitivity of microbiological testing for the pandemic organism may not be known at the beginning or even during the pandemic[17]. It is anticipated that initial analysis of the pandemic model will occur without application of this pandemic confirmation status strata but this would be applied when there was sufficient confidence about the operating characteristics of diagnostic tests in patients who are critically ill. If the pandemic confirmation status is applied, the probabilities derived from patients who have confirmed pandemic infection will be used to determine the RAR proportions for patients receiving treatment assignments in the pandemic specific domains within the PISOP stratum. Borrowing is permitted between the pandemic infection confirmed stratum and the pandemic infection not present stratum, using the methods outlined in the Core Protocol (with gamma = 0.15).

If eligibility criteria were modified to allow inclusion of a wider spectrum of illness severity, an additional strata may be applied within the PISOP stratum to distinguish current versus extended severity of illness.

Domains incorporated in the pandemic model and use of informative priors derived from the interpandemic model

The domains that will be included within the pandemic model will be determined at the onset of a pandemic by the ITSC with advice from the PWG. Where appropriate and prior to the first adaptive analysis that is undertaken after activation of the PAtC, informative priors, derived from the interpandemic model (comprising patients enrolled in the REMAP prior to the pandemic), may be applied. If informative priors are applied, this is done by the Statistical Analysis Committee (SAC) who review the frequent adaptive analyses (and communicate these results to the DSMB on a regular basis). This will occur without knowledge of the values of the priors by the ITSC or any other investigator. The amount of influence that priors apply and how quickly priors are applied in combination with accruing new data will be specified by the ITSC. Coding that specifies the weighting of priors will be done by statisticians who are separate to the SAC and blind to results from adaptive analyses. With regard to selection of domains and the use of informative priors, the following principles will be applied.

Non-influenza pandemic organism

If the pandemic organism is not influenza, the following domains are intended to be included within the pandemic model:

- Corticosteroid Domain, without application of informative priors.
- Macrolide Duration Domain, without application of informative priors.
- New domains, as appropriate for the pandemic organism, without application of informative priors.

The Antiviral Domain (which includes only antiviral agents active against influenza) would not be applied in the pandemic model. It is noted that a patient at baseline could have suspected influenza and suspected pandemic infection which could lead to enrolment in the influenza domain (evaluated in the interpandemic model) and enrollment in other domains (evaluated in the pandemic model). It is not anticipated that the Antibiotic Domain is evaluated in the pandemic model, though this may be revised if the pandemic was caused by a bacterial pathogen. In this situation only those antibiotics that are known to be active against the pandemic organism would be available within the Antibiotic Domain for patients in the PISOP stratum.

Influenza pandemic

If the pandemic organism is influenza, the following domains are intended to be included within the pandemic model:

- Corticosteroid Domain, using informative priors derived from the influenza present stratum.
- Antiviral domain, using informative priors derived from the influenza positive stratum but with exclusion of any antiviral interventions that are clinically inappropriate because of the resistance profile of the pandemic strain of influenza. If there were no antiviral agents to which the pandemic strain of influenza was susceptible the Antiviral domain would not be applied in the PISOP stratum. During the pandemic if the pandemic strain of influenza acquired resistance to antiviral agents in the Antiviral Domain, these agents would be withdrawn from the domain at affected sites.
- Macrolide Duration Domain using informative priors derived from the unit-of-analysis of the Macrolide Duration Domain in the interpandemic model.
- New domains, as appropriate, without application of informative priors.

A number of other domains, related to organ failure support may be operative at the time of a pandemic. Domains such as oxygen saturation and hemodynamic targets would be expected to remain active during a pandemic. The default plan is that during a pandemic, patients in the PISOP and PINSNIP stratum will be eligible to receive an assignment in these domains and will be analyzed in the interpandemic model which will continue to be analyzed for statistical triggers and platform conclusions. Patients with pandemic infection will have their treatment assignments in such domains weighted according to RAR as specified by the interpandemic model which will continue to be updated during a pandemic.

The ventilation domain, which utilizes a statistical model that applies only to that domain, is expected to continue during a pandemic. If appropriate, the pandemic strata may be applied to this domain. If so, the PISOP stratum would apply informative priors.

Any new domain that is initiated during a pandemic will be submitted for ethical review and require ethical approval prior to commencement.

Use of informative priors derived from information available from outside the REMAP

The default position is that informative priors derived from information that is external to the REMAP will not be utilized. However, if appropriate, based on high quality evidence,

informative priors may be applied. The decision to apply informative priors lies with the ITSC and must involve consultation with relevant external stakeholders, the DSMB, and appropriate statistical advice regarding the potential implications for the use of informative priors.

Endpoints

Pandemic primary endpoint

Specified domains, for patients in the PISOP stratum, will be analyzed using a separate statistical model, for which the primary endpoint is called the "pandemic primary endpoint". The default pandemic primary endpoint will be a composite end-point that comprises the number of whole and part study days for which the patient is alive and not admitted to an ICU up until the end of study day 21. All patients who die before discharge from an acute hospital, irrespective of whether this occurs before or after D21, will be coded as zero days. Patients who die between D21 and discharge from an acute hospital will be updated at the time of the next adaptive analysis. All whole and part days after discharge from an acute hospital and before D21 will be counted as being not admitted to an ICU. Hospital readmission that included a new admission to ICU between first discharge from an acute hospital and D21 will not contribute to the primary end-point.

If appropriate, based on an understanding of clinical and biological factors, as well as operational factors, an alternative pandemic primary end-point may be specified at the time of activation of the PAtC. Other possible primary end-points include days alive and outside the ICU with alternative durations of follow up or the use of an alternative composite based on days alive without organ support. The pandemic primary endpoint will be used for the adaptive analyses that inform the RAR and for Statistical Triggers.

Secondary endpoints

All secondary endpoints that are specified in the Core Protocol and active DSAs will continue to be active. The primary end-point specified in the Core Protocol (all-cause mortality at day 90) is a secondary end-point in the PISOP stratum.

Principles of the statistical analysis

Adaptive analyses

Adaptive analyses may be conducted more frequently and with varying cadence during a pandemic. For analyses conducted in the pandemic model and the PISOP stratum of the ventilation model, data from all available patients will be utilized using, where appropriate, modelling to impute missing data. Adaptive analyses may be conducted at different frequency for the PISOP and PINSNP stratum.

Response adaptive randomization

For PISOP patients, RAR proportions for domains that are analyzed using the pandemic model will be derived from the pandemic model and the RAR proportions for domains that are analyzed using the interpandemic model will be derived from the interpandemic model. For PINSNP patients, the RAR proportions for all qualifying domains will be derived from the interpandemic model.

If feasible, the option of allowing sites to start with imbalanced RAR proportions may be utilized. During a pandemic, issues related to equipoise for sites to participate may be facilitated by allowing sites to select from a range of starting RAR proportions that are imbalanced. Being able to implement this would be dependent on logistic feasibility as well as evaluation to exclude any adverse impact on inference.

Thresholds for statistical triggers

Introduction

The Core Protocol specifies thresholds for Statistical Triggers that apply to superiority, inferiority, and equivalence. For PISOP patients, different thresholds for Statistical Triggers may apply during a pandemic. The decision to modify a statistical threshold will be made by the ITSC prior to the first adaptive analysis of the pandemic model. Different thresholds may be applied to different domains. Thresholds can also be specified that are asymmetric for example less stringent for inferiority than superiority. Factors that the ITSC will take into account in considering whether to modify a threshold include whether the interventions being evaluated are comparative effectiveness options (i.e. interventions that are available as part of standard care and available outside the platform) or experimental interventions with uncertain safety and risk profile that may be available only within the platform.
All decisions regarding thresholds for Statistical Triggers will be communicated to participating sites and placed in the public domain on the study website. Once specified, thresholds cannot be modified unless recommended by the DSMB.
The default thresholds are outlined in the following sections.

Intervention Superiority Statistical Trigger

At any adaptive analysis, if a single intervention has at least a 0.95 posterior probability of being a member of the optimal regimen, for that unit-of-analysis, then that intervention will be deemed as being superior to all other interventions in that domain in that target population.
The declaration of a Platform Conclusion by the DSMB for superiority will result in application of 100% RAR (see section 7.6.4). Following implementation of 100% RAR, the posterior probability will continue to be updated and evaluated by the DSMB who are empowered to act if they have concerns regarding the validity of a Platform Conclusion.

Intervention Inferiority Statistical Trigger

At any adaptive analysis, if a single intervention has less than a 0.05 posterior probability of being a member of the optimal regimen, for a unit-of-analysis, then that intervention will be deemed as being inferior to other interventions in the domain for that target population. An asymmetrical inferiority statistical trigger may be set, particularly if an active intervention was being evaluated against an intervention that specifies no active treatment in that domain.

Equivalence

The equivalence boundary (delta) for different endpoints selected for the PISOP stratum may be changed depending on the clinical impact of the delta for the chosen endpoint. The default delta for the Core Protocol will be used to select clinically similar effects on the chosen primary endpoint. If a 21-day ICU-free day endpoint is selected the 20% proportional odds equivalency delta will be the default.

Actions when a Statistical Trigger is achieved

The actions that occur when a statistical trigger is achieved are those which are specified in the Core Protocol. At the time of a Platform Conclusion that is relevant to public health or clinical management of patients with suspected or proven pandemic infection, the DSMB and ITSC are empowered to liaise directly with relevant public health authorities prior to public presentation or publication of results.

Pre-specified subgroup analyses after achievement of a platform conclusion

Pre-specified subgroup analyses that will be conducted after a Platform Conclusion are outlined in each DSA. If a DSA does not specify a sub-group analysis related to the pandemic strata such analysis is permitted if the PISOP stratum has been open.

Closure of the PISOP stratum and incorporation of data from pandemic statistical model into the interpandemic statistical model

The ITSC is permitted to close or suspend the PISOP stratum. At this time, evaluation of new patients within the pandemic model will cease. After the permanent closure of the PISOP stratum, the information related to domains that have been analyzed for PISOP patients within the pandemic model will be added to the interpandemic model retaining, if appropriate, a co-variate or stratum status, to reflect that the patient was enrolled in the PISOP stratum.

Domains with their own statistical model

It is intended that domains with their own statistical model (e.g. as anticipated for the ventilation domain) will continue to be analyzed using the separate statistical model. If the PISOP stratum was applied to such a domain it is intended that a pandemic version of the separate model would be commenced and enroll only patients in the PISOP stratum. This model would utilize the pandemic primary end-point and would use informative priors derived from the preceding model. An operational decision may be made to apply an end-point that is different to the pandemic primary end-point in a domain with its own model.

GOVERNANCE, ETHICAL, AND OPERATIONAL CONSIDERATIONS IN A PANDEMIC

Decision to activate pandemic stratum

The decision to open the pandemic stratum lies with the ITSC. In deciding to activate the pandemic stratum the ITSC should take into account, but is not dependent on, declaration of a pandemic by the WHO and decisions about pandemic activation by regional pandemic preparedness consortia.
The decision to open will be communicated to RCCs and participating sites as an operational document. Each RCC will maintain a log of the dates for which sites were activated for the PISOP stratum.

Data collection and management

A pandemic is likely to result in a substantial increase in clinical workload for sites participating in REMAP-CAP. This is acknowledged by the REMAP-CAP management, as is the primacy of patient care. The importance of contemporaneous data collection, particularly with

respect to variables that are needed for adaptive analyses will be emphasized to sites. RCCs will seek to support sites as much as possible, including with requests to healthcare systems, public health authorities, and funding agencies to provide resources that allow sites to maintain data collection that is timely and complete.

Role of the DSMB

In a pandemic the role of the DSMB is modified, taking into account the public health importance of clinical evidence during a pandemic. In meeting the requirements of their Charter during a pandemic the DSMB should consider issues of public health in addition to the well-being of participants and the scientific integrity of the platform. The in-principle views of the DSMB may be obtained by the ITSC with regard to the setting of modified thresholds for statistical triggers.
While the PISOP stratum is open the DSMB is also permitted to liaise with public health authorities regarding the results and appropriate interpretation of adaptive analyses in keeping with prevailing international standards. If the DSMB communicates with public health authorities the ITSC must be informed that such communication has occurred but the content of that communication may remain confidential between the DSMB and the relevant public health authorities. The DSMB may recommend to the ITSC that public reporting of posterior probabilities that have not attained a threshold for a Statistical Trigger should occur.
The workload of the DSMB may be substantial during a pandemic and, if requested by the DSMB, the ITSC will appoint additional members.

Communication of trial results

Any Platform Conclusion that is relevant to public health that occurs during a pandemic will be presented or published as soon as possible, noting that additional work to report baseline status and secondary end-points will need to occur prior to presentation and publication of results.

- ***Funding of the trial***

The trial is currently funded as described in the Core Protocol.
During the interpandemic period and during a pandemic, additional funding will be sought to provide resources for activities that exceed those that will be occurring during the interpandemic period. Possible sources of additional resources include, but are not limited to, healthcare systems, public health authorities, and local and international research funding bodies.

Monitoring

It is acknowledged that during a pandemic site monitoring may be delayed for logistical reasons. The operational monitoring plan may be updated to reflect issues that are specific to a pandemic. As outlined in Core Protocol, the DSMB will take into account intensity of monitoring and time of consideration of a Platform Conclusion. If appropriate, the contribution of data that has not been monitored as per the non-pandemic monitoring plan will be acknowledged in the public reporting of Platform Conclusions.

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Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP):

PANDEMIC APPENDIX TO THE CORE PROTOCOL (REMAP-COVID)

REMAP-CAP Pandemic Appendix to the Core Protocol Version 2.0 dated 18 May 2020

Summary

Background: REMAP-CAP is an adaptive platform trial that evaluates multiple aspects of care of patients who are admitted to an Intensive Care Unit (ICU) with severe Community Acquired Pneumonia. It is reasonable to presume that any pandemic respiratory infection of major significance to public health will manifest as severe Community Acquired Pneumonia with concomitant admission to an ICU. Previous pandemics and more localized outbreaks of respiratory emerging infections have resulted in severe Community Acquired Pneumonia (CAP) and admission to an Intensive Care Unit[1-3]. Admission to an ICU may occur at the time of first presentation to a hospital or may be preceded by admission to a non-ICU ward or floor. For patients admitted to a non-ICU ward there is an opportunity to intervene to prevent the development of severe CAP. A pandemic of respiratory infection is much more likely to be caused by a virus than a bacterium. Differences in trial design may be required for influenza, viruses which are known to result in periodic but unpredictable pandemics, in comparison with other viruses, such as Coronaviruses that may also have pandemic potential.

Previous pandemics and outbreaks of emerging infectious diseases have outlined the urgent need for evidence, preferably from Randomized Clinical Trials, to guide best treatment. However, there are substantial challenges associated with being able to organize such trials when the time of onset of a pandemic and its exact nature are unpredictable[4-6]. As an adaptive platform trial that enrolls patients during the interpandemic period, REMAP-CAP is ideally positioned to adapt, in the event of a respiratory pandemic, to evaluate existing potential as well as novel treatment approaches.

The precise nature of a respiratory pandemic cannot be known in advance. The Pandemic Appendix to the Core Protocol lists potential adaptations to trial design and management that are generic, in that they will occur irrespective of the nature of the pandemic, as well as adaptations that are possible, depending on the nature of the pandemic, and the process for determining which adaptations will be applied.

The Pandemic Appendix to the Core Protocol also achieves alignment with a separate document, REMAP-COVID Core Protocol, which comprises only those elements of the Core Protocol of REMAP-CAP and the Pandemic Appendix that applies to the COVID-19 pandemic. For the COVID-19 pandemic, a site can utilize either the REMAP-CAP Core Protocol combined with the Pandemic Appendix to the Core Protocol, or REMAP-COVID Core Protocol. Both sets of documents specify identical methods and data requirements. Data derived from sites using either set of documents is

analyzed in the same pandemic statistical model. A single site must use either REMAP-COVID Core Protocol or REMAP-CAP Core Protocol with this associated pandemic appendix.

The objective of the Pandemic Appendix to the Core Protocol (PAtC) is to describe the adaptations to the Core Protocol that would apply during a pandemic, including how analyses of domains already operative during the interpandemic period as well as domains that are pandemic-specific, will be integrated during a pandemic. This includes scientific, as well as governance and logistic aspects.

Aim: The primary objective of the REMAP during a pandemic is to identify the effect of a range of interventions to improve outcome for patients admitted to a hospital with acute illness due to suspected or proven pandemic infection, as defined by the pandemic primary end-point.

Methods: The methods that will be utilized during a pandemic are those in the Core Protocol but with potential for changes to the primary end-point, frequency and process for adaptive analyses, and determination of which domains will be analyzed using a statistical model that includes data from patients with proven or suspected pandemic infection. During a pandemic, patients who are neither suspected nor proven to have pandemic infection and for certain pre-existing domains, will continue to be analyzed using the statistical model that is outlined in the Core Protocol that was operating during the pre-pandemic period. Depending on the characteristics of a pandemic, one or more interpandemic domains may be analyzed within the pandemic statistical model and one or more pandemic-specific domains may be commenced for patients with suspected or proven pandemic infection.

Lay description

REMAP-CAP is a global trial examining the best treatments for community-acquired pneumonia. In the setting of a pandemic that causes life-threatening respiratory infection, some key aspects of the study will be changed to integrate new interventions into the trial, evaluate existing interventions within the trial specifically in patients with pandemic infection, alter trial governance, and provide time-critical data for public health. This will allow the platform to identify which treatments work best for patients during a pandemic.

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1. ABBREVIATIONS

CAP	Community-Acquired Pneumonia
CRF	Case Report Form
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
MERS-CoV	Middle-Eastern Respiratory Syndrome Coronavirus
NAI	Neuraminidase inhibitors
PAtC	Pandemic Appendix to the Core Protocol
PINSNP	Pandemic infection is neither suspected nor proven
PISOP	Pandemic infection is either suspected or proven
PWG	Pandemic Working Group
RAR	Response Adaptive Randomization
REMAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RCC	Regional Coordinating Center
RCT	Randomized Controlled Trial
RSA	Region Specific Appendix
SAC	Statistical Analysis Committee
SARS	Severe Acute Respiratory Syndrome
WHO	World Health Organization

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see glossary, Section 1.2 Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), a Registry Appendix, this Pandemic Appendix to the Core Protocol, and multiple Regions-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject of a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis, because the analysis model will change over time in accordance with the domain and intervention trial adaptations, but this information is contained in the Statistical Analysis Appendix. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within an RSA. This includes information related to local management, governance, and ethical and regulatory

aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

3. PANDEMIC APPENDIX TO THE CORE PROTOCOL VERSION

The version of the Pandemic Appendix to the Core Protocol is in this document's header and on the cover page.

3.1. Version History

Version 1: Approved by the Pandemic Working Group on 31st January, 2020

Version 1.1: Approved by the Pandemic Working Group on 12th February, 2020

Version 2.0: Approved by the Pandemic Working Group on 18th May, 2020

4. PANDEMIC APPENDIX TO THE CORE PROTOCOL GOVERNANCE

The study administration structure is outlined in the Core Protocol. As outlined in the Core Protocol, a Pandemic Working Group (PWG) is established and works in conjunction with the International Trial Steering Committee (ITSC), to take responsibility for the Pandemic Appendix to the Core Protocol (PAtC) and to advise on operational aspects following emergence of a pandemic.

4.1. Pandemic Working Group

The responsibility of the PWG is to maintain and update this PAtC and to advise the ITSC regarding application of the PAtC during a pandemic. The PWG will liaise with individuals and organizations that are external to REMAP-CAP as required. Membership of the PWG is flexible. The core membership is listed but additional members can be added at any time and as required.

Chair: The Chair of the ITSC will Chair the Pandemic Working Group

Members: Prof. Derek Angus

Prof. Yaseen Arabi

Prof. Richard Beasley

A/Prof. Scott Berry

Prof. Frank Brunkhorst

Dr. Lennie Derde

Dr. Robert Fowler

Prof. Anthony Gordon

Mr. Cameron Green

Dr. Ed Litton

Prof. John Marshall

Dr. Colin McArthur

A/Prof Bryan McVerry

Dr. Srinivas Murthy

Prof. Alistair Nichol

Ms. Jane Parker

Prof. Kathy Rowan

Prof. Tim Uyeki

Prof. Steve Webb

4.2. Contact Details

Chair: Professor Steve Webb

Department of Epidemiology and Preventive Medicine

School of Public Health and Preventive Medicine, Monash University

Level 3, 533 St Kilda Road

Melbourne, Victoria, 3004

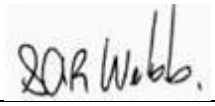
AUSTRALIA

Phone: +61 3 9903 0343

Email: steven.webb@monash.edu

5. PANDEMIC WORKING GROUP AUTHORISATION

The Pandemic Working Group have read the appendix and authorize it as the official Pandemic Appendix to the Core Protocol for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair  Date 18th May, 2020

Steve Webb

6. BACKGROUND AND RATIONALE

6.1. Introduction

It is reasonable to presume that any pandemic respiratory infection of major significance to public health will manifest as life-threatening respiratory infection including Severe Acute Respiratory illness and severe Community Acquired Pneumonia (CAP) with concomitant admission to hospital, and for some patients, admission to an Intensive Care Unit (ICU). Previous pandemics and more localized outbreaks of respiratory emerging infections have resulted in severe CAP and ICU admission[1-3]. A pandemic of respiratory infection is much more likely to be caused by a virus than a bacterium and, among viruses a distinction should be drawn between influenza, which is known to result in periodic but unpredictable pandemics, and other viruses, such as Coronaviruses, that may have pandemic potential, as the features of trial design may be different.

Previous pandemics and outbreaks of emerging infectious diseases have outlined the urgent need for evidence, preferably from Randomized Controlled Trials (RCTs), to guide best treatment. However, there are substantial challenges associated with being able to organize such trials when the time of onset of a pandemic and its exact nature are unpredictable[4-6]. As an adaptive platform trial that enrolls patients during the interpandemic period, REMAP-CAP is ideally positioned to adapt, in the event of a respiratory pandemic, to evaluate existing treatments as well as novel approaches.

One of the challenges associated with planning clinical trials during a pandemic is that the precise nature of the infecting organism, clinical consequences, and suitable interventions (particularly those that are pathogen-specific) cannot be reliably known in advance. The speed of clinical progression, from initial infection to life-threatening severe respiratory infection is another feature

that cannot be reliably known in advance. It is likely that a proportion of patients will present with severe CAP but other patients may present to medical attention with illness that is less severe, but remain at risk of progression to severe illness. Patients who require hospital admission, but have less severe illness are a particularly important group, because early intervention at this stage of illness may prevent progression to life-threatening illness. It is also possible that proposed treatment interventions may have differential treatment effect depending on the level of illness severity at the time that treatment is commenced, including treatment effects that are divergent. Nevertheless, a range of scenarios can be anticipated and used to provide direction and guidance regarding the most appropriate research response.

The most likely organism responsible for a respiratory pandemic is a novel influenza virus that has undergone antigenic shift[7]; the most recent influenza pandemic occurred during 2009-2010. In recent years, there have been outbreaks of severe Community Acquired Pneumonia due to novel Coronaviruses which resulted in the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003 and the Middle-Eastern Respiratory Syndrome Coronavirus (MERS-CoV) outbreak that commenced in 2012. SARS-CoV-2 is the cause of a pandemic of severe respiratory disease (COVID-19), including pneumonia, that commenced in 2019. The pre-specified adaptations to REMAP-CAP will need to be different for influenza in comparison to a non-influenza pandemic pathogen.

6.2. Pandemic research preparedness

6.2.1. Introduction

The conceptual approach to pandemic preparedness has been influenced substantially by the occurrence of the 2009 Influenza A H1N1(2009)pdm pandemic, outbreaks of SARS and MERS-CoV, the Zika pandemic, and Ebola virus disease outbreaks in West Africa[8]. A broad conclusion from these outbreaks is that it is likely that high quality research can change the incidence and consequences of the epidemic but that such research is extremely difficult because planning of research only commences after the discovery of the epidemic. As a consequence, researchers and organizations interested in developing improved processes for research have identified three key elements to facilitate time-critical research about an epidemic. These elements are that the research must be pre-planned, pre-approved, and practiced[9,10]. REMAP-CAP and, in particular, the PAtC, is an attempt to establish these pre-requisites and to guide treatment for patients who may be critically ill with pneumonia as a consequence of infection with a pandemic organism.

The World Health Organization (WHO) has recommended establishing and strengthening outbreak-ready, multi-center clinical research networks in geographically diverse regions to facilitate research

during pandemics.[11] It has also recommended testing of protocols during interpandemic periods and stressed the value of such clinical research consortia in collecting and distributing information during a future pandemic.

6.2.2. Pre-planned

Pre-planned means that the trial protocol is written and that the trial processes related to project management, screening, recruitment, delivery of interventions, data collection, data management, analysis, and reporting are all in place. The PAtC, in conjunction with the existing REMAP-CAP protocol documents and trial processes, will mean that all aspects that can be pre-planned have been.

6.2.3. Pre-approved

The PAtC is a key component of the of the pre-approval strategy. The availability of this document allows ethics review boards, hospital research governance staff, existing and potential sites to understand and approve the study processes that would be implemented during a pandemic. Where different options need to exist, depending on the nature of the pandemic, these are pre-specified, as much as possible. Any unanticipated substantive deviation from this Appendix would be subject to an amendment, hopefully expedited, in the event of a pandemic. The PAtC, like the Core Protocol, does not specify any interventions that are evaluated within the REMAP. It is highly likely that one or more research questions (in domains already approved during the interpandemic period) will be relevant specifically in patients with severe respiratory disease including pneumonia caused by the pandemic infection. The PAtC allows these questions to continue to be answered specifically in patients with pandemic infection, where appropriate, using Bayesian prior probabilities derived from patients already enrolled during the interpandemic period. It is proposed to develop 'sleeping domains', which could be activated if appropriate during a pandemic, as well as retain the option of developing one or more completely new domains following the emergence of pandemic, which would require separate ethical approval and contracts with participating sites.

This strategy, as part of the study design, offers an ethically, clinically and legally acceptable mechanism for research in the context of a pandemic that can be initiated rapidly.

There are two further aspects relevant to ethical approval of the PAtC. The first is that existing or pandemic-specific domains of REMAP-CAP may include an intervention that specifies no treatment within that domain (noting that the Core Protocol specifies that all additional standard care is provided with treatment decisions being made by the treating clinician). This is clinically and

ethically appropriate as the response of critically ill patients to a range of different treatments has proven to be unpredictable. There are many examples of treatments that have resulted in harm[12] and situations in which surrogate outcome measures were not reliable indicators of improvement in patient-centered outcomes. As such, there should not be any presumption that it is better for patients to receive active interventions.

The second is the capacity to apply Response Adaptive Randomization (RAR) within the REMAP. As outlined in the Core Protocol, RAR results in an increasing proportion of patients being allocated to any intervention within a domain that has a higher probability of being superior with that proportion increasing as statistical confidence accrues. Participants within REMAP-CAP during a pandemic may be able to benefit from information about the relative effectiveness of interventions that is not in the public domain and not available to patients who are not participants in REMAP-CAP. As outlined in the Core Protocol, any intervention confirmed to be superior within the REMAP is then implemented by application of a RAR proportion that is equal to 100%. RAR will be implemented for pandemic patients as soon as sufficient data have accrued and operational implementation is feasible.

6.2.4. Practiced

REMAP-CAP will be recruiting during the interpandemic period in multiple countries in both Southern and Northern Hemispheres with the support of several Regional Coordinating Centers. This research activity, during the interpandemic period, ensures that sites, site training, project management, data management, analysis processes, and trial governance are functional and practiced. Furthermore, the eligibility process and delivery of trial interventions are optimized for embedding which allows study processes to occur within minimal disruption to the delivery of clinical care, which may well be under substantial strain during a pandemic. There is already extensive experience with the Case Report Form (CRF) that is used and will continue to be used during a pandemic.

6.2.5. Implications of REMAP design during a pandemic

6.2.5.1. Time-critical generation of evidence

A pandemic will likely result in a large number of affected persons with cases occurring over a short period of time, perhaps as short as a few months. Conventional clinical trials that utilize frequentist statistical techniques require a fixed sample size with limited capacity to analyze the results of the trial until recruitment is completed. The setting of the sample size requires an estimate of the size of the treatment effect and it is known that the assumptions that are made in setting the size of the

treatment effect are often incorrect[13,14]. A frequentist trial that over-estimates the size of the treatment effect may conclude without reaching a valid conclusion, whereas one that under-estimates the size of the treatment effect is delayed in providing time-critical information that the treatment is even more effective than estimated.

REMAP-CAP utilizes Bayesian statistical methods which allow frequent adaptive analyses to occur. This will ensure that time-critical information about the effectiveness of treatment interventions is not delayed unnecessarily. The REMAP design is particularly suited to pandemics because it requires no pre-trial assumptions about the size of the treatment effect and will allow dissemination of evidence as soon as possible. Furthermore, as the trial progresses during a pandemic the Data Safety Monitoring Board (DSMB) has access to information from adaptive analyses that may not achieve thresholds to allow reporting as a Platform Conclusion but may be relevant to public health which, under appropriate circumstances, can be shared with public health authorities and the DSMBs of other trials evaluating the same or similar interventions without threatening the scientific validity of the ongoing trial.

6.2.5.2. Multifactorial design and evaluation of interactions

If there are multiple interventions, each of which may have independent effects on outcome, the multi-factorial nature of a REMAP allows these to be evaluated simultaneously, rather than in series or in separate parallel trials (see *Figure 1*). This design feature contributes to efficiency and is also anticipated to result in more clinical evidence being generated more rapidly during a time-critical pandemic.

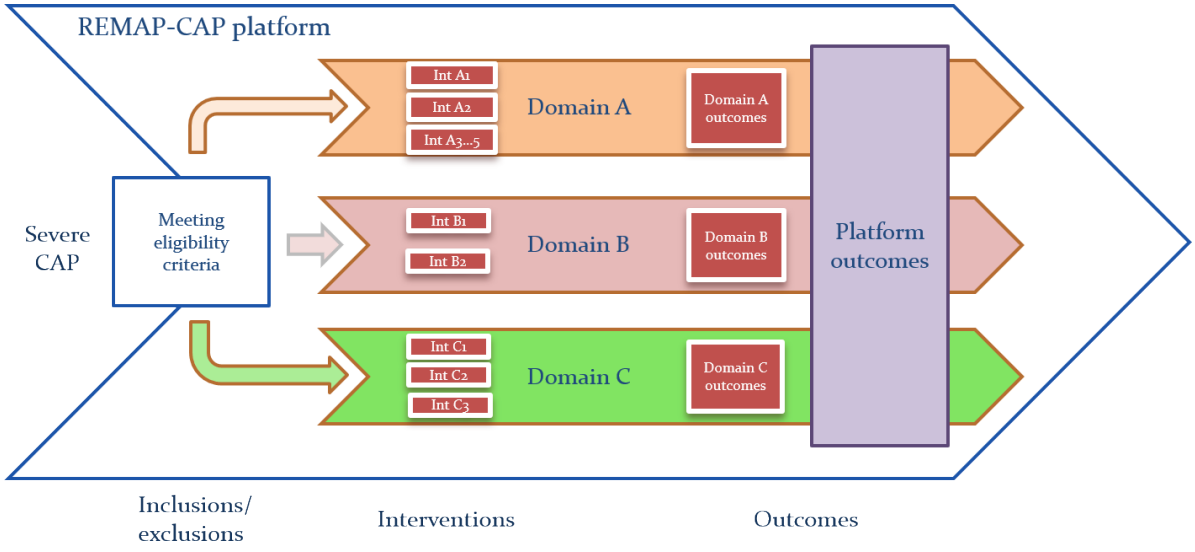


Figure 1. The multifactorial structure of REMAP-CAP

Furthermore, where pre-specified, the statistical model utilized in REMAP-CAP will allow estimation of treatment effect of interventions that may be contingent on other treatment assignments within the pandemic component of the REMAP. For example, it is plausible that the effectiveness of an intervention for immune modulation is dependent on co-delivery of an agent that is effective at inhibiting growth or replication of the pathogen. Conventional trials, in which only a single domain of treatment is evaluated, are not capable of detecting this type of treatment-by-treatment interaction, and thereby unable to identify the best overall treatment strategy for these patients.

6.2.6. Setting of research priorities

In 2017, the WHO outlined the research priorities for a pandemic that was caused by a novel strain of influenza. These priorities were:

- Research on the effectiveness of empirical treatment with oseltamivir and other neuraminidase inhibitors (NAI) in critically ill patients, including placebo-controlled trials during seasonal as well as pandemic influenza.
- Investigating alternative strategies to NAI monotherapy to increase antiviral potency and improve clinical outcomes.
- Research on immune-modulatory strategies in severe influenza, including corticosteroids and macrolides.
- A need for high quality data on the effectiveness of most aspects of supportive care related to influenza.
- A need to assess the roles of virologic factors (e.g. replication sites, duration and viral load levels) in larger numbers of patients (including critically ill patients) in causing severe disease and associated complications, linking them to clinical outcomes.

REMAP-CAP is not able to meet all of these requirements but is well suited to evaluate the effectiveness of antiviral therapies active against influenza, immune modulatory strategies and different aspects of supportive care[15]. Identical or similar research questions would exist for any pandemic caused by an organism that was not influenza and REMAP-CAP has also similar capabilities in this scenario.

6.3. WHO endorsement

REMAP-CAP has been designated by the WHO as a Pandemic Special Study. Under this designation, it has been tasked with helping answer crucial questions during a declared pandemic, as listed above. This designation ensures that knowledge translation of clinical trial results can occur directly

with policymakers and public health officials for rapid implementation around the globe. It ensures that results generated from REMAP-CAP during a declared pandemic can be translated in an efficient and transparent manner to benefit affected patients.

7. ADAPTATION OF REMAP-CAP DURING A PANDEMIC

This PAtC supplements the Core Protocol during a pandemic including deactivation at the conclusion of a pandemic. Decisions regarding the operationalization of the Pandemic Appendix to the Core Protocol are made by the ITSC with advice from the PWG (see Section 8.1). The Appendix sets out all potential adaptations of the Core Protocol and unless otherwise specified, all other aspects of the Core Protocol remain active. Activation of the PAtC will be advised to the DSMB with specification of the selected operational characteristics.

7.1. Objectives

The primary objective of this REMAP during a pandemic is to identify the effect of a range of interventions to improve outcome for adult patients admitted to hospital with acute illness due to suspected or proven pandemic infection, as defined by the pandemic primary end-point.

The secondary objective is to determine the effect of a range of interventions on additional endpoints, including endpoints developed by the World Health Organization and adopted core outcome sets.

7.2. Study setting: definition of an ICU and relationship of setting to severity of illness

During the interpandemic period, the REMAP recruits only participants who are admitted to an ICU, and a combination of admission to ICU as well as provision of treatments to support failed organs is used to define severity and eligibility. During a pandemic, there are several factors that may influence the relationship between admission to an ICU and severity of illness. Firstly, there may be insufficient ICU beds available to care for all critically ill patients. This may result in provision of advanced organ support occurring in locations that do not usually provide ICU-level care. During a pandemic, such a location is referred to as a re-purposed ICU. However, a re-purposed ICU needs to be distinguished from a usual hospital ward that is capable of providing some forms of organ support, such as non-invasive ventilation. During a pandemic, there may be substantial delays in transferring a patient from an emergency department to either a ward or an ICU (or a re-purposed ICU). Patients in an emergency department who have been accepted for admission to an ICU are regarded as being admitted to an ICU. Patients in an emergency department who have been

accepted for admission to a ward are regarded as being admitted to a ward. Secondly, patients who are not critically ill may be treated on an ICU for reasons that are not related to severity of illness, such as access to single rooms to achieve objectives related to infection control and prevention. This can influence both admission as well as discharge practices. Thirdly, the threshold at which support for failed organs is provided may be influenced by infection control practices. For example, some forms of respiratory support may be withheld because of concerns related to the risk that staff who are caring for patients may acquire the infection.

To minimize these issues, during a pandemic, the primary determinant of severity is the provision of ICU-level care, which can be interpreted in conjunction with the physical location in which care is being provided. Determination of severity may also take into account a decision to withhold some form of organ failure support that would otherwise have be provided. Where a definition of an ICU is needed, at sites at which the pandemic stratum (see below) has been activated, an area within the hospital that is repurposed so as to be able to deliver one or more of the qualifying organ failure supports specified in the Core Protocol (non-invasive ventilation, invasive ventilation, and vasopressor therapy) will meet the definition of an Intensive Care Unit. It is preferred in such circumstances that the patient is under the care of a specialist who is trained in the provision of critical care, but this is not an essential requirement. A respiratory or other ward that provides non-invasive ventilation (including oxygen therapy delivered by high flow nasal cannula) and continues to do so during a pandemic, will not, generally, meet the definition of an ICU, particularly if the patient is not under the care of a specialist who is trained in the provision of critical care.

In some DSAs, an exclusion criteria is applied to only permit enrollment during a time-window that commences with ICU admission. For the reasons noted above, this may be operationalized using a time-window, of the same duration, that commences with the provision of sustained organ failure support.

7.3. Eligibility criteria

Platform-level eligibility criteria may be modified if necessary to accommodate a published case definition, to align with criteria specified in guidelines, such as the ATS/IDSA guidelines on CAP[16], or to accommodate necessary modifications to the online eligibility system used for enrollment. In previous epidemics of community-based infection, nosocomial acquisition has been well described. Relaxation of the requirement for community acquisition or organ failure criteria or both may be appropriate. In this regard, Version 2.0 of this Appendix modifies the organ failure support criteria so that these no longer apply as a platform-level inclusion criteria, permitting the enrollment of

patients into the platform who are admitted to hospital or an ICU, either with or without organ failure support criteria. In association with the removal of the organ failure requirement, the requirement for a patient to meet criteria for pneumonia may be replaced with a requirement for acute illness due to suspected or proven pandemic infection. All changes to eligibility criteria would apply only to patients in the pandemic stratum (see section 7.4).

As such, the modified platform-level inclusion and exclusion criteria are:

In order to be eligible to participate in the pandemic aspects of REMAP-CAP, a patient must meet the following criteria:

1. Adult patient admitted to hospital with acute illness due to suspected or proven pandemic infection

A potentially eligible patient who meets any of the following criteria will be excluded from participation in this trial:

1. Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment
2. Patient is expected to be discharged from hospital today or tomorrow
3. More than 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven pandemic infection
4. Previous participation in this REMAP within the last 90 days

This extension of the platform-level inclusion criteria can apply to patients admitted to an ICU or a ward. In association with the involvement of different clinical teams, the domains and interventions that are available for patients admitted to a ward compared with those admitted to an ICU are permitted to be, but do not have to be, different.

7.4. Pandemic stratum

7.4.1. Introduction

As outlined in the Core Protocol, a pre-specified stratum of the REMAP is the presence or absence of suspected or proven pandemic infection. This is maintained as a 'passive stratum' during the interpandemic period that can become active during a pandemic. It consists of two exclusive strata categories: pandemic infection is neither suspected nor proven (PINSNP) and pandemic infection is

either suspected or proven (PISOP) at baseline. At times when the PAtC is not activated, i.e. during the interpandemic period, all participants are categorized as PINSNP.

7.4.2. Activation and deactivation of the PAtC and PISOP stratum

In response to a pandemic (see section 8.1), the PISOP stratum is activated using a two-step process. First there is a decision of the ITSC to open the PISOP stratum for the platform. The second step is site-by-site activation of the PISOP stratum, requiring agreement of both the site and the Regional Coordinating Centre (RCC). This allows variation in activity of the pandemic infection to be accommodated with sites only open for PISOP recruitment when there is active pandemic infection locally. Switching-on of the stratum can occur at any time and expected to always be available with less than 24 hours lead time. The capacity to enroll patients into the PISOP stratum can be switched-off on a site-by-site basis, but the ITSC can switch off the PISOP stratum for all sites if it is believed that a pandemic is no longer ongoing. The REMAP applies a new and separate statistical model for participants in the PISOP stratum which can utilize, where appropriate, informative priors derived from pre-pandemic PINSNP participants.

It should be noted that for sites in which the pandemic stratum is open, that the REMAP allows for continued recruitment of patients into the REMAP who are in the PINSNP stratum. For example, during an influenza pandemic, PINSNP would include patients with infection that has been proven to be a non-pandemic strain of influenza. During a pandemic, patients who are in the PINSNP stratum continue to be analyzed using the interpandemic statistical model (see below). As such, there are two categories of PINSNP participants- those included during the interpandemic phase and those included during a pandemic. Both categories of patients contribute to the interpandemic model for all active domains.

The PAtC is activated and deactivated for a site at the same time as the PISOP stratum is opened and closed. If a pandemic commences prior to ethical and governance approval of the PAtC, the PISOP stratum can be activated using approvals for the Core Protocol, and the PAtC would be activated as soon as ethical approval is obtained.

7.5. The pandemic statistical model

7.5.1. Introduction

The model that is active during the pandemic and includes only PISOP patients (for some or all domains) is referred to as the ***pandemic model***. The model that is active before (and after) the

pandemic, which includes PINSNP patients during the pandemic and may include some PISOP patients for some domains, is referred to as the ***interpandemic model*** (see *Figure 2*).

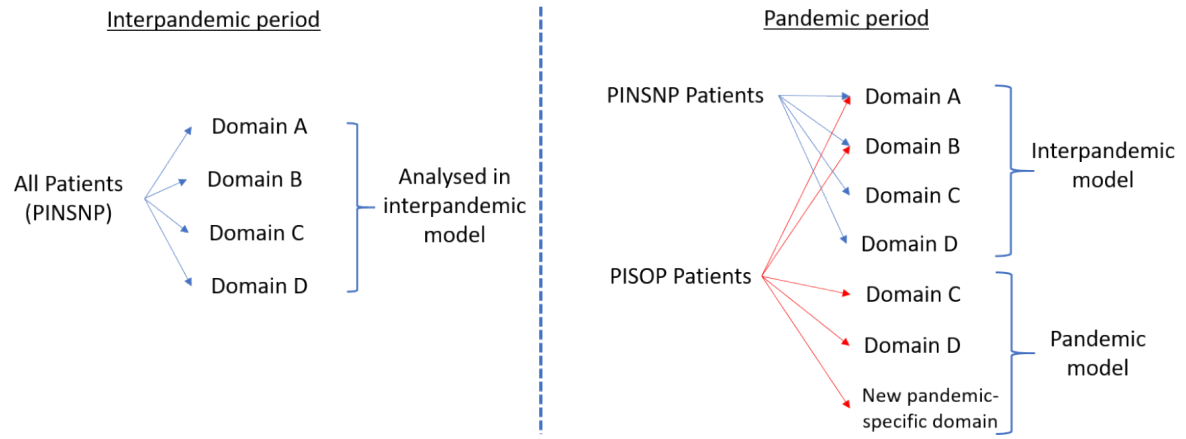


Figure 2. Diagram of the interpandemic and pandemic models

The pandemic model is only used for PISOP participants and only for those domains selected by the ITSC. A PISOP patient can contribute to both the pandemic and interpandemic model in different domains but each patient's contribution to a model is mutually exclusive with respect to each domain. The ITSC will select the domains to be included in the pandemic model where a differential treatment effect is postulated in the presence of pandemic infection or the need exists to learn about the outcome quickly, or both. The extension of this platform-level entry criteria does not apply to domains that are analyzed exclusively within the interpandemic statistical model.

A consequence of the application of two separate statistical models is that treatment-by-treatment interactions can only be evaluated for those domains that are in the same model. The principal advantages of the use of two models are:

- that this is necessary where the pandemic model requires a different primary end-point
- the platform is able to continue recruitment of patients with CAP who are neither suspected nor proven to have pandemic infection
- where appropriate informative priors can be included at commencement of the pandemic model
- where appropriate thresholds for a Statistical Trigger can be modified
- only those domains that are relevant to the pandemic are included within the pandemic model.

During the interpandemic period, it is intended that there may be some domains, for example the Ventilation Domain, that will utilize a separate domain-specific statistical model. It should be noted

that during the interpandemic period, such a domain is not part of the interpandemic statistical model. During a pandemic any such domain would continue to be evaluated with its own domain-specific statistical model. During a pandemic, the operating characteristics of the domain-specific statistical model may be modified in the same way that the pandemic model is modified from the interpandemic model. For example, PISOP patients may be analyzed within a pandemic version of the domain specific statistical model utilizing a modified primary end-point, with application of informative priors derived from the interpandemic time period.

7.5.2. Pre-specification of trial parameter options

There are many clinical features of a respiratory pandemic that cannot be predicted in advance. For several parameters related to trial design and statistical analysis, this Appendix pre-specifies a range of options from which the actual modifications will be chosen at the commencement of a pandemic. The appendix provides guidance regarding the principles that would guide selection from within the available options and often provides the planned default option. The provision of flexibility regarding limited aspects of trial design provides the capacity to tailor aspects of the trial to the characteristics of the pandemic. For these decisions, the ITSC has decision-making responsibility, with advice from the PWG. These decisions would be regarded as operational and, unless otherwise specified (5.3.4), will be made prior to the conduct of the first adaptive analysis using the pandemic model and would be made only from within the range of options pre-specified in this Appendix. It is not intended that the selected parameters would be modified in any way during the pandemic unless advised to do so by the DSMB. The selected trial parameters would be placed in the public domain, on the study website, and provided as an update to participating sites and relevant ethical review bodies prior to the first adaptive analysis of the PISOP stratum. These parameters are set out in a document termed Operating Characteristics and this document applies to both REMAP-CAP core protocol documents as well as the REMAP-COVID Core Protocol, to the extent that is necessary. It is also acknowledged that specification in a new domain, may influence a pre-existing domain, such as specification of evaluation of an interaction between domains. In this situation, the DSA for the pre-existing domain will not necessarily be amended immediately with the most recently approved or amended DSA serving to specify the inter-relationship between the two domains.

7.5.3. Application of other strata specified in the Core Protocol in the pandemic model

The shock strata may be applied to the PISOP stratum. The default position is that the shock strata will not be applied to the PISOP stratum.

If the pandemic is caused by a novel strain of influenza the pre-existing influenza strata is not applied in the pandemic model. For PINSNP patients, the “influenza present” stratum would continue to apply and would be used to differentiate patients infected with a non-pandemic strain of influenza from patients in the “influenza not present” stratum. Membership of PISOP and influenza present stratum are mutually exclusive. It is anticipated that the influenza present stratum would apply only to patients with infection due to a proven non-pandemic strain of influenza at baseline. Patients in whom influenza was suspected, but the results of strain-specific diagnostic tests were not available at the time of assessment of eligibility, will be allocated to the PISOP stratum at sites where the stratum is active.

7.5.4. Strata within the PISOP stratum

A strata applied within the PISOP stratum is the confirmation status of pandemic infection, defined in two categories, present or absent, based on the results of microbiological tests for the pandemic organism. Any patient with clinically suspected pandemic infection who is not tested or the result is not yet known will be deemed positive.

The availability and interpretation of microbiological tests are likely to change during the pandemic and an operational document will be used to specify how different tests are interpreted. It is noted that pandemic infection confirmed status is defined by the final results of testing for the pandemic organism which may include analysis of samples collected after enrollment where it is reasonable to presume that the sample reflected pandemic infection status at time of enrollment.

The sensitivity of microbiological testing for the pandemic organism may not be known at the beginning or even during the pandemic[17]. It is anticipated that initial analysis of the pandemic model will occur without application of this pandemic confirmation status strata but this would be applied when there was sufficient confidence about the operating characteristics of diagnostic tests in patients who are critically ill. If the pandemic confirmation status is applied, the probabilities derived from patients who have confirmed pandemic infection will be used to determine the RAR proportions for patients receiving treatment assignments in the pandemic specific domains within the PISOP stratum. Borrowing is permitted between the pandemic infection confirmed stratum and the pandemic infection not present stratum, using the methods outlined in the Core Protocol (with gamma = 0.15).

If eligibility criteria were modified to allow inclusion of a wider spectrum of illness severity, two or more states, related to severity of illness, may be applied within the PISOP stratum to distinguish current versus extended severity of illness.

7.5.5. States within the PISOP stratum

The Core Protocol defines 'state' as a set of mutually exclusive and exhaustive categories, defined by characteristics of a patient within the REMAP, that are capable of changing over time for a single patient at different time-points during the patient's participation in the REMAP (i.e. they can be dynamic). During the pandemic, and only for patients in the PISOP stratum, two or more states may be defined, depending on illness severity. The default categorization of severity will be into two categories:

- Severe State, defined by receiving organ failure support in an ICU
- Moderate State, defined by
    - Not being admitted to an ICU, or
    - Admitted to an ICU but not receiving organ failure support

Organ failure supports that qualify a patient as severe are aligned to those that previously determined eligibility to the platform (i.e. the Severe State corresponds to the previous platform eligibility criteria). These criteria are:

- Provision of invasive mechanical ventilation
- Provision of non-invasive mechanical ventilation (including high flow nasal cannula with a flow rate of at least 30 litres per minutes and a fractional inspired oxygen concentration of 40% or higher)
- Receiving infusion of vasopressor or inotropes or both

Where states are defined, eligibility for domains or selected interventions within a domain, may be specified according to state. As such, a domain may be available in one or more states. Where a domain is available in two or more states, the interventions available in that domain in each state are permitted to vary. States can also be utilized within the statistical model to define the unit-of-analysis, with declaration of Platform Conclusions, independently in one or more states, with borrowing permitted between states.

A single patient can move between states, one or more times, during a period of time which the patient is potentially eligible within the REMAP. For the purposes of assessment of eligibility for one or more domains, state is 'instantaneous' as at the time of that assessment. A patient who has previously received non-invasive ventilation or an infusion of vasopressor or inotrope or both, but is not receiving either of those therapies at time of assessment is deemed to be in the Moderate State. A patient who has been in the Severe State, as a consequence of receiving invasive mechanical

ventilation in an ICU, cannot re-enter the Moderate State for the purposes of assessment of eligibility. A patient who receives an assignment in the REMAP while in the Severe State cannot receive any subsequent assignments in the Moderate State. Where trial related processes, such as reveal of assignment or obtaining consent, create a time gap between initial assessment of eligibility and awareness of the patient's assignment, the state in which the patient is analyzed is that which occurred at the time of assessment, not the time of reveal of the assignment.

A patient enrolled while in the Moderate State, if reassessed for eligibility for additional domains having progressed to the Severe State, may have new microbiological information that has accumulated during this interval of time. This could result in a patient with suspected pandemic infection having information that results in pandemic infection being excluded, at the time of reassessment. In this situation, the patient is analyzed in the pandemic model, as enrolled, in the Moderate State and is not eligible for enrollment in new domains in the Severe State (including domains evaluated in the interpandemic model). It is also noted that, for a patient who is enrolled in both states, that other time-varying basline variables may have changed between each enrolment. For such aptients, potentially time-varying baseline variables will be collected in reference to enrolment in the Moderate State and again in reference to enrolment in the Severe State.

7.5.6. Domains incorporated in the pandemic model and use of informative priors derived from the interpandemic model

The domains that will be included within the pandemic model will be determined at the onset of a pandemic by the ITSC with advice from the PWG. Where appropriate and prior to the first adaptive analysis that is undertaken after activation of the PAtC, informative priors, derived from the interpandemic model (comprising patients enrolled in the REMAP prior to the pandemic), may be applied. If informative priors are applied, this is done by the Statistical Analysis Committee (SAC) who review the frequent adaptive analyses (and communicate these results to the DSMB on a regular basis). This will occur without knowledge of the values of the priors by the ITSC or any other investigator. The amount of influence that priors apply and how quickly priors are applied in combination with accruing new data will be specified by the ITSC. Coding that specifies the weighting of priors will be done by statisticians who are separate to the SAC and blind to results from adaptive analyses. With regard to selection of domains and the use of informative priors, the following principles will be applied.

7.5.6.1. Non-influenza pandemic organism

If the pandemic organism is not influenza, the following domains are intended to be included within the pandemic model:

- Corticosteroid Domain, without application of informative priors.
- Macrolide Duration Domain, without application of informative priors.
- New domains, as appropriate for the pandemic organism, without application of informative priors.

The Influenza Antiviral Domain (which includes only antiviral agents active against influenza) would not be applied in the pandemic model. It is noted that a patient at baseline could have suspected influenza and suspected pandemic infection which could lead to enrollment in the influenza domain (evaluated in the interpandemic model) and enrollment in other domains (evaluated in the pandemic model). It is not anticipated that the Antibiotic Domain is evaluated in the pandemic model, though this may be revised if the pandemic was caused by a bacterial pathogen. In this situation only those antibiotics that are known to be active against the pandemic organism would be available within the Antibiotic Domain for patients in the PISOP stratum.

7.5.6.2. Influenza pandemic

If the pandemic organism is influenza, the following domains are intended to be included within the pandemic model:

- Corticosteroid Domain, using informative priors derived from the influenza present stratum.
- Antiviral domain, using informative priors derived from the influenza positive stratum but with exclusion of any antiviral interventions that are clinically inappropriate because of the resistance profile of the pandemic strain of influenza. If there were no antiviral agents to which the pandemic strain of influenza was susceptible the Antiviral domain would not be applied in the PISOP stratum. During the pandemic if the pandemic strain of influenza acquired resistance to antiviral agents in the Antiviral Domain, these agents would be withdrawn from the domain at affected sites.
- Macrolide Duration Domain using informative priors derived from the unit-of-analysis of the Macrolide Duration Domain in the interpandemic model.
- New domains, as appropriate, without application of informative priors.

A number of other domains, related to organ failure support may be operative at the time of a pandemic. Domains such as oxygen saturation and hemodynamic targets would be expected to remain active during a pandemic. The default plan is that during a pandemic, patients in the PISOP and PINSNP strata will be eligible to receive an assignment in these domains and will be analyzed in the interpandemic model which will continue to be analyzed for statistical triggers and platform conclusions. Patients with pandemic infection will have their treatment assignments in such domains

weighted according to RAR as specified by the interpandemic model which will continue to be updated during a pandemic.

The ventilation domain, which utilizes a statistical model that applies only to that domain, is expected to continue during a pandemic. If appropriate, the pandemic strata may be applied to this domain. If so, the PISOP stratum would apply informative priors.

Any new domain that is initiated during a pandemic will be submitted for ethical review and require ethical approval prior to commencement.

7.5.7. Use of informative priors derived from information available from outside the REMAP

The default position is that informative priors derived from information that is external to the REMAP will not be utilized. However, if appropriate, based on high quality evidence, informative priors may be applied. The decision to apply informative priors lies with the ITSC and must involve consultation with relevant external stakeholders, the DSMB, and appropriate statistical advice regarding the potential implications for the use of informative priors.

7.6. Endpoints

7.6.1. Pandemic primary endpoint

Specified domains, for patients in the PISOP stratum, will be analyzed using a separate statistical model, for which the primary endpoint is called the “pandemic primary endpoint”. The default pandemic primary endpoint will be an ordinal scale that is a composite end-point that comprises mortality during the acute hospital admission and the number of whole and part study days for which the patient is alive and not requiring organ failure support while admitted to an ICU up until the end of study day 21. All patients who die before discharge from an acute hospital, irrespective of whether this occurs before or after D21, will be coded as –1 day. All patients who never receive organ failure support while admitted to an ICU will be coded as 22. Patients who die between D21 and discharge from an acute hospital will be updated at the time of the next adaptive analysis. All whole and part days after discharge from an acute hospital and before D21 will be counted as being not admitted to an ICU. Hospital readmission that included a new admission to ICU between first discharge from an acute hospital and D21 will not contribute to the primary end-point.

If appropriate, based on an understanding of clinical and biological factors, as well as operational factors, an alternative pandemic primary end-point may be specified at the time of activation of the PAtC or at any time prior to the first interim analysis using the pandemic statistical model. Other

possible primary end-points include days alive and outside the ICU with alternative durations of follow up or the use of an alternative composite based on admission to ICU. The pandemic primary endpoint will be used for the adaptive analyses that inform the RAR and for Statistical Triggers.

If the primary end-point includes a time-based outcome measure, assignment to one or more domains will occur at different time-points if the patient receives assignments in one or more domains while in the Moderate State and one or more domains in the Severe State. The commencement of the period of observation commences at the time of assignment, which can lead to the same patient having different values for different domains, as determined by the state in which enrollment occurred. This can be accommodated because there are separate statistical models for each state. Where a patient is eligible for two or more domains in a state, assignment can only occur at a single time-point, i.e. it is not possible to have more than one time of assignment for different domains in the same state.

7.6.2. Secondary endpoints

All secondary endpoints that are specified in the Core Protocol and active DSAs will continue to be active. The primary end-point specified in the Core Protocol (all-cause mortality at day 90) is a secondary end-point in the PISOP stratum.

7.7. Principles of the statistical analysis

7.7.1. Adaptive analyses

Adaptive analyses may be conducted more frequently and with varying cadence during a pandemic. For analyses conducted in the pandemic model and the PISOP stratum of the ventilation model, data from all available patients will be utilized using, where appropriate, modelling to impute missing data. Adaptive analyses may be conducted at different frequency for the PISOP and PINSNP stratum.

7.7.2. Response adaptive randomization

For PISOP patients, RAR proportions for domains that are analyzed using the pandemic model will be derived from the pandemic model and the RAR proportions for domains that are analyzed using the interpandemic model will be derived from the interpandemic model. For PINSNP patients, the RAR proportions for all qualifying domains will be derived from the interpandemic model.

If feasible, the option of allowing sites to start with imbalanced RAR proportions may be utilized. During a pandemic, issues related to equipoise for sites to participate may be facilitated by allowing sites to select from a range of starting RAR proportions that are imbalanced. Being able to

implement this would be dependent on logistic feasibility as well as evaluation to exclude any adverse impact on inference.

Within the PISOP stratum, and only for domains with five or more interventions, the minimum RAR proportion may be decreased to less than 10% but will not be decreased to less than 5%.

7.7.3. Unit-of-analysis

7.7.3.1. Application of additional strata

Patients within the PISOP stratum may be further stratified dependent on whether pandemic infection is confirmed or not confirmed by microbiological testing. Additional strata may be applied and this can be specified in a DSA. Any or all of these strata can be utilized to determine eligibility for a domain or an intervention within a domain. These strata can also be used to define a unit-of-analysis in the pandemic statistical model.

7.7.3.2. Application of state

The state, at time of first enrollment, can also be used to determine eligibility or be used to define a unit-of-analysis or both. Where specified in the statistical model, the treatment effect of an intervention is allowed to vary between different states. A Bayesian Hierarchical Model (BHM) is used for all treatment-by-state interactions. In the BHM a hyperprior is used for the differing treatment effects across states. The standard deviation of the hyperprior, gamma, is a modelling starting estimate for the variation in the magnitude of the difference in treatment effects between states. By default, the starting estimate of the difference is zero. The gamma parameter influences the extent to which the treatment effect of interventions is permitted to vary between states. At the commencement of a model, the gamma parameter must be set, for each domain-state pair.

In this REMAP, only three options are permitted with respect to specifying the gamma parameter for each domain-state pair. Firstly, gamma may be set to zero. The effect of this is that treatment effect of an intervention is assumed proportional between specified states. The unit-of-analysis is not sub-divided according to state. If gamma is set to zero for all states for a domain, the unit of analysis is all patients randomized in that domain. Secondly, and at the opposite extreme, gamma can be set to infinity. In this situation treatment effect is evaluated separately and independently in each state (with no borrowing between states). Thirdly, gamma may be set to a defined number between zero and infinity. This parameter value cannot be varied for different domain-state pairs, a global REMAP value has been selected. This specified value for gamma places a constraint on the variance of the difference in treatment effect in different states but permits the model to estimate treatment effect for patients enrolled in one state by borrowing from patients enrolled in one or more adjacent

states. Borrowing occurs to the extent that it is supported by the accumulated data, but the setting of gamma influences the amount of borrowing and how quickly borrowing is able to occur. The value of gamma that has been chosen has been determined by simulations to achieve a compromise between type I and type II error in baseline scenarios that assume either equivalence or superiority. Where a value for gamma is specified in the pandemic statistical model, in this REMAP the value of gamma will be 0.15.

A patient who is enrolled in a defined state, may have a clinical course that evolves with the patient entering a new state. Progression from one state, to another, may trigger eligibility for one or more domains. Where this occurs and the change in state defines a new unit-of-analysis, the RAR proportions may be different in each state. In this situation the RAR proportions that are relevant to that patient's state will be applied. In this regard, randomization to one or more domains in an initial state will occur, using RAR proportions that apply to that state with a separate subsequent randomization to one or more domains occurring if the patient enters a new state, with RAR proportions that apply to that state. When a new state commences there may be insufficient patients to determine valid RAR proportions for that domain in the new state. In this situation either RAR proportions are balanced or RAR proportions from an adjacent state are applied (unless otherwise specified in a DSA).

The RAR proportions that apply when state is used to define a unit-of-analysis are derived from all patients who receive an assignment in a domain in that state, irrespective of whether the patient was assigned an intervention in a different domain in a different state.

7.7.3.3. Analyses for combinations of therapies

Unless otherwise specified in a DSA, a Platform Conclusion can be reached for combinations of treatments that are being evaluated within the platform. This applies to interventions within a domain as well as interventions in different domains. As such, all of the following can be reported as Platform Conclusions: an interaction between interventions in different domains and that the treatment effect of more than one active intervention is different to a no treatment (standard of care) intervention. A domain that contains two or more treatments, each of which is assigned against a no treatment control in a factorial manner (i.e. the N x N table of yes / no for n treatments) will be analyzed as an N x N factorial. Structuring the analysis in this way allows the model to learn more quickly about the effectiveness of each treatment, recognizing common treatment exposure across intervention assignments.

7.7.4. Thresholds for statistical triggers

7.7.4.1. Introduction

The Core Protocol specifies thresholds for Statistical Triggers that apply to superiority, inferiority, and equivalence. For PISOP patients, different thresholds for Statistical Triggers may apply during a pandemic. The decision to modify a statistical threshold will be made by the ITSC prior to the first adaptive analysis of the pandemic model. Different thresholds may be applied to different domains. Thresholds can also be specified that are asymmetric for example less stringent for inferiority than superiority. Factors that the ITSC will take into account in considering whether to modify a threshold include whether the interventions being evaluated are comparative effectiveness options (i.e. interventions that are available as part of standard care and available outside the platform) or experimental interventions with uncertain safety and risk profile that may be available only within the platform.

All decisions regarding thresholds for Statistical Triggers will be communicated to participating sites and placed in the public domain on the study website. Once specified, thresholds cannot be modified unless recommended by the DSMB.

The default thresholds are outlined in the following sections.

7.7.4.2. Intervention Superiority Statistical Trigger

At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being a member of the optimal regimen, for that unit-of-analysis, then that intervention will be deemed as being superior to all other interventions in that domain in that target population.

The declaration of a Platform Conclusion by the DSMB for superiority will result in application of 100% RAR (see section 7.6.4). Following implementation of 100% RAR, the posterior probability will continue to be updated and evaluated by the DSMB who are empowered to act if they have concerns regarding the validity of a Platform Conclusion.

7.7.4.3. Intervention Efficacy Statistical Trigger

For any domain that has (or had) a non-active control intervention, statistical triggers for efficacy of other interventions can be determined. At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being superior to the inactive control intervention, for that unit-of-analysis, then that intervention will be deemed as being effective in that domain in that target population. At any adaptive analysis, if a single intervention has a greater than 90% probability of

being harmful, compared to an inactive control intervention, for that unit-of-analysis, then the intervention will be deemed as being harmful in that domain in that target population.

The declaration of a Platform Conclusion by the DSMB for efficacy may not result in any actions and may occur after the non-active intervention has been removed. This Platform Conclusion mathematically would occur simultaneously to Superiority in a 2-intervention domain. If a determination of efficacy for an intervention with a currently randomized non-active control then the non-active control should be dropped and the RAR set to 0. In contrast, declaration of a Platform Conclusion for harm will result in removal of that intervention from the platform for that unit-of-analysis, together with Public Disclosure.

7.7.4.4. Intervention Inferiority Statistical Trigger

At any adaptive analysis, if a single intervention has less than a 0.01 posterior probability of being a member of the optimal regimen, for a unit-of-analysis, then that intervention will be deemed as being inferior to other interventions in the domain for that target population. The 0.01 threshold is reduced as a function of how many units-of-analysis are available for the inferiority calculation (divided by the number of units minus 1). An asymmetrical inferiority statistical trigger may be set, particularly if an active intervention was being evaluated against an intervention that specifies no active treatment in that domain.

7.7.4.5. Equivalence and futility

The equivalence boundary (delta) for different endpoints selected for the PISOP stratum may be changed depending on the clinical impact of the delta for the chosen endpoint. The default delta for the Core Protocol will be used to select clinically similar effects on the chosen primary endpoint. If a mortality or 21-day ICU- or organ support-free day endpoint is selected the 20% proportional odds equivalency delta will be the default.

Alternatively, a DSA may specify a futility boundary (delta) with respect to the primary end-point. For the pandemic primary end-point, the default futility boundary for an intervention will be set as a posterior probability of less than 0.05 for at least a 20% odds-ratio improvement. This rule corresponds to the one-sided equivalency region.

7.7.4.6. Statistical thresholds for early phase interventions

During the pandemic there may be need to test multiple candidate interventions that are at an early phase of development, identifying those interventions that are most promising to be retained within the platform. Such interventions may be evaluated after a fixed recruitment against a ‘stop-go’

criteria for retention, and expansion, within the platform. The default threshold for retention and expansion of an intervention will be a posterior probability of 0.5 or more that there is at least a 30% benefit in odds ratio.

7.7.5. Actions when a Statistical Trigger is achieved

The actions that occur when a statistical trigger is achieved are those which are specified in the Core Protocol. At the time of a Platform Conclusion that is relevant to public health or clinical management of patients with suspected or proven pandemic infection, the DSMB and ITSC are empowered to liaise directly with relevant public health authorities prior to public presentation or publication of results.

7.7.6. Pre-specified subgroup analyses after achievement of a platform conclusion

Pre-specified subgroup analyses that will be conducted after a Platform Conclusion are outlined in each DSA. If a DSA does not specify a sub-group analysis related to the pandemic strata such analysis is permitted if the PISOP stratum has been open.

7.7.7. Closure of the PISOP stratum and incorporation of data from pandemic statistical model into the interpandemic statistical model

The ITSC is permitted to close or suspend the PISOP stratum. At this time, evaluation of new patients within the pandemic model will cease. After the permanent closure of the PISOP stratum, the information related to domains that have been analyzed for PISOP patients within the pandemic model will be added to the interpandemic model retaining, if appropriate, a co-variate or stratum status, to reflect that the patient was enrolled in the PISOP stratum.

7.7.8. Domains with their own statistical model

It is intended that domains with their own statistical model (e.g. as anticipated for the ventilation domain) will continue to be analyzed using the separate statistical model. If the PISOP stratum was applied to such a domain it is intended that a pandemic version of the separate model would be commenced and enroll only patients in the PISOP stratum. This model would utilize the pandemic primary end-point and would use informative priors derived from the preceding model. An operational decision may be made to apply an end-point that is different to the pandemic primary end-point in a domain with its own model.

8. GOVERNANCE, ETHICAL, AND OPERATIONAL CONSIDERATIONS IN A PANDEMIC

8.1. Decision to activate pandemic stratum

The decision to open the pandemic stratum lies with the ITSC. In deciding to activate the pandemic stratum the ITSC should take into account, but is not dependent on, declaration of a pandemic by the WHO and decisions about pandemic activation by regional pandemic preparedness consortia.

The decision to open will be communicated to RCCs and participating sites as an operational document. Each RCC will maintain a log of the dates for which sites were activated for the PISOP stratum.

8.2. Safety Monitoring and Reporting

During the interpandemic period, the platform evaluates solely or predominantly interventions that are in widespread clinical use for severe CAP and for which the safety profile of the intervention is well described. During a pandemic, the platform may evaluate therapeutic agents that have been repurposed or are an Investigational Medical Product. Such therapeutic agents may not have an established safety profile or an established safety profile when used in critically ill patients. Where an intervention is not regarded as having an established safety profile, this will be specified in the DSA. For this type of interventions more specific or more detailed SAE reporting will be required that is specified in the Core Protocol, as follows.

This may include Adverse Events of Special Interest (AESI). SAEs that might be attributable to specific interventions are included as secondary endpoints in each DSA but are recorded only for participants who are enrolled in that domain. If more detailed SAE or AE/AESI reporting is required for an intervention, then this additional safety reporting requirement will be specified in the relevant DSA and recorded only for participants who are enrolled in that domain. The following arrangements apply to such

When submitting the SAE form the local site PI should determine if the SAE is attributable to one or more study interventions in this trial. The local PI will assess if it is possible, probable, or certain that there is a direct link between a trial intervention and the SAE (a Serious Adverse Drug Reaction, SADR).

The regional / country project manager should review the SAE form for completeness and query any missing data with the site. Preliminary SAE report forms should be submitted as soon as the site becomes aware. It is recognised that follow-up information may be available later.

The regional lead investigator, or medically qualified designee, should review the SAE to assess expectedness and causality. The regional lead investigator or delegate cannot downgrade the site's assessment of expectedness and causality. The following requirements are specified:

- The regional Sponsor should be made aware of the SAE within 24 hours of the SAE being reported.
- All SAEs must be followed-up until resolution, or end of trial if this is sooner.
- SAEs will be reported to the relevant ethics committee and competent authority according to local regulations and requirements.

All SAEs, pooled from all regions, will be reported to the DSMB at intervals agreed by the REMAP-CAP investigators and the DSMB. This may vary depending on the specific intervention being evaluated. The DSMB may request additional specialist review of safety data for certain interventions.

If drugs have been supplied by a pharmaceutical company, then reporting of safety data to the company may be required. The details of this reporting will be included in individual Safety Data Exchange Agreements (SDEA).

On an annual basis a Developmental Safety Update Report (DSUR) will be produced including all SAE data from all regions in REMAP-CAP and will be submitted to the relevant competent authorities as required. This may be shared with pharmaceutical companies as part of the SDEA.

If an SAE is determined to be unexpected (not previously described in the Summary of Product Characteristics / Investigator Brochure / Protocol) and related to the study medication then it is considered a SUSAR. In these cases, the following steps should also be undertaken, in addition the performing the steps described above for handling SAEs:

- The relevant competent authorities and ethics committees should be notified of the SUSAR by the Sponsor or designee in each region.
- A SUSAR that results in death or is life-threatening, should be reported to the aforementioned bodies within 7 days of the Sponsor (or designee) becoming aware of the

event. Further relevant information should be sought and a follow-up report completed as soon as possible and submitted within 8 additional days.

A SUSAR which does not result in death or is not life-threatening should be reported within 15 days of the Sponsor (or designee) becoming aware of the event or in accordance with the local regulatory requirements. Further relevant information should be given as soon as possible. The regional / country project managers should notify all investigators at all sites that a SUSAR has occurred. The REMAP-CAP DSMB should be notified that a SUSAR has occurred.

It may be necessary to take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety, without prior authorisation from a regulatory body. If this occurs the regulatory bodies should be notified as soon as possible and in any event within three days, in the form of a substantial amendment, that such measures have been taken and the reasons why.

SAEs reported will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA). Coding will be to lowest level terms. The preferred term, and the primary system organ class will be listed. Summaries of all SAEs by treatment group will include:

- The number and percentage of patients with at least 1 SAE by system organ class and preferred term
- The number of SAEs by relationship to treatment (related, not related), presented by system organ class and preferred term

8.3. Data collection and management

A pandemic is likely to result in a substantial increase in clinical workload for sites participating in REMAP-CAP. This is acknowledged by the REMAP-CAP management, as is the primacy of patient care. The importance of contemporaneous data collection, particularly with respect to variables that are needed for adaptive analyses will be emphasized to sites. RCCs will seek to support sites as much as possible, including with requests to healthcare systems, public health authorities, and funding agencies to provide resources that allow sites to maintain data collection that is timely and complete.

8.4. Role of the DSMB

In a pandemic the role of the DSMB is modified, taking into account the public health importance of clinical evidence during a pandemic. In meeting the requirements of their Charter during a pandemic

the DSMB should consider issues of public health in addition to the well-being of participants and the scientific integrity of the platform. The in-principle views of the DSMB may be obtained by the ITSC with regard to the setting of modified thresholds for statistical triggers.

While the PISOP stratum is open the DSMB is also permitted to liaise with public health authorities, regulatory authorities, or the DSMBs of trials evaluating the same or similar interventions regarding the results and appropriate interpretation of adaptive analyses in keeping with prevailing international standards. If the DSMB communicates with external groups the ITSC may be informed that such communication has occurred but the content of that communication may remain confidential between the DSMB and the relevant group. The DSMB may recommend to the ITSC that public reporting of posterior probabilities that have not attained a threshold for a Statistical Trigger should occur.

The workload of the DSMB may be substantial during a pandemic and, if requested by the DSMB, the ITSC will appoint additional members.

8.5. Communication of trial results

Any Platform Conclusion that is relevant to public health that occurs during a pandemic will be presented or published as soon as possible, noting that additional work to report baseline status and secondary end-points will need to occur prior to presentation and publication of results.

8.6. Funding of the trial

The trial is currently funded as described in the Core Protocol.

During the interpandemic period and during a pandemic, additional funding will be sought to provide resources for activities that exceed those that will be occurring during the interpandemic period. Possible sources of additional resources include, but are not limited to, healthcare systems, pharmaceutical companies, public health authorities, and local and international research funding bodies.

A section of the Core Protocol indicates that “the trial will not enter into a contract with a commercial organization unless the contract specifies that, among other clauses, “that all data are owned by the trial and the commercial organization has no authority to access data”. This clause should not be interpreted as indicating that access to data by a commercial organization is not permitted. Such as access can be agreed, for example, by licensing access to data, if agreed by both a commercial partner and trial sponsors.

8.7. Monitoring

It is acknowledged that during a pandemic site monitoring may be delayed for logistical reasons. The operational monitoring plan may be updated to reflect issues that are specific to a pandemic. As outlined in Core Protocol, the DSMB will take into account intensity of monitoring and time of consideration of a Platform Conclusion. If appropriate, the contribution of data that has not been monitored as per the non-pandemic monitoring plan will be acknowledged in the public reporting of Platform Conclusions.

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REMAP-CAP Pandemic Appendix to Core Protocol Amendment Summary Version 1 dated 24 May 2020

AMENDMENT 1

The Pandemic Appendix to the Core Protocol document underwent an amendment in May 2020. There are two broad objectives associated with this amendment. Firstly, some aspects of the Appendix were updated to reflect accumulated knowledge and experience of how the Appendix applies to the COVID-19 pandemic. Secondly, in some regions of the world a separate and new Core Protocol had been developed, termed REMAP-COVID, which combines elements of the REMAP-CAP Core Protocol with the Pandemic Appendix to the Core Protocol, has been developed, approved and implemented. The REMAP-COVID Core Protocol is used in countries and locations that were not participating in REMAP-CAP prior to the COVID-19 pandemic and where the only objective of the platform was to evaluate treatments in patients with proven or suspected COVID-19 infection. Patients enrolled at locations in which REMAP-COVID Core Protocol is approved, as well as patients enrolled at locations in which the REMAP-CAP Core Protocol and Pandemic Appendix to the Core Protocol is approved, are all analyzed in the same pandemic statistical model. This version of the Pandemic Appendix achieves alignment between both sets of core documents.

Summary of changes

Section	Original text	New Text	Reason
Front page and whole document header	REMAP-CAP Pandemic Appendix to the Core Protocol Version 1.1 dated 12 February 2020	REMAP-CAP Pandemic Appendix to the Core Protocol (REMAP-COVID) Version 2 dated 18 May 2020	Administrative change
Summary Page 2	REMAP-CAP is an adaptive platform trial that evaluates multiple aspects of care of patients who are admitted to an Intensive Care Unit with severe Community Acquired Pneumonia. It is reasonable to presume that any pandemic respiratory infection of major significance to public health will manifest as severe Community Acquired Pneumonia with concomitant admission to an Intensive Care Unit. Previous pandemics and more localized outbreaks of respiratory emerging infections have resulted in severe Community Acquired Pneumonia and admission to an Intensive Care Unit.	REMAP-CAP is an adaptive platform trial that evaluates multiple aspects of care of patients who are admitted to an Intensive Care Unit (ICU) with severe Community Acquired Pneumonia. It is reasonable to presume that any pandemic respiratory infection of major significance to public health will manifest as severe Community Acquired Pneumonia with concomitant admission to an ICU. Previous pandemics and more localized outbreaks of respiratory emerging infections have resulted in severe Community Acquired Pneumonia (CAP) and admission to an Intensive Care Unit.	Administrative change
	Blank	Admission to an ICU may occur at the time of first presentation to a hospital or may be preceded by admission to a non-ICU ward or floor. For patients admitted to a non-ICU ward there is an opportunity to intervene to prevent the development of severe CAP.	Definition updated to align with the REMAP-COVID Core protocol that enrolls patients who are hospitalized but not in an ICU

	Blank	The Pandemic Appendix to the Core Protocol also achieves alignment with a separate document, REMAP-COVID Core Protocol, which comprises only those elements of the Core Protocol of REMAP-CAP and the Pandemic Appendix that applies to the COVID-19 pandemic. For the COVID-19 pandemic, a site can utilize either the REMAP-CAP Core Protocol combined with the Pandemic Appendix to the Core Protocol, or REMAP-COVID Core Protocol. Both sets of documents specify identical methods and data requirements. Data derived from sites using either set of documents is analyzed in the same pandemic statistical model. A single site must use either REMAP-COVID Core Protocol or REMAP-CAP Core Protocol with this associated pandemic appendix.	Explanation of the reason for amending this document
Summary Page 3	The objective of the Pandemic Appendix to the Core Protocol (PAtC) is to describe the adaptations to the Core Protocol that would apply during a pandemic, including how analyses of domains already operative during the interpandemic period as well as domains that are pandemic-specific, will be integrated during a pandemic.	The objective of the Pandemic Appendix to the Core Protocol (PAtC) is to describe the adaptations to the Core Protocol that would apply during a pandemic, including how analyses of domains already operative during the interpandemic period as well as domains that are pandemic-specific, will be integrated during a pandemic.	Administrative change
	The primary objective of the REMAP during a pandemic is to identify the effect of a range of interventions to improve outcome for patients with severe Community	The primary objective of the REMAP during a pandemic is to identify the effect of a range of interventions to improve outcome for patients admitted to a hospital with	Definition updated to align with the REMAP-COVID Core protocol that enrolls patients who are

	Acquired Pneumonia, as defined by the pandemic primary end-point.	acute illness due to suspected or proven pandemic infection, as defined by the pandemic primary end-point.	hospitalized but not in an ICU
	REMAP-CAP is a global trial examining the best treatments for community-acquired pneumonia. In the setting of a pandemic that causes pneumonia, some key aspects of the study will be changed to integrate new interventions into the trial, evaluate existing interventions within the trial specifically in patients with pandemic infection, alter trial governance, and provide time-critical data for public health.	REMAP-CAP is a global trial examining the best treatments for community-acquired pneumonia. In the setting of a pandemic that causes life-threatening respiratory infection, some key aspects of the study will be changed to integrate new interventions into the trial, evaluate existing interventions within the trial specifically in patients with pandemic infection, alter trial governance, and provide time-critical data for public health.	Updated to align with the REMAP-COVID Core protocol nomenclature. The disease of interest for both sets of core documents is acute illness due to suspected or proven COVID-19. A requirement for the presence of pneumonia no longer applies.
SECTION 3 PANDEMIC APPENDIX TO THE CORE PROTOCOL VERSION	**Original text**	**New Text**	**Reason**
3.1. Version History Page 9	Version 1.1: Approved by the Pandemic Working Group on 12th February, 2020	Version 2.0: Approved by the Pandemic Working Group on 18th May, 2020	Administrative change
SECTION 4 COVID-19 ANTIVIRAL DOMAIN GOVERNANCE	**Original text**	**New Text**	**Reason**

4.1. Members Page 9	Prof. Derek Angus Prof. Yaseen Arabi Prof. Richard Beasley A/Prof. Scott Berry Prof. Frank Brunkhorst Dr. Lennie Derde Dr. Robert Fowler Prof. Anthony Gordon Mr. Cameron Green Dr. Ed Litton Prof. John Marshall Dr. Colin McArthur Dr. Srinivas Murthy Prof. Alistair Nichol Ms. Jane Parker Prof. Kathy Rowan Prof. Tim Uyeki Prof. Steve Webb	Prof. Derek Angus Prof. Yaseen Arabi Prof. Richard Beasley A/Prof. Scott Berry Prof. Frank Brunkhorst Dr. Lennie Derde Dr. Robert Fowler Prof. Anthony Gordon Mr. Cameron Green Dr. Ed Litton Prof. John Marshall Dr. Colin McArthur A/Prof Bryan McVerry Dr. Srinivas Murthy Prof. Alistair Nichol Ms. Jane Parker Prof. Kathy Rowan Prof. Tim Uyeki Prof. Steve Webb	Addition of investigator
SECTION 6 BACKGROUND AND RATIONALE	**Original text**	**New Text**	**Reason**

6.1 Introduction Page 11	It is reasonable to presume that any pandemic respiratory infection of major significance to public health will manifest as severe Community Acquired Pneumonia (CAP) with concomitant admission to an Intensive Care Unit (ICU).	It is reasonable to presume that any pandemic respiratory infection of major significance to public health will manifest as life-threatening respiratory infection including Severe Acute Respiratory illness and severe Community Acquired Pneumonia (CAP) with concomitant admission to hospital, and for some patients, admission to an Intensive Care Unit (ICU).	Updated to align with the REMAP-COVID Core protocol nomenclature
	One of the challenges associated with planning clinical trials during a pandemic is that the precise nature of the infecting organism, clinical consequences, and suitable interventions (particularly those that are pathogen-specific) cannot be reliably known in advance. Nevertheless, a range of scenarios can be anticipated and used to provide direction and guidance regarding the most appropriate research response.	One of the challenges associated with planning clinical trials during a pandemic is that the precise nature of the infecting organism, clinical consequences, and suitable interventions (particularly those that are pathogen-specific) cannot be reliably known in advance. The speed of clinical progression, from initial infection to life-threatening severe respiratory infection is another feature that cannot be reliably known in advance. It is likely that a proportion of patients will present with severe CAP but other patients may present to medical attention with illness that is less severe, but remain at risk of progression to severe illness. Patients who require hospital admission, but have less severe illness are a particularly important group, because early intervention at this stage of illness may prevent progression to life-threatening illness. It is also possible that proposed treatment interventions may have differential treatment	Updated to align with the REMAP-COVID Core protocol that enrolls patients who are hospitalized but not in an ICU

		effect depending on the level of illness severity at the time that treatment is commenced, including treatment effects that are divergent. Nevertheless, a range of scenarios can be anticipated and used to provide direction and guidance regarding the most appropriate research response.	
Page 12	The pandemic potential of a novel Coronavirus that causes pneumonia is not known.	SARS-CoV-2 is the cause of a pandemic of severe respiratory disease (COVID-19), including pneumonia, that commenced in 2019.	Updated to acknowledge that Coronaviruses can result in a pandemic.
6.2.3. Pre-approved Page 13	It is highly likely that one or more research questions (in domains already approved during the interpandemic period) will be relevant specifically in patients with CAP caused by the pandemic infection.	It is highly likely that one or more research questions (in domains already approved during the interpandemic period) will be relevant specifically in patients with severe respiratory disease including pneumonia caused by the pandemic infection.	Updated to align with the REMAP-COVID Core protocol nomenclature
6.2.5.1. Time-critical generation of evidence Page15	Furthermore, as the trial progresses during a pandemic the Data Safety Monitoring Board (DSMB) has access to information from adaptive analyses that may not achieve thresholds to allow reporting as a Platform Conclusion but may be relevant to public health which, under appropriate circumstances, can be shared with public health authorities without threatening the scientific validity of the ongoing trial.	Furthermore, as the trial progresses during a pandemic the Data Safety Monitoring Board (DSMB) has access to information from adaptive analyses that may not achieve thresholds to allow reporting as a Platform Conclusion but may be relevant to public health which, under appropriate circumstances, can be shared with public health authorities and the DSMBs of other trials evaluating the same or similar interventions without threatening the scientific validity of the ongoing trial.	Updated to acknowledge that communication between DSMBs of different trials that are evaluating the same or similar interventions may be an important component of timely

			generation of evidence during a pandemic.
SECTION 7 ADAPTATION OF REMAP-CAP DURING A PANDEMIC	**Original text**	**New Text**	**Reason**
7.1. Objectives Page 17	Blank	The primary objective of this REMAP during a pandemic is to identify the effect of a range of interventions to improve outcome for adult patients admitted to hospital with acute illness due to suspected or proven pandemic infection, as defined by the pandemic primary end-point. The secondary objective is to determine the effect of a range of interventions on additional endpoints, including endpoints developed by the World Health Organization and adopted core outcome sets.	Trial objectives updated to include an extended definition of the disease of interest and to incorporate collection of WHO recommended outcome measures as a secondary objective
7.2. Study setting: definition of an ICU and relationship of setting to severity of illness Page 18	Study setting: definition of an ICU During the interpandemic period, the REMAP recruits only participants who are admitted to an ICU. During a pandemic, there may be insufficient ICU beds available to care for all critically ill patients resulting in provision of advanced organ support occurring in locations other than an ICU. For sites at which the pandemic stratum (see below) has been activated, an area within the hospital that is able to	Study setting: definition of an ICU and relationship of setting to severity of illness During the interpandemic period, the REMAP recruits only participants who are admitted to an ICU, and a combination of admission to ICU as well as provision of treatments to support failed organs is used to define severity and eligibility. During a pandemic, there are several factors that may influence the relationship between admission to an ICU and severity of illness.	This section has been updated extensively as a consequence of practical experience with COVID-19. Definitions of both what constitutes an ICU and assumptions regarding a level of severity of illness that

	deliver one or more of the qualifying organ failure supports specified in the Core Protocol (non-invasive ventilation, invasive ventilation, and vasopressor therapy) will meet the definition of an Intensive Care Unit. It is preferred in such circumstances that the patient is under the care of a specialist who is trained in the provision of critical care, but this is not an essential requirement.	Firstly, there may be insufficient ICU beds available to care for all critically ill patients. This may result in provision of advanced organ support occurring in locations that do not usually provide ICU-level care. During a pandemic, such a location is referred to as a re-purposed ICU. However, a re-purposed ICU needs to be distinguished from a usual hospital ward that is capable of providing some forms of organ support, such as non-invasive ventilation. During a pandemic, there may be substantial delays in transferring a patient from an emergency department to either a ward or an ICU (or a re-purposed ICU). Patients in an emergency department who have been accepted for admission to an ICU are regarded as being admitted to an ICU. Patients in an emergency department who have been accepted for admission to a ward are regarded as being admitted to a ward. Secondly, patients who are not critically ill may be treated on an ICU for reasons that are not related to severity of illness, such as access to single rooms to achieve objectives related to infection control and prevention. This can influence both admission as well as discharge practices. Thirdly, the threshold at which support for failed organs is provided may be influenced by infection control practices. For example, some forms	occurs in association with admission to an ICU are or have been important operational characteristics. These updates are needed to ensure adequate matching between intention of protocol documents and need for operational definitions that take into account changes in practice and policy in healthcare systems in which REMAP-CAP is active.

		of respiratory support may be withheld because of concerns related to the risk that staff who are caring for patients may acquire the infection. To minimize these issues, during a pandemic, the primary determinant of severity is the provision of ICU-level care, which can be interpreted in conjunction with the physical location in which care is being provided. Determination of severity may also take into account a decision to withhold some form of organ failure support that would otherwise have be provided. Where a definition of an ICU is needed, at sites at which the pandemic stratum (see below) has been activated, an area within the hospital that is repurposed so as to be able to deliver one or more of the qualifying organ failure supports specified in the Core Protocol (non-invasive ventilation, invasive ventilation, and vasopressor therapy) will meet the definition of an Intensive Care Unit. It is preferred in such circumstances that the patient is under the care of a specialist who is trained in the provision of critical care, but this is not an essential requirement. A respiratory or other ward that provides non-invasive ventilation (including oxygen therapy delivered by high flow nasal cannula) and continues to do so during a pandemic, will not, generally, meet the definition of an ICU, particularly	

		if the patient is not under the care of a specialist who is trained in the provision of critical care. In some DSAs, an exclusion criteria is applied to only permit enrolment during a time-window that commences with ICU admission. For the reasons noted above, this may be operationalized using a time-window, of the same duration, that commences with the provision of sustained organ failure support.	
7.3. Eligibility criteria Page 19	Platform-level eligibility criteria may be modified if necessary to accommodate a published case definition, to align with criteria specified in guidelines, such as the ATS/IDSA guidelines on CAP16, or to accommodate necessary modifications to the online eligibility system used for enrolment. In previous epidemics of community-based infection, nosocomial acquisition has been well described. Relaxation of the requirement for community acquisition or organ failure criteria or both may be appropriate. All changes to eligibility criteria would apply only to patients in the pandemic stratum (see section 7.3).	Platform-level eligibility criteria may be modified if necessary to accommodate a published case definition, to align with criteria specified in guidelines, such as the ATS/IDSA guidelines on CAP16, or to accommodate necessary modifications to the online eligibility system used for enrolment. In previous epidemics of community-based infection, nosocomial acquisition has been well described. Relaxation of the requirement for community acquisition or organ failure criteria or both may be appropriate. In this regard, Version 2.0 of this Appendix modifies the organ failure support criteria so that these no longer apply as a platform-level inclusion criteria, permitting the enrolment of patients into the platform who are admitted to hospital or an ICU, either with or without organ failure support criteria. In association with the removal of the organ failure requirement, the	Updated eligibility criteria to align with the REMAP-COVID Core protocol that enrolls patients who are hospitalized but not in an ICU and to align the nomenclature

		requirement for a patient to meet criteria for pneumonia may be replaced with a requirement for acute illness due to suspected or proven pandemic infection. All changes to eligibility criteria would apply only to patients in the pandemic stratum (see section 7.4). As such, the modified platform-level inclusion and exclusion criteria are: In order to be eligible to participate in the pandemic aspects of REMAP-CAP, a patient must meet the following criteria: 1. Adult patient admitted to hospital with acute illness due to suspected or proven pandemic infection A potentially eligible patient who meets any of the following criteria will be excluded from participation in this trial: 1. Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment 2. Patient is expected to be discharged from hospital today or tomorrow 3. More than 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven pandemic infection	

		4. Previous participation in this REMAP within the last 90 days This extension of the platform-level inclusion criteria can apply to patients admitted to an ICU or a ward. In association with the involvement of different clinical teams, the domains and interventions that are available for patients admitted to a ward compared with those admitted to an ICU are permitted to be, but do not have to be, different.	
7.5.1. Introduction Page 21	A PISOP patient can contribute to both the pandemic and interpandemic model in different domains but each patient's contribution to a model is mutually exclusive with respect to each domain. The ITSC will select the domains to be included in the pandemic model where a differential treatment effect is postulated in the presence of pandemic infection or the need exists to learn about the outcome quickly, or both.	A PISOP patient can contribute to both the pandemic and interpandemic model in different domains but each patient's contribution to a model is mutually exclusive with respect to each domain. The ITSC will select the domains to be included in the pandemic model where a differential treatment effect is postulated in the presence of pandemic infection or the need exists to learn about the outcome quickly, or both. The extension of this platform-level entry criteria does not apply to domains that are analyzed exclusively within the interpandemic statistical model.	Updated to improve clarity of disposition of patients and domains with respect to the interpandemic and the pandemic statistical models.
Page 22	For example, PISOP patients may be analyzed within a pandemic version of the domain specific statistical model utilizing a modified primary end-point, with application	For example, PISOP patients may be analyzed within a pandemic version of the domain specific statistical model utilizing a modified primary end-point, with application	Correction of spelling errors. The protocols use US spelling.

	of informative priors derived from the interpandemic time period.	of informative priors derived from the interpandemic time period.	
7.5.2. Pre-specification of trial parameter options Page 22	The selected trial parameters would be placed in the public domain, on the study website, and provided as an update to participating sites and relevant ethical review bodies prior to the first adaptive analysis of the PISOP stratum.	The selected trial parameters would be placed in the public domain, on the study website, and provided as an update to participating sites and relevant ethical review bodies prior to the first adaptive analysis of the PISOP stratum. These parameters are set out in a document termed Operating Characteristics and this document applies to both REMAP-CAP core protocol documents as well as the REMAP-COVID Core Protocol, to the extent that is necessary. It is also acknowledged that specification in a new domain, may influence a pre-existing domain, such as specification of evaluation of an interaction between domains. In this situation, the DSA for the pre-existing domain will not necessarily be amended immediately with the most recently approved or amended DSA serving to specify the inter-relationship between the two domains.	Updated to improve clarity regarding the role of the Operating Characteristics document
7.5.3. Application of other strata specified in the Core Protocol in the pandemic model Page 23	For PINSNIP patients, the “influenza present” stratum would continue to apply and would be used to differentiate patients infected with a non-pandemic strain of influenza from patients in the “influenza not present” stratum.	For PINSNP patients, the “influenza present” stratum would continue to apply and would be used to differentiate patients infected with a non-pandemic strain of influenza from patients in the “influenza not present” stratum.	Correction of acronym spelling error. PINSNP - Pandemic infection is neither suspected nor proven

Page 24	If eligibility criteria were modified to allow inclusion of a wider spectrum of illness severity, an additional strata may be applied within the PISOP stratum to distinguish current versus extended severity of illness.	If eligibility criteria were modified to allow inclusion of a wider spectrum of illness severity, two or more states, related to severity of illness, may be applied within the PISOP stratum to distinguish current versus extended severity of illness.	The possibility of enrolling patients with a wider spectrum of illness severity, i.e. patients with less severe illness, was acknowledged in the previous version but this should have identified the dynamic nature of severity of illness, i.e. a state not a strata.
7.5.5. States within the PISOP stratum Page 24	Blank	The Core Protocol defines 'state' as a set of mutually exclusive and exhaustive categories, defined by characteristics of a patient within the REMAP, that are capable of changing over time for a single patient at different time-points during the patient's participation in the REMAP (i.e. they can be dynamic). During the pandemic, and only for patients in the PISOP stratum, two or more states may be defined, depending on illness severity. The default categorization of severity will be into two categories: • Severe State, defined by receiving organ failure support in an ICU • Moderate State, defined by	New paragraph that recapitulates the definition of 'state' from the Core Protocol and defines two states that will apply to PISOP patients during this pandemic. Added to align with the REMAP-COVID Core protocol

		o Not being admitted to an ICU, or o Admitted to an ICU but not receiving organ failure support Organ failure supports that qualify a patient as severe are aligned to those that previously determined eligibility to the platform (i.e. the Severe State corresponds to the previous platform eligibility criteria). These criteria are: • Provision of invasive mechanical ventilation • Provision of non-invasive mechanical ventilation (including high flow nasal cannula with a flow rate of at least 30 litres per minutes and a fractional inspired oxygen concentration of 40% or higher) • Receiving infusion of vasopressor or inotropes or both Where states are defined, eligibility for domains or selected interventions within a domain, may be specified according to state. As such, a domain may be available in one or more states. Where a domain is available in two or more states, the interventions available in that domain in each state are permitted to vary. States can also be utilized within the statistical model to define the unit-of-analysis, with declaration of Platform Conclusions, independently in one or more states, with borrowing permitted between states.	

		A single patient can move between states, one or more times, during a period of time which the patient is potentially eligible within the REMAP. For the purposes of assessment of eligibility for one or more domains, state is 'instantaneous' as at the time of that assessment. A patient who has previously received non-invasive ventilation or an infusion of vasopressor or inotrope or both, but is not receiving either of those therapies at time of assessment is deemed to be in the Moderate State. A patient who has been in the Severe State, as a consequence of receiving invasive mechanical ventilation in an ICU, cannot re-enter the Moderate State for the purposes of assessment of eligibility. A patient who receives an assignment in the REMAP while in the Severe State cannot receive any subsequent assignments in the Moderate State. Where trial related processes, such as reveal of assignment or obtaining consent, create a time gap between initial assessment of eligibility and awareness of the patient's assignment, the state in which the patient is analyzed is that which occurred at the time of assessment, not the time of reveal of the assignment. A patient enrolled while in the Moderate State, if reassessed for eligibility for additional domains having progressed to the Severe State, may have new	

		microbiological information that has accumulated during this interval of time. This could result in a patient with suspected pandemic infection having information that results in pandemic infection being excluded, at the time of reassessment. In this situation, the patient is analyzed in the pandemic model, as enrolled, in the Moderate State and is not eligible for enrolment in new domains in the Severe State (including domains evaluated in the interpandemic model). It is also noted that, for a patient who is enrolled in both states, that other time-varying baseline variables may have changed between each enrolment. For such patients, potential time-varying baseline variables will be collected in reference to enrolment in the Moderate State and again in reference to enrolment in the Severe State.	
7.5.6.1. Non-influenza organism Page 26	The Antiviral Domain (which includes only antiviral agents active against influenza) would not be applied in the pandemic model.	The Influenza Antiviral Domain (which includes only antiviral agents active against influenza) would not be applied in the pandemic model.	Addition of the word *influenza* to differentiate between the Antiviral Domain for pandemic (non-influenza) patients and the Antiviral Domain for non-pandemic (influenza) patients.

7.5.6.2. Influenza pandemic Page 27	The default plan is that during a pandemic, patients in the PISOP and PINSNIP stratum will be eligible to receive an assignment in these domains and will be analyzed in the interpandemic model which will continue to be analyzed for statistical triggers and platform conclusions.	The default plan is that during a pandemic, patients in the PISOP and PINSNP strata will be eligible to receive an assignment in these domains and will be analyzed in the interpandemic model which will continue to be analyzed for statistical triggers and platform conclusions.	Correction of acronym spelling error. PINSNP - Pandemic infection is neither suspected nor proven. Correction of grammatical error *stratum* changed to *strata.*
7.6.1. Pandemic primary endpoint Page 27	The default pandemic primary endpoint will be a composite end-point that comprises the number of whole and part study days for which the patient is alive and not admitted to an ICU up until the end of study day 21. All patients who die before discharge from an acute hospital, irrespective of whether this occurs before or after D21, will be coded as zero days. If appropriate, based on an understanding of clinical and biological factors, as well as operational factors, an alternative pandemic primary end-point may be specified	The default pandemic primary endpoint will be an ordinal scale that is a composite end-point that comprises mortality during the acute hospital admission and the number of whole and part study days for which the patient is alive and not requiring organ failure support while admitted to an ICU up until the end of study day 21. All patients who die before discharge from an acute hospital, irrespective of whether this occurs before or after D21, will be coded as 1 day. All patients who never receive organ failure support while admitted to an ICU will be coded as 22. If appropriate, based on an understanding of clinical and biological factors, as well as operational factors, an alternative pandemic primary end-point may be specified	This represents a change to the primary end-point. The first interim analysis utilizing the pandemic statistical model has not yet occurred. The change in definition relates to the need for an end-point that is suitable for less severe patients as well as the observation that, in some locations, policies related to admission and discharge from the ICU are modified because of

	at the time of activation of the PAtC. Other possible primary end-points include days alive and outside the ICU with alternative durations of follow up or the use of an alternative composite based on days alive without organ support. The pandemic primary endpoint will be used for the adaptive analyses that inform the RAR and for Statistical Triggers.	at the time of activation of the PAtC or at any time prior to the first interim analysis using the pandemic statistical model. Other possible primary end-points include days alive and outside the ICU with alternative durations of follow up or the use of an alternative composite based on admission to ICU. The pandemic primary endpoint will be used for the adaptive analyses that inform the RAR and for Statistical Triggers. If the primary end-point includes a time-based outcome measure, assignment to one or more domains will occur at different time-points if the patient receives assignments in one or more domains while in the Moderate State and one or more domains in the Severe State. The commencement of the period of observation commences at the time of assignment, which can lead to the same patient having different values for different domains, as determined by the state in which enrolment occurred. This can be accommodated because there are separate statistical models for each state. Where a patient is eligible for two or more domains in a state, assignment can only occur at a single time-point, i.e. it is not possible to have more than one time of assignment different domains in the same state.	ICU-bed availability or infection control policies or both. As such, location of the patient no longer served as a valid surrogate for severity of illness. As a consequence, the primary end-point has been updated to capture actual provision of organ failure support while admitted to an ICU. Additionally, to improve the operating characteristics of the original ordinal scale, new categories have been created at either end of the scale to differentiate patients who die from those who have provision of organ failure support throughout 21 days of an

			ICU admission and to differentiate patients ever admitted to an ICU from those who are never admitted. Operational clarity of how the end-point is applied to a patient who receives an assignment in the platform at different time points, while in different states, is provided.
7.7.2. Response adaptive randomization Page 29	Blank	Within the PISOP stratum, and only for domains with five or more interventions, the minimum RAR proportion may be decreased to less than 10% but will not be decreased to less than 5%.	An update to how RAR is applied in domains with a large number of interventions to maintain appropriate statistical properties with respect to participant assignment.
7.7.3. Unit-of-analysis Page 29	Blank	7.7.3. Unit-of-analysis 7.7.3.1. Application of additional strata Patients within the PISOP stratum may be further stratified dependent on whether pandemic infection is confirmed or not confirmed by microbiological testing.	New sub-headings to distinguish application of additional strata and application of state are applied.

		Additional strata may be applied and this can be specified in a DSA. Any or all of these strata can be utilized to determine eligibility for a domain or an intervention within a domain. These strata can also be used to define a unit-of-analysis in the pandemic statistical model. 7.7.3.2. Application of state The state, at time of first enrolment, can also be used to determine eligibility or be used to define a unit-of-analysis or both. Where specified in the statistical model, the treatment effect of an intervention is allowed to vary between different states. A Bayesian Hierarchical Model (BHM) is used for all treatment-by-state interactions. In the BHM a hyperprior is used for the differing treatment effects across states. The standard deviation of the hyperprior, gamma, is a modelling starting estimate for the variation in the magnitude of the difference in treatment effects between states. By default, the starting estimate of the difference is zero. The gamma parameter influences the extent to which the treatment effect of interventions is permitted to vary between states. At the commencement of a model, the gamma parameter must be set, for each domain-state pair.	Application of state is an entirely new section that deals with aspects of the statistical analysis that occur as a consequence of the specification and application of states.

		In this REMAP, only three options are permitted with respect to specifying the gamma parameter for each domain-state pair. Firstly, gamma may be set to zero. The effect of this is that treatment effect of an intervention is assumed proportional between specified states. The unit-of-analysis is not sub-divided according to state. If gamma is set to zero for all states for a domain, the unit of analysis is all patients randomized in that domain. Secondly, and at the opposite extreme, gamma can be set to infinity. In this situation treatment effect is evaluated separately and independently in each state (with no borrowing between states). Thirdly, gamma may be set to a defined number between zero and infinity. This parameter value cannot be varied for different domain-state pairs, a global REMAP value has been selected. This specified value for gamma places a constraint on the variance of the difference in treatment effect in different states but permits the model to estimate treatment effect for patients enrolled in one state by borrowing from patients enrolled in one or more adjacent states. Borrowing occurs to the extent that it is supported by the accumulated data, but the setting of gamma influences the amount of borrowing and how quickly borrowing is able to occur. The value of gamma	

		that has been chosen has been determined by simulations to achieve a compromise between type I and type II error in baseline scenarios that assume either equivalence or superiority. Where a value for gamma is specified in the pandemic statistical model, in this REMAP the value of gamma will be 0.15. A patient who is enrolled in a defined state, may have a clinical course that evolves with the patient entering a new state. Progression from one state, to another, may trigger eligibility for one or more domains. Where this occurs and the change in state defines a new unit-of-analysis, the RAR proportions may be different in each state. In this situation the RAR proportions that are relevant to that patient's state will be applied. In this regard, randomization to one or more domains in an initial state will occur, using RAR proportions that apply to that state with a separate subsequent randomization to one or more domains occurring if the patient enters a new state, with RAR proportions that apply to that state. When a new state commences there may be insufficient patients to determine valid RAR proportions for that domain in the new state. In this situation either RAR proportions are balanced or RAR proportions from an	

		adjacent state are applied (unless otherwise specified in a DSA). The RAR proportions that apply when state is used to define a unit-of-analysis are derived from all patients who receive an assignment in a domain in that state, irrespective of whether the patient was assigned an intervention in a different domain in a different state. 7.7.3.3. Analyses for combinations of therapies Unless otherwise specified in a DSA, a Platform Conclusion can be reached for combinations of treatments that are being evaluated within the platform. This applies to interventions within a domain as well as interventions in different domains. As such, all of the following can be reported as Platform Conclusions: an interaction between interventions in different domains and that the treatment effect of more than one active intervention is different to a no treatment (standard of care) intervention. A domain that contains two or more treatments, each of which is assigned against a no treatment control in a factorial manner (i.e. the N x N table of yes / no for n treatments) will be analyzed as an N x N factorial. Structuring the analysis in this way allows the model to learn more quickly about the effectiveness	

		of each treatment, recognizing common treatment exposure across intervention assignments.	
7.7.4.2. Intervention Inferiority Statistical Trigger Page 31	At any adaptive analysis, if a single intervention has at least a 0.95 posterior probability of being a member of the optimal regimen, for that unit-of-analysis, then that intervention will be deemed as being superior to all other interventions in that domain in that target population.	At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being a member of the optimal regimen, for that unit-of-analysis, then that intervention will be deemed as being superior to all other interventions in that domain in that target population.	Updated to a more stringent probability as a consequence of the conduct of simulations which demonstrated inadequate control of type I error with previous threshold probability.
7.7.4.3. Intervention Efficacy Statistical Trigger Page 32	Blank	7.7.4.3. Intervention Efficacy Statistical Trigger For any domain that has (or had) a non-active control intervention, statistical triggers for efficacy of other interventions can be determined. At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being superior to the inactive control intervention, for that unit-of-analysis, then that intervention will be deemed as being effective in that domain in that target population. At any adaptive analysis, if a single intervention has a greater than 90% probability of being harmful, compared to an inactive control intervention, for that unit-of-analysis, then the intervention will be deemed as being harmful in that domain in that target population.	Addition of a new type of statistical trigger. The need for this has emerged as a consequence of several of the COVID-19 specific domains having a 'no intervention control' (i.e. standard of care control) rather than a comparative effectiveness structure. As such, the inclusion of this type of statistical trigger permits

		The declaration of a Platform Conclusion by the DSMB for efficacy may not result in any actions and may occur after the non-active intervention has been removed. This Platform Conclusion mathematically would occur simultaneously to Superiority in a 2-intervention domain. If a determination of efficacy for an intervention with a currently randomized non-active control then the non-active control should be dropped and the RAR set to 0. In contrast, declaration of a Platform Conclusion for harm will result in removal of that intervention from the platform for that unit-of-analysis, together with Public Disclosure.	conclusions to be drawn regarding effectiveness of an intervention against just the standard of care control, which corresponds to a highly clinically relevant question.
7.7.4.4. Intervention Inferiority Statistical Trigger Page 32	At any adaptive analysis, if a single intervention has less than a 0.05 posterior probability of being a member of the optimal regimen, for a unit-of-analysis, then that intervention will be deemed as being inferior to other interventions in the domain for that target population. An asymmetrical inferiority statistical trigger may be set, particularly if an active intervention was being evaluated against an intervention that specifies no active treatment in that domain.	At any adaptive analysis, if a single intervention has less than a 0.01 posterior probability of being a member of the optimal regimen, for a unit-of-analysis, then that intervention will be deemed as being inferior to other interventions in the domain for that target population. The 0.01 threshold is reduced as a function of how many units-of-analysis are available for the inferiority calculation (divided by the number of units minus 1). An asymmetrical inferiority statistical trigger may be set, particularly if an active intervention was being evaluated against an intervention that specifies no active treatment in that domain.	Updated to a more stringent probability as a consequence of the conduct of simulations which demonstrated inadequate control of type I error with previous threshold probability. Operationally, this permits removal of standard of care control when the aggregate

			effect of two or more active interventions is superior to the control, even if it is not yet known which active interventions are effective or their relative effectiveness. Similarly, it permits, with an asymmetric trigger, the removal of an intervention that is worse than a standard of care control.
7.7.4.5. Equivalence and futility Page 32	7.6.3.4. Equivalence The equivalence boundary (delta) for different endpoints selected for the PISOP stratum may be changed depending on the clinical impact of the delta for the chosen endpoint. The default delta for the Core Protocol will be used to select clinically similar effects on the chosen primary endpoint. If a 21-day ICU free day endpoint is selected the 20% proportional odds equivalency delta will be the default.	7.7.4.5. Equivalence and futility The equivalence boundary (delta) for different endpoints selected for the PISOP stratum may be changed depending on the clinical impact of the delta for the chosen endpoint. The default delta for the Core Protocol will be used to select clinically similar effects on the chosen primary endpoint. If a mortality or 21-day ICU or organ support free day endpoint is selected the 20% proportional odds equivalency delta will be the default.	There is no change to the evaluation of equivalence but introduces a trigger for futility, which corresponds to a 'one-sided' evaluation of equivalence, which is appropriate for a standard of care control.

	Alternatively, a DSA may specify a futility boundary (delta) with respect to the primary end-point. For the pandemic primary end-point, the default futility boundary for an intervention will be set as a posterior probability of less than 0.05 for at least a 20% odds-ratio improvement. This rule corresponds to the one-sided equivalency region.	Alternatively, a DSA may specify a futility boundary (delta) with respect to the primary end-point. For the pandemic primary end-point, the default futility boundary for an intervention will be set as a posterior probability of less than 0.05 for at least a 20% odds-ratio improvement. This rule corresponds to the one-sided equivalency region.	
7.7.4.6. Statistical thresholds for early phase interventions Page 33	Blank	7.7.4.6. Statistical thresholds for early phase interventions During the pandemic there may be need to test multiple candidate interventions that are at an early phase of development, identifying those interventions that are most promising to be retained within the platform. Such interventions may be evaluated after a fixed recruitment against a 'stop-go' criteria for retention, and expansion, within the platform. The default threshold for retention and expansion of an intervention will be a posterior probability of 0.5 or more that there is at least a 30% benefit in odds ratio.	This is an entirely new section that is designed for early phase (i.e. phase II type) interventions for which rapid learning is desirable.
SECTION 8 GOVERNANCE, ETHICAL, AND OPERATIONAL	**Original text**	**New Text**	**Reason**

CONSIDERATIONS IN A PANDEMIC			
8.2 Safety Monitoring and Reporting Page 34	Blank	8.2. Safety Monitoring and Reporting During the interpandemic period, the platform evaluates solely or predominantly interventions that are in widespread clinical use for severe CAP and for which the safety profile of the intervention is well described. During a pandemic, the platform may evaluate therapeutic agents that have been repurposed or are an Investigational Medical Product. Such therapeutic agents may not have an established safety profile or an established safety profile when used in critically ill patients. Where an intervention is not regarded as having an established safety profile, this will be specified in the DSA. For this type of interventions more specific or more detailed SAE reporting will be required that is specified in the Core Protocol, as follows. This may include Adverse Events of Special Interest (AESI). SAEs that might be attributable to specific interventions are included as secondary endpoints in each DSA but are recorded only for participants who are enrolled in that domain. If more detailed SAE or AE/AESI reporting is required for an intervention, then this additional safety reporting requirement will be specified	New section which substantially updates the approach to safety monitoring and reflects incorporation within the platform of some interventions that are re-purposed medications, as well as others which are unlicensed medicines. In both of these situations the prior safety knowledge of the intervention in this patient population is substantially less than when the platform was evaluating solely or predominantly comparative effectiveness

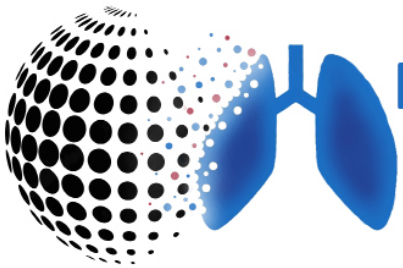
		in the relevant DSA and recorded only for participants who are enrolled in that domain. The following arrangements apply to such When submitting the SAE form the local site PI should determine if the SAE is attributable to one or more study interventions in this trial. The local PI will assess if it is possible, probable, or certain that there is a direct link between a trial intervention and the SAE (a Serious Adverse Drug Reaction, SADR). The regional / country project manager should review the SAE form for completeness and query any missing data with the site. Preliminary SAE report forms should be submitted as soon as the site becomes aware. It is recognized that follow-up information may be available later. The regional lead investigator, or medically qualified designee, should review the SAE to assess expectedness and causality. The regional lead investigator or delegate cannot downgrade the site's assessment of expectedness and causality. The following requirements are specified: • The regional Sponsor should be made aware of the SAE within 24 hours of the SAE being reported. • All SAEs must be followed-up until resolution, or end of trial if this is sooner.	interventions that were in widespread use.

		• SAEs will be reported to the relevant ethics committee and competent authority according to local regulations and requirements. All SAEs, pooled from all regions, will be reported to the DSMB at intervals agreed by the REMAP-CAP investigators and the DSMB. This may vary depending on the specific intervention being evaluated. The DSMB may request additional specialist review of safety data for certain interventions. If drugs have been supplied by a pharmaceutical company, then reporting of safety data to the company may be required. The details of this reporting will be included in individual Safety Data Exchange Agreements (SDEA). On an annual basis a Developmental Safety Update Report (DSUR) will be produced including all SAE data from all regions in REMAP-CAP and will be submitted to the relevant competent authorities as required. This may be shared with pharmaceutical companies as part of the SDEA. If an SAE is determined to be unexpected (not previously described in the Summary of Product Characteristics / Investigator Brochure / Protocol) and related to the study medication then it is considered a SUSAR. In these cases,	

		the following steps should also be undertaken, in addition the performing the steps described above for handling SAEs: • The relevant competent authorities and ethics committees should be notified of the SUSAR by the Sponsor or designee in each region. • A SUSAR that results in death or is life-threatening, should be reported to the aforementioned bodies within 7 days of the Sponsor (or designee) becoming aware of the event. Further relevant information should be sought and a follow-up report completed as soon as possible and submitted within 8 additional days. A SUSAR which does not result in death or is not life-threatening should be reported within 15 days of the Sponsor (or designee) becoming aware of the event or in accordance with the local regulatory requirements. Further relevant information should be given as soon as possible. The regional / country project managers should notify all investigators at all sites that a SUSAR has occurred. The REMAP-CAP DSMB should be notified that a SUSAR has occurred. It may be necessary to take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety,	

		without prior authorization from a regulatory body. If this occurs the regulatory bodies should be notified as soon as possible and in any event within three days, in the form of a substantial amendment, that such measures have been taken and the reasons why. SAEs reported will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA). Coding will be to lowest level terms. The preferred term, and the primary system organ class will be listed. Summaries of all SAEs by treatment group will include: • The number and percentage of patients with at least 1 SAE by system organ class and preferred term • The number of SAEs by relationship to treatment (related, not related), presented by system organ class and preferred term	
8.4. Role of the DSMB Page 37	While the PISOP stratum is open the DSMB is also permitted to liaise with public health authorities, regarding the results and appropriate interpretation of adaptive analyses in keeping with prevailing international standards. If the DSMB communicates with public health authorities the ITSC must be informed that such communication has occurred but the content of that communication may remain confidential between the	While the PISOP stratum is open the DSMB is also permitted to liaise with public health authorities, regulatory authorities, or the DSMBs of trials evaluating the same or similar interventions regarding the results and appropriate interpretation of adaptive analyses in keeping with prevailing international standards. If the DSMB communicates with external groups the ITSC may be informed that such communication has occurred but	The description of external groups that the DSMB may liaise with has been expanded to be include the DSMB of overlapping trials. The word *must* has been changed to *may* to clarify

	DSMB and the relevant public health authorities. The DSMB may recommend to the ITSC that public reporting of posterior probabilities that have not attained a threshold for a Statistical Trigger should occur.	the content of that communication may remain confidential between the DSMB and the relevant group. The DSMB may recommend to the ITSC that public reporting of posterior probabilities that have not attained a threshold for a Statistical Trigger should occur.	that the DSMB is not obliged to inform the ITSC regarding communication with external groups.
8.6. Funding of the trial Page 37	Possible sources of additional resources include, but are not limited to, healthcare systems, public health authorities, and local and international research funding bodies.	Possible sources of additional resources include, but are not limited to, healthcare systems, pharmaceutical companies, public health authorities, and local and international research funding bodies. A section of the Core Protocol indicates that "the trial will not enter into a contract with a commercial organization unless the contract specifies that, among other clauses, "that all data are owned by the trial and the commercial organization has no authority to access data". This clause should not be interpreted as indicating that access to data by a commercial organization is not permitted. Such as access can be agreed, for example, by licensing access to data, if agreed by both a commercial partner and trial sponsors.	*Pharmaceutical companies* added to reflect that medicine interventions have been added that might be externally funded



REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP):

PANDEMIC APPENDIX TO THE CORE PROTOCOL

REMAP-CAP Pandemic Appendix to the Core Protocol Version 1.1 dated 12th February, 2020

Summary

Background: REMAP-CAP is an adaptive platform trial that evaluates multiple aspects of care of patients who are admitted to an Intensive Care Unit with severe Community Acquired Pneumonia. It is reasonable to presume that any pandemic respiratory infection of major significance to public health will manifest as severe Community Acquired Pneumonia with concomitant admission to an Intensive Care Unit. Previous pandemics and more localized outbreaks of respiratory emerging infections have resulted in severe Community Acquired Pneumonia and admission to an Intensive Care Unit[1-3]. A pandemic of respiratory infection is much more likely to be caused by a virus than a bacterium. Differences in trial design may be required for influenza, viruses which are known to result in periodic but unpredictable pandemics, in comparison with other viruses, such as Coronaviruses that may also have pandemic potential.

Previous pandemics and outbreaks of emerging infectious diseases have outlined the urgent need for evidence, preferably from Randomized Clinical Trials, to guide best treatment. However, there are substantial challenges associated with being able to organize such trials when the time of onset of a pandemic and its exact nature are unpredictable[4-6]. As an adaptive platform trial that enrolls patients during the interpandemic period, REMAP-CAP is ideally positioned to adapt, in the event of a respiratory pandemic, to evaluate existing potential as well as novel treatment approaches.

The precise nature of a respiratory pandemic cannot be known in advance. The Pandemic Appendix to the Core Protocol lists potential adaptations to trial design and management that are generic, in that they will occur irrespective of the nature of the pandemic, as well as adaptations that are possible, depending on the nature of the pandemic, and the process for determining which adaptations will be applied.

The objective of the Pandemic Appendix to the Core Protocol is to describe the adaptations to the Core Protocol that would apply during a pandemic, including how analyses of domains already operative during the interpandemic period as well as domains that are pandemic-specific, will be integrated during a pandemic. This includes scientific, as well as governance and logistic aspects.

Aim: The primary objective of the REMAP during a pandemic is to identify the effect of a range of interventions to improve outcome for patients with severe Community Acquired Pneumonia, as defined by the pandemic primary end-point.

Methods: The methods that will be utilized during a pandemic are those in the Core Protocol but with potential for changes to the primary end-point, frequency and process for adaptive analyses, and determination of which domains will be analyzed using a statistical model that includes data from patients with proven or suspected pandemic infection. During a pandemic, patients who are neither suspected nor proven to have pandemic infection and for certain pre-existing domains, will continue to be analyzed using the statistical model that is outlined in the Core Protocol that was operating during the pre-pandemic period. Depending on the characteristics of a pandemic, one or more interpandemic domains may be analyzed within the pandemic statistical model and one or

more pandemic-specific domains may be commenced for patients with suspected or proven pandemic infection.

Lay description

REMAP-CAP is a global trial examining the best treatments for community-acquired pneumonia. In the setting of a pandemic that causes pneumonia, some key aspects of the study will be changed to integrate new interventions into the trial, evaluate existing interventions within the trial specifically in patients with pandemic infection, alter trial governance, and provide time-critical data for public health. This will allow the platform to identify which treatments work best for patients during a pandemic.

TABLE OF FIGURES

ABBREVIATIONS

CAP	Community-Acquired Pneumonia
CRF	Case Report Form
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
MERS-CoV	Middle-Eastern Respiratory Syndrome Coronavirus
NAI	Neuraminidase inhibitors
PAtC	Pandemic Appendix to the Core Protocol
PINSNP	Pandemic infection is neither suspected nor proven
PISOP	Pandemic infection is either suspected or proven
PWG	Pandemic Working Group
RAR	Response Adaptive Randomization
REMAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RCC	Regional Coordinating Center
RCT	Randomized Controlled Trial
RSA	Region Specific Appendix
SAC	Statistical Analysis Committee
SARS	Severe Acute Respiratory Syndrome
WHO	World Health Organization

PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see glossary, Section 1.2 Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

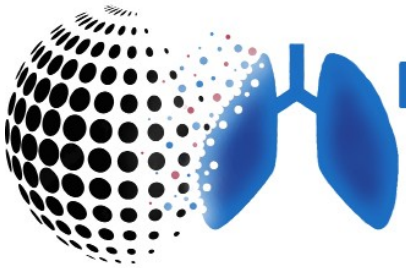
The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), a Registry Appendix, this Pandemic Appendix to the Core Protocol, and multiple Regions-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject of a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis, because the analysis model will change over time in accordance with the domain and intervention trial adaptations, but this information is contained in the Statistical Analysis Appendix. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within an RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.



Domain-Specific Appendix: COVID-19 Therapeutic Anticoagulation

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Therapeutic Anticoagulation Domain-Specific Appendix Version 1.0 dated 20th April 2020


NIHR | National Institute for Health Research
HRB
An Bord Taighde Sláinte Health Research Board
Australian Government
National Health and Medical Research Council
NHMRC
hrc
Health Research Council of New Zealand
SPOR SRAP
SEVENTH FRAMEWORK PROGRAMME

Summary

In this domain of the REMAP-CAP trial, participants meeting the platform entry criteria for REMAP-CAP admitted to participating intensive care units with suspected or microbiological testing- confirmed COVID-19 infection will be randomized to one of two interventions:

- Local standard venous thromboprophylaxis
- Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin

This domain will enroll patients only in the pandemic infection is suspected or proven (PISOP) stratum and be analyzed in the Pandemic Statistical Model as outlined from the Pandemic Appendixto Core (PAtC).

At this participating site the following interventions have been selected within this domain:

☐ Local standard venous thromboprophylaxis

☐ Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin

REMAP-CAP: COVID-19 Therapeutic Anticoagulation Domain Summary	
Interventions	• Local standard venous thromboprophylaxis • Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin
Unit of Analysis and Strata	The default unit-of-analysis for this domain will be the pandemic infection suspected or confirmed (PISOP) stratum. Analysis and Response Adaptive Randomization are applied by PISOP stratum. Unit of analysis may be modified to allow analysis to be stratified by SARS-CoV-2 infection confirmed or not confirmed with borrowing permitted. If this occurs, Response Adaptive Randomization will be applied to patients in the PISOP stratum using probabilities derived from SARC-CoV-2 confirmed stratum. A strata related to D-dimer level may also be applied.
Evaluable treatment-by-treatment Interactions	No interactions will be evaluated with any other domain.
Nesting	None
Timing of Reveal	Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal if prospective agreement to participate is required.
Inclusions	Patients will be eligible for this domain if: • COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing • Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • More than 48 hours has elapsed since ICU admission • Clinical or laboratory bleeding risk or both that is sufficient to contraindicate therapeutic anticoagulation, including intention to continue or commence dual anti-platelet therapy • Therapeutic anticoagulation is already present due to prior administration of any anticoagulant agent that is known or likely to still be active or a clinical decision has been made to commence therapeutic anticoagulation • Enrolment in a trial evaluating anticoagulation for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial • Known or suspected previous adverse reaction to UFH or LMWH including heparin induced thrombocytopenia (HIT). • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	None

Outcome measures	Primary REMAP endpoint: as defined in an operational document specified from the Pandemic Appendix to the Core Protocol Section 7.5.1 Secondary REMAP endpoints: as defined in an operational document specified from Pandemic Appendix to the Core Protocol Section 7.5.2 Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment): • Serious Adverse Events (SAE) as defined in Core Protocol

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ABBREVIATIONS

ACE2	Angiotensin-Converting Enzyme 2
aPTT	Activated partial thromboplastin time
ARDS	Acute Respiratory Distress Syndrome
CCP	Clinical Characterization Protocol
DSA	Domain-Specific Appendix
DIC	Disseminated Intravascular Coagulation
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
HIT	Heparin Induced Thrombocytopenia
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
LMWH	Low Molecular Weight Heparin
MERS-CoV	Middle East respiratory syndrome coronavirus
PAtC	Pandemic Appendix to the Core Protocol
PE	Pulmonary Embolus
PISOP	Pandemic infection is suspected or proven
RCT	Randomized controlled trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS	Serious Acute Respiratory Syndrome
UFH	Unfractionated heparin

VTE	Venous Thromboembolism
WHO	World Health Organization

PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a‘modular’ protocol design. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see glossary, Section 1.2 Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study); a Statistical Analysis Appendix (details of the current statistical analysis planand models); Simulations Appendix (details of the current simulations of the REMAP); multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain); and multiple Region-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. TheCore Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s), within each domain,because one of the trial adaptations is that domains and interventions will change over time.
Information about interventions within each domain is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, atone level, and removal and addition of entire domains, at another level. Each modification to a DSAwill be subject to a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations,because the analytic model will also change over time in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in whichthe trial is conducted, as the locations that participate in the trial are also anticipated to increase

over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatoryaspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the Core Protocol, DSAs, RSAs and the Statistical Analysis Appendix is listed inthe Protocol Summary and on the study website (www.remapcap.org).

3 COVID-19 THERAPEUTIC ANTICOAGULATION DOMAIN-SPECIFIC APPENDIXVERSION

The version of the COVID-19 Therapeutic Anticoagulation Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the COVID-19 Domain-Specific Working Group (DSWG) on 20th April 2020.

4 COVID-19 THERAPEUTIC ANTICOAGULATION THERAPY DOMAIN GOVERNANCE

4.1. Domain members

Chair:

Dr. Ryan Zarychanski

Deputy Chair:

Dr. Ewan Goligher

Members:

Professor Derek Angus Dr.
Scott Berry
Dr. Shailesh Bihari
Dr. Charlotte Bradbury
Professor Marc Carrier Dr.
Colin McArthur

Professor Dean Fergusson Professor Anthony GordonDr. Patrick Lawler Professor Robert Fowler Professor Anand Kumar Dr. Patrick Lawless Dr. Sylvain Lother Professor John MarshallDr. Zoe McQuilten Dr. Alexis Turgeon Professor Simon Stanworth Professor Steve Webb

4.2. Contact Details

Chair: Dr. Ryan Zarychanski

ON4005 – 675 McDermot Ave Winnipeg, Manitoba, Canada.

R3M 3M6Email: rzarychanski@cancercare.mb.ca

Phone: +1 (204) 899 4288

4.3. COVID-19 Therapeutic Anticoagulation therapy Domain-Specific Working Group Authorization

The COVID-19 Domain-Specific Working Group have read the appendix and authorize it as the officialCOVID-19 Therapeutic Anticoagulation Domain-Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair Date 20th April 2020

Dr. Ryan Zarychanski

5. BACKGROUND AND RATIONALE

5.1. Domain definition

This is a domain within the REMAP-CAP to test the effectiveness of therapeutic anticoagulation for suspected or microbiological testing-confirmed COVID-19 in patients with concomitant severe pneumonia who are admitted to an Intensive Care Unit (ICU).

5.2. Domain-specific background

5.2.1. COVID-19 infection

The first report of infection with COVID-19 occurred in Wuhan, China, in late 2019. Since that time, and as of the time of writing of this DSA, there have been over 1 million reported cases across the world with a range of severity, approximately 60,000 deaths and sustained human-human transmission. On January 30th 2020, the World Health Organization (WHO) declared this outbreak a Public Health Emergency of International Concern (https://www.who.int/news-room/detail/30-01- 2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency- committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)). Given past history with novelcoronaviruses, such as Severe Acute Respiratory Syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS-CoV), public health agencies have responded aggressively to the urgent need to acquire knowledge regarding this emerging infection. An important component of this urgently needed knowledge includes understanding the effectiveness of alternative treatment strategies in patients with suspected or proven infection. It should also be noted that clinical guidance issued by the WHO indicates that unproven therapies should be administered preferably only as part of a clinical trial (https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf).

Estimates of the burden of critical illness among patients infected with COVID-19 vary, with estimates of case-fatality and proportion of patients who become critically ill being unstable. Severalfactors contribute to this uncertainty including differential timing between diagnosis and development of critical illness or death, the true incidence of infection being uncertain because of possible under-reporting of asymptomatic or mild cases driven largely by limitations in the number of diagnostic tests that can be performed.

The first case descriptions of COVID-19 disease were communicated by Chinese investigators. These reports describe a progressive severe pneumonia, with a significant proportion of patients requiring mechanical ventilation and some reports of multi-organ dysfunction. In a study of 41 hospitalized patients with laboratory-confirmed COVID-19 infection, 13 (32%) patients were admitted to an ICU and six (15%) died. Invasive mechanical ventilation was required in four (10%) patients, with two patients (5%) receiving extracorporeal membrane oxygenation as salvage therapy (Huang et al.). In another study of 99 hospitalized patients with COVID-19 pneumonia, 23 (23%) were admitted to ICU,17 (17%) developed acute respiratory distress syndrome (ARDS), three (3%) acute renal failure and four (4%) septic shock. In a study of 138 patients with COVID-19 infection, 36/138 (26%) required ICUcare. Patients admitted to ICU were older and were more likely to have underlying comorbidities. In the ICU, four patients (11% of those admitted to ICU) received high-flow oxygen and 15 (44.4%) received noninvasive ventilation. Invasive mechanical ventilation was required in 17 patients (47.2%), four of whom received extracorporeal membrane oxygenation as rescue therapy. A total of 13 patients received vasopressors and two patients received kidney replacement therapy (Wang et al., 2020a). In a study from the Chinese Centers for Disease Control that reported on 72,314 patients, 49% of patients defined as critically ill died before hospital discharge (1,023 of 2,087) (Wu and McGoogan, 2020).

As with the other major coronaviruses that have circulated in outbreaks in recent decades, SARS andMERS-CoV, no specific therapy, or an element of supportive care, has been formally evaluated in randomized controlled trials with sufficient statistical power to identify changes in patient-centered outcomes.

Interim recommendations from the WHO for clinical care of infected patients focus upon supportivecare, including organ support as needed, prevention of complications, with any specific therapy to only be provided as part of a research protocol (https://www.who.int/docs/default- source/coronaviruse/clinical-management-of-novel-cov.pdf).

5.2.2. Clinical trials for COVID-19 infection

5.2.2.1 *Current clinical trials and interventions being evaluated*

As of 24th February 2020, more than 150 clinical studies from China had been registered on trial registration sites. Many of these trials are single center and with sample sizes that are unlikely to besufficient to detect plausible treatment effects, with some studies being uncontrolled or observational. There is also a rapid decline in incidence of new infection in China and many clinical trials are unlikely to achieve their planned sample size.

A wide range of interventions are being evaluated in trials that have been registered including arbidol, lopinavir/ritonavir, darunavir/cobicistat, remdesivir, favipiravir, baloxavir, chloroquine, intravenous immunoglobulin, inhaled and parenteral interferon-α or interferon-β glucocorticoids (different agents and doses), mesenchymal and other stem cells, microbiota transplantation, and arange of traditional Chinese medicines.

WHO has provided guidance regarding both trial design and prioritization of candidate therapies. With regards to trial design, WHO notes that there are no treatments with proven efficacy in patients with COVID-19. As such, WHO guidance is that trials should utilize a 'standard of care' comparator, that is, a control group that does not receive an agent intended to be active against COVID-19 infection, its associated immune response or other complications (https://apps.who.int/iris/bitstream/handle/10665/330694/WHO-HEO-RDBlueprintnCoV-2020.4-eng.pdf?ua=1).

This Therapeutic Anticoagulation Domain will evaluate the effect of therapeutic anticoagulation with intravenous unfractionated heparin (UFH) or subcutaneous low molecular weight heparin (LMWH) compared to standard venous thromboprophylaxis (delivered according to local practice in each region) in critically ill patients with COVID-19.

5.2 *Need for evidence in patients who are critically ill*

There is need to evaluate interventions for COVID-19 infection in patients who are critically ill. The number of current studies that are focused on patients who are critically ill is uncertain and, for those studies that are enrolling hospitalized patients, it is unclear if stratification by severity is a design feature. The need for studies that focus on patients who are critically ill arises because of thepossibility of differential treatment effect between patients who are critically ill compared with noncritically ill patients.

Among trials that evaluate interventions in patients who are critically ill it is common for the results of the trial to be different to that which was predicted based on a prior understanding of mechanismof action combined with known mechanism of disease (Landoni et al., 2015, Webb, 2015). This observation reinforces the importance of not necessarily relying on extrapolation of results (both positive and negative) from patients who are not critically ill.

5.2.3. Intervention strategy for this domain

This domain will test the potential benefits of different approaches to achieving therapeutic anticoagulation compared to usual care, comprising local standard-of-care venous pharmacological thromboprophylaxis.

If at, any stage, evidence of harm or definitive evidence of absence of effectiveness in critically ill patients emerges for one or more interventions specified in this domain, the ITSC, as advised by theDSWG, may remove the intervention(s) prior to declaration of a Platform Conclusion. If this occurs, presentation and publication of results that relate to the intervention will occur, so as to contributeadditional weight of evidence in the public domain.

5.2.4. Rationale for therapeutic anticoagulation in COVID-19

Although respiratory mechanics in COVID-19-associated ARDS has not yet been systematically described, there are widespread reports that patients exhibit surprisingly high respiratory compliance despite profoundly impaired gas exchange and radiological opacities. The gas exchangeimpairment characteristically involves severe hypoxemia but also markedly elevated physiological dead space and elevated respiratory drive (Liu et al., 2020).

Severe illness from COVID-19 seems to be characterized by important derangements in coagulation resulting in a hypercoagulable state. These derangements are strongly associated with poor clinical outcomes and various lines of evidence suggest that the prothrombotic state is causally related to poor outcomes. In a series of 183 patients, patients who died (11%) exhibited markedly elevated D-dimers and elevated fibrin degradation products; 15 of the patients who died met criteria for disseminated intravascular coagulation (DIC), whereas only 1 survivor developed DIC (Tang et al., 2020b). Similar derangements in hemostasis were documented in a separate case series of 94 patients (Lippi and Plebani, 2020). Development of DIC correlated with clinical deterioration.
Ischemic injury of the fingers and toes has also been reported in patients with severe COVID-19 (Li etal., 2020). In multiple large case series, elevated D-dimer is consistently associated with a higher risk of developing ARDS and death (Wu et al., 2020, Zhou et al., 2020). Reports of acute cardiovascular collapse with echocardiographic evidence of right heart strain has also been reported. In a consecutive case series of 184 COVID-19 positive patients admitted to a Dutch teaching hospital, theincidence of a composite outcome comprised of symptomatic PE, deep-vein thrombosis, ischemic stroke, myocardial infarction, or systemic arterial embolism occurred in 31% of patients (Klok et al., 2020).

The exact mechanism of coagulopathy and DIC is uncertain. SARS-CoV-2 can bind angiotensin- converting enzyme 2 (ACE2) and infect and injure endothelium, leading to tissue factor expression,endothelial activation and activation of the coagulation cascade (Zhang et al., 2020).

Endothelial dysfunction and microvascular thrombosis could explain the constellation of pulmonary findings in severe COVID-19—high dead space and impaired oxygenation in the absence of significant increase in pulmonary elastance (Liu et al., 2020). These features suggest that the pathophysiology of severe COVID-19 is quite different from typical ARDS, where shunt and dead space increase in proportion to the loss of lung volume and resulting increase in elastance. The limited autopsy data suggest a constellation of pulmonary pathological findings including thrombus in pulmonary microvessels. Endothelial dysfunction and microvascular thrombosis could also account for the high rate of cardiac injury with elevated Troponin-I and arrhythmia—both associatedwith poor outcome (Guo et al., 2020).

The SARS-CoV-2 spike protein has been shown to interact with UFH and LMWH. Upon binding heparin, the spike protein undergoes significant conformational change that may prevent it from binding ACE2 (https://www.biorxiv.org/content/10.1101/2020.02.29.971093v1). Heparin has been shown to prevent cellular invasion by SARS-CoV-1 (Vicenzi et al., 2004, Lang et al., 2011), and is known to inhibit attachment and entry of other enveloped viruses such as Human ImmunodeficiencyVirus and Herpes Simplex Virus (Moulard et al., 2000). Thus, heparin may exert a direct antiviral effect to prevent invasion of pulmonary epithelium, myocardium, and vascular endothelium, as well as potentially act to counteract complications that arise because of a hypercoagulable state.

Independent of its role as an anticoagulant, UFH has been shown to neutralize endotoxin and increase serum tumor necrosis factor binding protein-I, thus limiting both activation of coagulationand inflammation (Anastase-Ravion et al., 2003). UFH is also a known inhibitor of complement andof adhesion molecule expression in the microvasculature, which may serve to limit hemolysis and decrease neutrophil adhesion in the setting of sepsis (Lever et al., 2000). More recently, UFH has been shown to modulate HDL and reduce oxidant induced cellular damage (Wu et al., 2004), likely by abrogating histone-mediated cytotoxicity (Wildhagen et al., 2014).

There are anecdotal reports of anticoagulation with UFH being used in the treatment of COVID-19 disease in many locations. As such, it is of substantial importance that the treatment effect of UFH isestablished in randomized controlled trials (RCTs).

5.2.5. Evidence of effect for anticoagulation in sepsis and COVID-19 disease

Animal data suggest a benefit of heparin in models of sepsis. UFH administration reduces activationof coagulation and increases survival in endotoxin-equivalent models (including live organism infusion) of septic shock (du Toit et al., 1991). A meta-analysis of studies in animal models of sepsis found that UFH reduced the odds of death (odds ratio 0.27, 95%CI 0.16 to 0.46; n = 10 studies) (Cornet et al., 2007).

In a propensity matched retrospective cohort study of patients with septic shock therapeutic dose UFH was associated with reduced 28-day when administered within 48 hours of ICU admission (Zarychanski et al., 2008). Subgroup analyses from 3 randomized trials studying natural anticoagulants (rhAPC, antithrombin, and tissue factor pathway inhibitor) in sepsis suggest a survivaladvantage associated with prophylactic dose heparin when administered as a co-intervention, independent of the study drug under investigation or whether the study drug was received (OR 0.69,95%CI 0.56 to 0.85) (Polderman and Girbes, 2004). In a meta-analysis of RCTs conducts conducted inpatients with sepsis and septic shock, compared to placebo or no intervention heparin was associated with a reduction in the odds of death (odd ratio 0.88 (95% CI, 0.77 to 1.00; I^2 = 0%) (Polderman and Girbes, 2004). Evidence of potential benefit was not dependent on the presence of DIC or coagulopathy. In a second meta-analysis that evaluated the effects of LMWH in Chinese trials that evaluated LWMH in sepsis, LMWH was associated with reduced 28-day mortality (Fan et al., 2016). In patients with septic shock, therapeutic UFH is currently being evaluated in an international phase II/III RCT (www.halointernational.org, NCT03378466).

Specific to COVID-19 disease, in an observational study of 449 hospitalized patients from Wuhan, China, among 99 patients who received heparin (primarily LMWH, but also UFH) at prophylactic doses, heparin was associated with reduced 28-day mortality in patients with sepsis-induced coagulopathy or who had d-dimers that were greater than 6-fold the upper limit of normal (Tang etal., 2020a).

High troponin has been reported to strongly be associated with poor outcomes in patients with COVID-19 disease (Inciardi et al., 2020, Wang et al., 2020b). Reports of arterial events in critically ill COVID-19 patient, including myocardial infarction and stroke occurring in COVID-19 positive patientshave also been forwarded. Platelet activation is known to occur in infection, DIC and hemophagocytic syndrome (de Stoppelaar et al., 2014). While the majority of interventional trials of anti-thrombotics in sepsis have focused on parenteral anticoagulants, the role of anti-platelet agentsin sepsis and in COVID-19 patients remains to be evaluated.

5.2.6. Intravenous unfractionated heparin

UFH is a naturally occurring glycosaminoglycan that exerts its anticoagulant effect by enhancing antithrombin mediated inactivation of factors Xa and IIa, but also factors IXa, XIa, and XIIa (Gans, 1975). Because its size, activity, and pharmacokinetics are variable, its anticoagulant effect requiresclose monitoring in hospital settings. Chains of UFH varies in length and molecular weights from 5,000 to over 40,000 Daltons.

5.2.7. Low molecular weight heparin

LMWH represent, on average, shorter chains of UFH with an average molecular weight less than 8,000 Daltons. LMWH is obtained by various methods including fractionation or depolymerization ofpolymeric heparin. LMWHs exert the majority of their anticoagulant effect through factor X compared to its effect on factor II (thrombin).

5.2.8. Safety of unfractionated heparin and Low molecular weight heparin

UFH and LMWH are anticoagulants and as such are associated with major and clinically relevant minor bleeding. The rate of bleeding however is typically less than 10% and may not be significantlydifferent between unselected critically ill patients receiving low dose thromboprophylaxis and selected patients receiving therapeutic dose heparin or LMWH.

In the PROTECT trial, a multi-national thromboprophylaxis RCT comparing UFH to LMWH (n=3764), the major bleeding rate was 5.6% (Group et al., 2011). In this trial, no relationship was detected between use of therapeutic heparin and the activated partial thromboplastin time (aPTT) (p = 0.41)(Lauzier et al., 2013).

In patients receiving therapeutic anticoagulation for the treatment of venous thromboembolism (VTE), the rate of major hemorrhage typically reported ranges from 2-3%. Rates of major hemorrhage in patients randomized to receive UFH or LMWH appear to be similar (Dolovich et al., 2000). In patients therapeutically anticoagulated for treatment of acute coronary syndrome, rates ofmajor hemorrhage in patients receiving UFH + a glycoprotein IIb/IIIa inhibitor is approximately 6% and similar (6%) in patients receiving LMWH (Navarese et al., 2015).

In the HALO pilot randomized trial (n = 76), where patients with septic shock were randomized toreceive therapeutic dose IV UFH for the treatment of VTE or dalteparin for venous thromboprophylaxis, two patients (6%, 95%CI 1 to 11%) randomized to IV UFH and 1 patient (3%,

95%CI 1 to 7%) randomized to dalteparin experienced major bleeding. None of these bleedingevents were adjudicated to contribute to morbidity or mortality.

The incidence of heparin-induced thrombocytopenia with LMWH and UFH when administered togeneral medical-surgical ICU patients is approximately 0.3 to 0.6% (Group et al., 2011).

DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of therapeutic anticoagulation for patients with severe pneumonia who have suspected or microbiological testing-confirmed COVID-19infection.

We hypothesize that the probability of the occurrence of the primary endpoint specified from the PAtC will differ based on the allocated anticoagulation strategy. The following interventions will beavailable:

- Local standard venous thromboprophylaxis
- Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin

We hypothesize that the treatment effect of therapeutic anticoagulation is different depending on whether COVID-19 infection is confirmed to be present or absent.

We hypothesize that the treatment effect of therapeutic anticoagulation is different depending onD-dimer strata status.

TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial (see Core Protocol Section 7). Treatment allocation will be based on response adaptive randomization, as described in the CoreProtocol Section 7.5.2 and from the PAtC.

7.1. Population

The REMAP enrolls patients with severe pneumonia admitted to ICU (see Core Protocol Section 7.3).

7.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria (see Core Protocol Section 7.4 and PAtC). Patients eligible for the REMAP may have conditions that exclude them from this specific COVID-19 Therapeutic Anticoagulation Domain.

7.2.1. Domain inclusion criteria

Patients are eligible for this domain if:

- COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing (i.e. PISOP stratum)
- Microbiological testing for SARS-CoV-2 of upper or lower respiratory tract secretions or both has occurred or is intended to occur

7.2.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- More than 48 hours has elapsed since ICU admission
- Clinical or laboratory bleeding risk or both that is sufficient to contraindicate therapeutic anticoagulation, including intention to continue or commence dual anti-platelet therapy
- Therapeutic anticoagulation is already present due to prior administration of any anticoagulant agent that is known or likely to still be active or a clinical decision has been made to commence therapeutic anticoagulation
- Enrolment in a trial evaluating anticoagulation for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial
- Known or suspected previous adverse reaction to UFH or LMWH including heparin induced thrombocytopenia (HIT).
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

7.2.3. Intervention exclusion criteria

None

7.3. Anticoagulant Interventions

Patients will be randomly assigned to receive either of the following open-label strategies. The interventions will be commenced immediately after allocation status is revealed.

☐ Local standard venous thromboprophylaxis

☐ Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin

Administration of venous thromboprophylaxis is based on local practice and is mandatory.

7.3.1. Local standard venous thromboprophylaxis

Standard venous thromboprophylaxis that complies with local guidelines or usual practice will be administered for 14 days following randomization. The dose of agent that is chosen should not be sufficient to result in therapeutic anticoagulation. After 14 days decisions regarding thromboprophylaxis and anticoagulation are at the discretion of the treating clinician.

Use of therapeutic anticoagulation in patients randomized to local standard venous thromboembolism 7.3.1.1.

Any patient who develops an accepted clinical indication for anticoagulation can have this treatment commenced by the treating clinician. Such indications include, but are not limited, to proven deep venous thrombosis, proven PE, acute coronary syndrome, systemic embolic event, intermittent hemodialysis or sustained low-efficiency daily dialysis.

Systemic therapeutic anticoagulation for continuous renal replacement therapy is not permitted, unless there is an additional indication for anticoagulation. Regional citrate, heparin priming and low-dose heparin administration (without measurable systemic anticoagulation) are permitted forcontinuous renal replacement therapy.

7.3.2. Therapeutic Anticoagulation

The patient will be administered either UFH or LMWH to achieve systemic anticoagulation. Eitheragent may be used and the same patient may be switched between UFH and LMWH at the discretion of the treating clinician

Unfractionated heparin 7.3.2.1.

If UFH is used, this is commenced, administered, and monitored according to local hospital policy, and guidelines that are used for the treatment of VTE (i.e. not for acute coronary syndrome). The target aPTT should typically be in the range of 1.5 to 2.5 times the upper limit of normal at the participating site. Alternately, therapeutic anti-Xa values (i.e. values targeted for the treatment of acute VTE) can be targeted based on local practice. If UFH is used, the availability of a local hospital policy that has specifies an aPTT

target in this range or an anti-Xa value is a requirement. Based on an assessment of risk of administration of a loading dose, an initial bolus of UFH may be withheld atthe discretion of the treating clinician.

Low molecular weight heparin 7.3.2.2.

LMWH is commenced, administered, and monitored according to local hospital policy, practice and guidelines that pertain to treatment of VTE (i.e. not thromboprophylactic doses). The dose selectedshould be based on measure or estimated weight of the patient.

Adjustment for impairment of renal function should be according to local practice and policy.

Duration of therapeutic anticoagulation 7.3.2.3.

The duration of therapeutic anticoagulation is 14 days. Therapeutic anticoagulation should be continued for any period of time that the patient is receiving invasive mechanical ventilation. Anticoagulation may be ceased 24 hours after cessation of mechanical ventilation or at ICU discharge as determined by the treating clinician. For patients not receiving invasive mechanicalventilation the heparin infusion may be ceased at ICU discharge.

After 14 days decisions regarding thromboprophylaxis and anticoagulation are at the discretion ofthe treating clinician.

7.3.3. Discontinuation of study intervention

Anticoagulation or local standard venous thromboprophylaxis should be discontinued if there is clinical bleeding or other complication sufficient to warrant cessation in the opinion of the treatingclinician. Major bleeding, including death due to bleeding, is an SAE. Anticoagulation or local standard venous thromboprophylaxis may be recommenced if deemed appropriate by the treatingclinician.

Occurrence of HIT must result in cessation UFH or LMWH without recommencement regardless of treatment assignment. Use of an acceptable alternative agent is required in this instance as clinically indicated. Occurrence of HIT is an SAE.

The study interventions can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient. Temporary cessation – for the shortest period of time possible, but not longer than 24 hours - such as to allow surgical or other procedures is not aprotocol deviation.

Temporary or permanent cessation of the study interventions for bleeding is not a protocol deviation.

7.3.4. COVID-19 anticoagulation strategy in patients negative for COVID-19 infection

In patients with suspected COVID-19 infection who receive an allocation status to receive active anticoagulation but who subsequently test negative for COVID-19 infection may have treatment ceased unless the treating clinician believes that doing so is not clinically appropriate. This decisionshould take into account the known or suspected local population incidence of COVID-19 infectionamong critically ill patients and sensitivity of testing for COVID-19 infection.

7.4. Concomitant care

Additional agents, other than those specified in the platform, that are intended to modify the patient's coagulation function as a treatment for COVID-19 infection should not be administered. Apatient who receives one or more agents that act to inhibit platelet function as a usual medication may have this medication continued. Commencement of any new agent that inhibits platelet function is not permitted unless there is an accepted clinical indication such as an acute coronary syndrome, ischemic stroke or transient ischemic event.

All other treatment that is not specified by assignment within the platform will be determined by thetreating clinician.

7.5. Endpoints

7.5.1. Primary endpoint

The primary endpoint for this domain is the primary outcome specified in an operational documentfrom within the options specified from the PAtC.

7.5.2. Secondary endpoints

All secondary endpoints as specified from the PAtC Section 7.5.2.

The domain-specific secondary outcome measures (from randomization, during the index hospitalization, censored 90 days after enrollment) will be:

- Serial detection of SARS-CoV-2 in upper or lower respiratory tract specimens (using only specimens collected for routine clinically indicated testing)
- Confirmed deep venous thrombosis
- Confirmed pulmonary embolism
- Total red cell blood cell units transfused between randomization and the end of study day 15
- SAE as defined in Core Protocol and this DSA below

8 TRIAL CONDUCT

8.1. Microbiology

Microbiological testing will be performed as per local practice, including bacterial and viral testing toguide clinical care. Results of these tests will be collected but no additional testing is specified in thisprotocol.

Sites that are participating in this domain are encouraged to also participate in the Clinical Characterization Protocol (CCP) for patients with COVID-19 that has been established by the International Severe Acute Respiratory and Emerging Infectious Consortium (https://isaric.tghn.org/CCP/). This protocol specifies the collection of biological samples from patients with COVID-19. Samples collected in patients who are enrolled in the CCP may be made available to REMAP-CAP investigators to evaluate aspects of host or pathogen biology associated with assignment in this domain. Ethical approval at such sites and agreement from patients toundertake the CCP will be obtained separately.

8.2. Domain-specific data collection

Additional domain-specific data will be collected.

- Baseline measures of coagulation including d-dimer
- Administration of anticoagulant agents
- Administration of agents that inhibit platelet function
- Transfusion of red cells

8.3. Criteria for discontinuation

Refer to Core Protocol Section 7.3 for criteria for discontinuation of participation in the REMAP-CAPtrial.

8.4. Blinding

8.4.1. Blinding

All medication will be administered on an open-label basis.

8.4.2. Unblinding

Not relevant.

9 STATISTICAL CONSIDERATIONS

9.1. Domain-specific stopping rules

The Platform Conclusion of equivalence in this domain will not be evaluated. Instead a Platform Conclusion of Futility will be considered. If the posterior probability of at least a 20% odds-ratio increase for therapeutic anticoagulation is less than 5% then therapeutic anticoagulation will be declared Futile as a Platform Conclusion. This rule corresponds to the one-sided equivalency region.

In all other respects the stopping rules for this domain are those outlined in the Core ProtocolSection and from the PAtC.

9.2. Unit-of-analysis and strata

The default unit-of-analysis, for both analysis of treatment effect and the Response Adaptive Randomization, will be the PISOP stratum, as specified from the PAtC. As determined by the ITSC, and based on an understanding of the sensitivity and availability of testing for COVID-19 infection, the unit-of analysis may be modified to allow separate analysis of the COVID-19 infection confirmedand not confirmed stratum. This will be an operational decision.

At the time of a Platform Conclusion, results will be reported for all randomized patients, patients inwhom COVID-19 infection is confirmed by microbiological testing, microbiological tests do not detect or isolate COVID-19 infection, and testing is not performed.

An additional strata may be applied to the unit-of-analysis which will determined by status with respect to the D-dimer collected closest to but before randomization. This strata will contain 2 or 3stratum, the breakpoints of which will be determined not later than the first interim analysis using data derived from patients enrolled in REMAP-CAP as well as any other trials that may utilize the same statistical model.

The shock strata will not contribute to unit-of-analysis for this domain, as this strata is not applied inthe Pandemic Statistical Model.

The influenza strata will not contribute to unit-of-analysis for this domain.

9.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal if prospective agreement to participate is required for this domain (see section 7.8.3.6 in Core Protocol).

9.4. Interactions with interventions in other domains

An *a priori* interaction with the Antibiotic Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the Macrolide Duration Domain is not considered possible will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Antiviral Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the Corticosteroid Domain is not considered possible will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Immune Modulation Domain is not considered possibleand will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Antiviral Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

No interaction is evaluable between the Ventilation Domain and this domain.

9.5. Nesting of interventions

Nesting is not applicable in this domain.

9.6. Threshold probability for superiority and inferiority

The threshold odds ratio delta for superiority and inferiority in this domain are those specified in the Operating Characteristics document derived from PAtC. It is noted that the threshold for superiority and inferiority in the current model has been modified from 0.95 to 0.99 to provide adequate control of type I error, following the evaluation of simulations. It is also noted that asymmetric probabilities may be specified for harm, to allow early cessation and declaration of a Platform Conclusion for interventions that are unlikely to be effective and may be harmful. If so, this will be specified in the Operating Characteristics document which is placed in the public domain.

9.7. Threshold odds ratio delta for equivalence

The Platform Conclusion of equivalence will not be evaluated in this domain. The same odds ratiodelta as specified in the PAtC (Section 7.8.8) for equivalence will be used for futility. This will be applied in a one-sided analysis for futility of therapeutic anticoagulation

9.8. Informative priors

This domain will launch with priors that are not informative for main effects.

9.9. Post-trial sub-groups

Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The *a priori* patient sub-groups of interest are:

- Proven concomitant bacterial co-infection, defined as having isolation or detection of a known pathogen that causes CAP from blood, pleural fluid, or lower respiratory tract specimen
- Whether therapeutic anticoagulation is initiated with UFH or LMWH
- Shock strata
- Receiving invasive mechanical ventilation at baseline
- Baseline troponin
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

10 ETHICAL CONSIDERATIONS

10.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, inferiority, or futility of different interventions withrespect to the primary endpoint is possible.

The DSMB should take into account the public health, as well as clinical significance, of the analysesof this domain and are empowered to discuss results with relevant international and national public health authorities, with rapid dissemination of results to the larger community being the goal.

10.2. Potential domain-specific adverse events

For patients assigned to any intervention, occurrence of any of the following should be reported asan SAE

- Major bleeding, including death due to bleeding
- Heparin-induced thrombocytopenia

Other SAEs should be reported only where, in the opinion of the site-investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see Core Protocol Section 8.13).

10.3. Domain-specific consent issues

As noted in the background, and endorsed by the WHO, in the absence of evidence of effectivenessof anticoagulation for COVID-19, the use of a usual care control is both appropriate and ethical.

Both forms of anticoagulation are being used, off-trial, and typically without consent, for patients with proven or suspected COVID-19 infection. Clinicians may choose not to enroll individual patientsif they feel that participation is not in patient's best interests, and safety criteria are used to excludepatients from this domain for appropriate clinical reasons.

Where all interventions that are available at a participating site and are regarded as being part of the acceptable spectrum of standard care and given the time imperative necessary to evaluate these interventions, entry to the study, for participants who are not competent to consent, is preferred to be via waiver-of-consent or some form of delayed consent.

During a pandemic, visiting by relatives of affected patients may not be possible. In such situations, alternative methods for confirming consent including electronic and telephone communication, as permitted by an appropriate ethical review body, may be acceptable methods for confirming agreement to participate in this (and other) domains of the platform.

GOVERNANCE ISSUES

11.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. This domainhas not received any additional domain-specific funding but such funding, from any source, may be obtained during the life-time of the domain.

11.2. Funding of domain interventions and outcome measures

All anticoagulant agents will be provided by participating hospitals. The cost of all agents specified inthis domain are known to be inexpensive.

11.3. Domain-specific declarations of interest

All investigators involved in REMAP-CAP maintain a registry of interests on the REMAP-CAP website.These are updated periodically and publicly accessible on the study website.

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APPENDIX 1. OVERVIEW OF DESIGN AND INITIAL RESULTS FOR THE THERAPEUTIC ANTICOAGUALTION DOMAIN

13.1. Introduction

This document describes the statistical design and analysis of the testing of therapeutic anticoagulation with intravenous UFH or subcutaneous LMWH compared to local standard venousthromboprophylaxis in the COVID-19 appendix as part of the REMAP-CAP trial. Our goal is to investigate whether this is independently beneficial in increasing the number of ICU- free days for patients with COVID-19.

13.1.1. Treatment Arms

The main effect for therapeutic anticoagulation in this domain will be modeled as specified in thePAtC.

13.1.2. Primary Endpoint

The primary efficacy endpoint is as specified in the PAtC, the ordinal endpoint, ICU-free days through21 days with the classification of in hospital death as the worst outcome.

13.2. Primary Analysis Model

The primary analysis is based on a Bayesian cumulative logistic regression assuming proportionalodds for intervention effects (reference the PAtC stats document??).

13.2.1. Domain Platform Conclusions.

The Platform Conclusions of Superiority and Inferiority are as specified in the PAtC and are unchanged.

This domain substitutes a Platform Conclusion of Futility in place of Equivalence for this domain as demonstration of equivalence in not relevant but a conclusion of Futility of therapeutic anticoagulation is relevant. If the probability of at least a 20% odds ratio improvement for therapeutic anticoagulation is less than 5% then the Statistical Trigger for Futility will have been met.This Futility trigger is the one-sided extension of the equivalence rule in PAtC. That is, Futility of therapeutic anticoagulation will be declared if $Pr(OR_1 > 1.2) < 0.05$, where OR_1 refers to the odd ratio for therapeutic anticoagulation compared to SOC for this domain.

13.3. Simulation Details

In this section, we outline the simulations conducted for understanding the performance of thisdomain. Simulations were conducted separately assuming only this domain, as there are no interactions with any other domains.

13.3.1. Standard-of-Care Rates and therapeutic anticoagulation effect assumptions

We created possible standard-of-care rates across the 23 levels of the outcome. We worked within afew clinically guided expected parameters: 20% mortality rate, 10% of patients are in the ICU 21 days, and median number of days in the ICU is 7 amongst those that did not die. Figure 1 shows the assumed rates for the ICU-free day endpoint in the left panel.

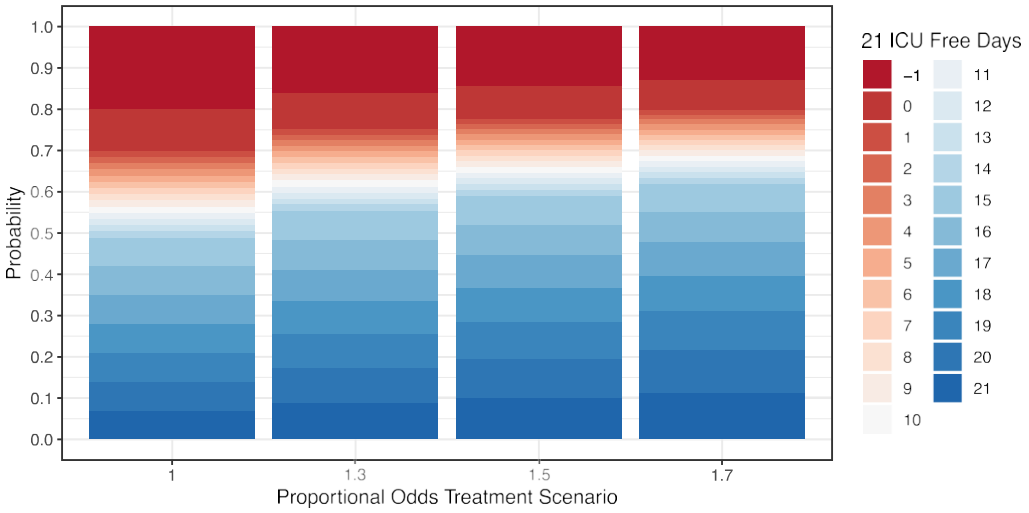

Figure 1. Control outcome probabilities for the ICU-free day end point (left panel) and then the probabilities for treatmenteffects of odds ratios of 1.3, 1.5, and 1.7.

For the simulations in this section interim analyses are assumed to occur at 200, 400, 600,800, 1000, 1500, 2000, 2500, and 3000 patients enrolled in this domain.

13.4. Operating Characteristics

Figure 2 presents the cumulative power to determine that therapeutic anticoagulation is superior tothe standard-of-care intervention as a function of the total number of patients enrolled (x-axis) and the assumed effect sizes (1.3, 1.5, and 1.7).

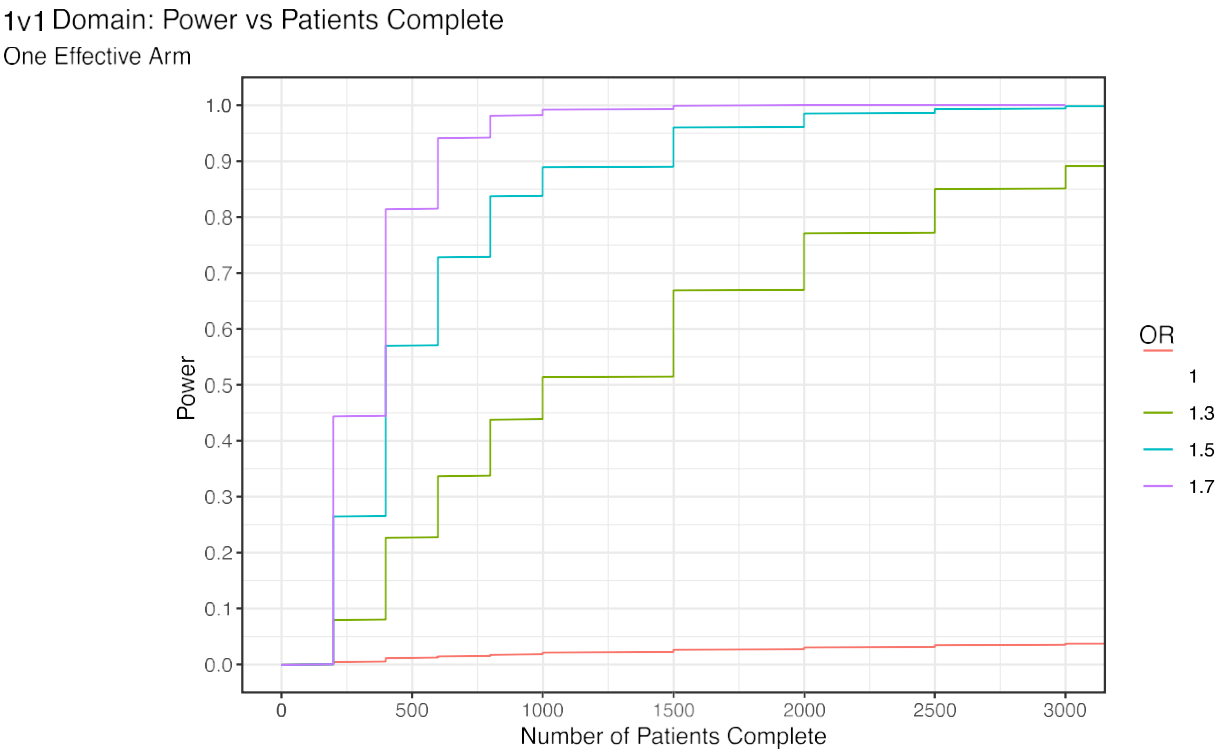

Figure 2: The cumulative power for each of the explored treatment effects (odds ratios of 1.3, 1.5, and 1.7). The cumulativetype I error is shown as the red line (effect size of 1).

13.5. Summary

The domain is designed to provide high-level evidence. The domain has 80% power to demonstrate superiority of therapeutic anticoagulation to standard-of-care by 400 patients enrolled assuming anodds ratio effect size of 1.7. For an effect size of 1.5 the power is 80% for 800 patients enrolled. Thecumulative type I error through 3000 patients is less than 5%.

Domain-Specific Appendix: COVID-19 Therapeutic Anticoagulation

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Therapeutic Anticoagulation Domain-Specific Appendix Version 2.0 dated 24th June 2020

Summary

In this domain of the REMAP-CAP trial, participants meeting the platform entry criteria with suspected or microbiological testing-confirmed COVID-19 infection will be randomized to one of two interventions:

- Local standard venous thromboprophylaxis
- Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin

At this participating site the following interventions have been selected within this domain:

☐ Local standard venous thromboprophylaxis

☐ Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin

This DSA applies to the following states and stratum:

Stratum	Pandemic infection suspected or proven (PISOP)			Pandemic infection neither suspected nor proven (PINSNP)
Core protocol documents	REMAP-CAP Core Protocol + Pandemic Appendix, or REMAP-COVID Core Protocol			REMAP-CAP Core Protocol
Illness Severity State	Moderate State		Severe State	Severe State
Interventions specified in this DSA	Local VT Therapeutic anticoagulation		Local VT Therapeutic anticoagulation	Not available
Interventions submitted for approval in this jurisdiction	☐ Local VT ☐ Therapeutic anticoagulation		☐ Local VT ☐ Therapeutic anticoagulation	Not available
Interventions offered at this site	Ward	ICU	ICU	ICU
	☐ Local VT ☐ Therapeutic anticoagulation	☐ Local VT ☐ Therapeutic anticoagulation	☐ Local VT ☐ Therapeutic anticoagulation	Not available

REMAP-CAP: COVID-19 Therapeutic Anticoagulation Domain Summary	
Interventions	• Local standard venous thromboprophylaxis • Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin
Unit of Analysis, Strata, and State	This domain is analyzed only in the pandemic statistical model. The pandemic statistical model includes only patients who are in the Pandemic Infection Suspected or Proven (PISOP) stratum. Within this stratum, the unit-of-analysis is defined by illness severity state at time of enrollment, defined as either Moderate State or Severe State. Unit-of-analysis may also be defined by SARS-CoV-2 infection or d-dimer strata or both. Borrowing is permitted between states and strata. If the SARS-CoV-2 strata is applied in analysis, Response Adaptive Randomization will be applied to all PISOP patients, in each illness severity state, using probabilities derived from the SARS-CoV-2 confirmed stratum. Response Adaptive Randomization may also be applied according to D-dimer strata status.
Evaluable treatment-by-treatment Interactions	No interaction will be evaluated with any other domain.
Nesting	None
Timing of Reveal	Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal if prospective agreement to participate is required.
Inclusions	Patients will be eligible for this domain if: • COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing • Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • More than 48 hours has elapsed since ICU admission (noting that this may be operationalized as more than 48 hours has elapsed since commencement of organ failure support) • Clinical or laboratory bleeding risk or both that is sufficient to contraindicate therapeutic anticoagulation, including intention to continue or commence dual anti-platelet therapy • Therapeutic anticoagulation is already present due to prior administration of any anticoagulant agent that is known or likely to still be active or a clinical decision has been made to commence therapeutic anticoagulation • Enrolment in a trial evaluating anticoagulation for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial • Known or suspected previous adverse reaction to UFH or LMWH including heparin induced thrombocytopenia (HIT). • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	None

Outcome measures	Primary REMAP endpoint: refer to REMAP-CAP Core Protocol + Pandemic Appendix and REMAP-COVID Core Protocol Secondary REMAP endpoints: refer to REMAP-CAP Core Protocol + Pandemic Appendix and REMAP-COVID Core Protocol Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment): • Confirmed deep venous thrombosis • Confirmed pulmonary embolism • Confirmed ischemic cerebrovascular event • Total red cell blood cell units transfused between randomization and the end of study day 15 • Acute myocardial infarction • Peak troponin • Major bleeding • Other thrombotic events including mesenteric ischemia and limb ischemia • Serious Adverse Events (SAE) as defined in relevant core protocol documents and this DSA

TABLE OF CONTENTS

1. ABBREVIATIONS

ACE2	Angiotensin-Converting Enzyme 2
aPTT	Activated partial thromboplastin time
ARDS	Acute Respiratory Distress Syndrome
CCP	Clinical Characterization Protocol
DSA	Domain-Specific Appendix
DIC	Disseminated Intravascular Coagulation
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
HIT	Heparin Induced Thrombocytopenia
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
LMWH	Low Molecular Weight Heparin
MERS-CoV	Middle East respiratory syndrome coronavirus
PAtC	Pandemic Appendix to the Core Protocol
PE	Pulmonary Embolus
PISOP	Pandemic infection is suspected or proven
RCT	Randomized controlled trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS	Serious Acute Respiratory Syndrome
UFH	Unfractionated heparin

VTE	Venous Thromboembolism
WHO	World Health Organization

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see glossary, Section 1.2 Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study); a Statistical Analysis Appendix (details of the current statistical analysis plan and models); Simulations Appendix (details of the current simulations of the REMAP); multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain); and multiple Region-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time.
Information about interventions within each domain is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject to a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analytic model will also change over time in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are

anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the relevant Core Protocol (either REMAP-CAP Core Protocol +/- Pandemic Appendix or REMAP-COVID Core Protocol), DSAs, RSAs, and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org).

3. COVID-19 THERAPEUTIC ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION

The version of the COVID-19 Therapeutic Anticoagulation Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the COVID-19 Therapeutic Anticoagulation Domain-Specific Working Group (DSWG) on 20th April 2020.

Version 2: Approved by the COVID-19 Therapeutic Anticoagulation DSWG on 24th June 2020

4. COVID-19 THERAPEUTIC ANTICOAGULATION THERAPY DOMAIN GOVERNANCE

4.1. *Domain members*

Chair: Dr. Ryan Zarychanski

Deputy Chair: Dr. Ewan Goligher

Members:

Prof. Derek Angus Dr. Scott

Berry Dr. Shailesh Bihari

Dr. Charlotte Bradbury

Prof. Marc Carrier

Prof. Dean Fergusson

Prof. Robert Fowler

A/Prof. Timothy Girard

Prof. Anthony Gordon

A/Prof. Ghady Haidar

A/Prof. Christopher Horvat

Prof. David Huang

Prof. Beverley Hunt

Prof. Anand Kumar

Prof. Mike Laffan

Dr. Patrick Lawler

Dr. Patrick Lawless

Dr. Sylvain Lother

Dr. Peter MacCallum

Dr. Colin McArthur

A/Prof. Bryan McVerry

Prof. John Marshall

Prof. Saskia Middeldorp

Dr. Zoe McQuilten

A/Prof. Matthew Neal

Prof. Alistair Nichol

Prof. John Pasi

A/Prof. Christopher Seymour

Prof. Roger Schutgens

Prof. Simon Stanworth

Dr. Alexis Turgeon

Prof. Steve Webb

A/Prof. Alexandra Weissman

4.2. *Contact Details*

Chair: Dr. Ryan Zarychanski

ON4005 – 675 McDermot Ave

Winnipeg, Manitoba, Canada.

R3M 3M6 Email:

rzarychanski@cancercare.mb.ca

Phone: +1 (204) 899 4288

4.3. *Interaction with ATTACC trial*

ATTACC is a trial that also evaluates the treatment effect of therapeutic anticoagulation in patients with COVID-19. There is overlap between the leadership of the ATTACC trial and the leadership of this domain. This domain and ATTACC have been designed to be complementary with pre-specified plans in relation to methods of analysis. It is intended that data from ATTACC will be incorporated into the pandemic statistical model of REMAP-CAP. The protocol, governance, and data management of ATTACC are separate from REMAP-CAP, but the REMAP-CAP DSMB will also serve the ATTACC trial.

5. COVID-19 THERAPEUTIC ANTICOAGULATION THERAPY DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The COVID-19 Domain-Specific Working Group have read the appendix and authorize it as the official COVID-19 Therapeutic Anticoagulation Domain-Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair
Dr. Ryan Zarychanski

Date 24th June 2020

6. BACKGROUND AND RATIONALE

6.1. *Domain definition*

This is a domain within the REMAP-CAP platform to test the effectiveness of therapeutic anticoagulation versus local venous thromboprophylaxis for patients with acute illness due to suspected or proven COVID-19.

6.2. *Domain-specific background*

6.2.1. COVID-19 infection

The first report of infection with COVID-19 occurred in Wuhan, China, in late 2019. Since that time, and as of the time of writing of this DSA, there have been over 1 million reported cases across the world with a range of severity, approximately 60,000 deaths and sustained human-human transmission. On January 30th 2020, the World Health Organization (WHO) declared this outbreak a Public Health Emergency of International Concern (https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency- committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)). Given past history with novel coronaviruses, such as Severe Acute Respiratory Syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS-CoV), public health agencies have responded aggressively to the urgent need to acquire knowledge regarding this emerging infection. An important component of this urgently needed knowledge includes understanding the effectiveness of alternative treatment strategies in patients with suspected or proven infection. It should also be noted that clinical guidance issued by the WHO indicates that unproven therapies should be administered preferably only as part of a clinical trial (https://www.who.int/docs/default-source/coronaviruse/clinical- management-of-novel-cov.pdf).

Estimates of the burden of critical illness among patients infected with COVID-19 vary, with estimates of case-fatality and proportion of patients who become critically ill being unstable. Several factors contribute to this uncertainty including differential timing between diagnosis and development of critical illness or death, the true incidence of infection being uncertain because of possible under-reporting of asymptomatic or mild cases driven largely by limitations in the number of diagnostic tests that can be performed.

The first case descriptions of COVID-19 disease were communicated by Chinese investigators. These reports describe a progressive severe pneumonia, with a significant proportion of patients requiring mechanical ventilation and some reports of multi-organ dysfunction. In a study of 41 hospitalized patients with laboratory-confirmed COVID-19 infection, 13 (32%) patients were admitted to an ICU and six (15%) died. Invasive mechanical ventilation was required in four (10%) patients, with two patients (5%) receiving extracorporeal membrane oxygenation as salvage therapy (Huang et al.). In another study of 99 hospitalized patients with COVID-19 pneumonia, 23 (23%) were admitted to ICU, 17 (17%) developed acute respiratory distress syndrome (ARDS), three (3%) acute renal failure and four (4%) septic shock. In a study of 138 patients with COVID-19 infection, 36/138 (26%) required ICU

care. Patients admitted to ICU were older and were more likely to have underlying comorbidities. In the ICU, four patients (11% of those admitted to ICU) received high-flow oxygen and 15 (44.4%) received noninvasive ventilation. Invasive mechanical ventilation was required in 17 patients (47.2%), four of whom received extracorporeal membrane oxygenation as rescue therapy. A total of 13 patients received vasopressors and two patients received kidney replacement therapy (Wang et al., 2020a). In a study from the Chinese Centers for Disease Control that reported on 72,314 patients, 49% of patients defined as critically ill died before hospital discharge (1,023 of 2,087) (Wu and McGoogan, 2020).

As with the other major coronaviruses that have circulated in outbreaks in recent decades, SARS and MERS-CoV, no specific therapy, or an element of supportive care, has been formally evaluated in randomized controlled trials with sufficient statistical power to identify changes in patient-centered outcomes.

Interim recommendations from the WHO for clinical care of infected patients focus upon supportive care, including organ support as needed, prevention of complications, with any specific therapy to only be provided as part of a research protocol (https://www.who.int/docs/default- source/coronaviruse/clinical-management-of-novel-cov.pdf).

6.2.2. Clinical trials for COVID-19 infection

6.2.2.1. *Current clinical trials and interventions being evaluated*

As of 24th February 2020, more than 150 clinical studies from China had been registered on trial registration sites. Many of these trials are single center and with sample sizes that are unlikely to be sufficient to detect plausible treatment effects, with some studies being uncontrolled or observational. There is also a rapid decline in incidence of new infection in China and many clinical trials are unlikely to achieve their planned sample size.

A wide range of interventions are being evaluated in trials that have been registered including arbidol, lopinavir/ritonavir, darunavir/cobicistat, remdesivir, favipiravir, baloxavir, chloroquine, intravenous immunoglobulin, inhaled and parenteral interferon-α or interferon-β glucocorticoids (different agents and doses), mesenchymal and other stem cells, microbiota transplantation, and a range of traditional Chinese medicines.

WHO has provided guidance regarding both trial design and prioritization of candidate therapies. With regards to trial design, WHO notes that there are no treatments with proven efficacy in

patients with COVID-19. As such, WHO guidance is that trials should utilize a 'standard of care' comparator, that is, a control group that does not receive an agent intended to be active against COVID-19 infection, its associated immune response or other complications (https://apps.who.int/iris/bitstream/handle/10665/330694/WHO-HEO-RDBlueprintnCoV-2020.4- eng.pdf?ua=1).

This Therapeutic Anticoagulation Domain will evaluate the effect of therapeutic anticoagulation with intravenous unfractionated heparin (UFH) or subcutaneous low molecular weight heparin (LMWH) compared to standard venous thromboprophylaxis (delivered according to local practice in each region) in critically ill patients with COVID-19.

6.2.2.2. *Need for evidence in patients who are critically ill as well as hospitalized patients*

There is need to evaluate interventions for COVID-19 infection in patients who are critically ill or hospitalized and not critically ill, separately, because of the possibility of differential treatment effect, depending on illness severity. The number of current studies that are focused on patients who are critically ill is

uncertain and, for those studies that are enrolling hospitalized patients, it is unclear if stratification by severity is a design feature.

Among trials that evaluate interventions in patients who are critically ill it is common for the results of the trial to be different to that which was predicted based on a prior understanding of mechanism of action combined with known mechanism of disease (Landoni et al., 2015, Webb, 2015). This observation reinforces the importance of not necessarily relying on extrapolation of results (both positive and negative) from patients who are not critically ill. It is also possible different disease mechanisms apply at different levels of illness severity and that this may also influence balance between beneficial and adverse effects of a particular intervention. This reinforces the importance of obtaining estimates of treatment effect dependent on the level of illness severity.

6.2.3. Intervention strategy for this domain

This domain will test the potential benefits of different approaches to achieving therapeutic anticoagulation compared to usual care, comprising local standard-of-care venous pharmacological thromboprophylaxis.

If at, any stage, evidence of harm or definitive evidence of absence of effectiveness in critically ill or ward patients or both emerges for one or more interventions specified in this domain, the ITSC, as

advised by the DSWG, may remove the intervention(s) prior to declaration of a Platform Conclusion. If this occurs, presentation and publication of results that relate to the intervention will occur, so as to contribute additional weight of evidence in the public domain.

6.2.4. Rationale for therapeutic anticoagulation in COVID-19

Although respiratory mechanics in COVID-19-associated ARDS has not yet been systematically described, there are widespread reports that patients exhibit surprisingly high respiratory compliance despite profoundly impaired gas exchange and radiological opacities. The gas exchange impairment characteristically involves severe hypoxemia but also markedly elevated physiological dead space and elevated respiratory drive (Liu et al., 2020).

Severe illness from COVID-19 seems to be characterized by important derangements in coagulation resulting in a hypercoagulable state. These derangements are strongly associated with poor clinical outcomes and various lines of evidence suggest that the prothrombotic state is causally related to poor outcomes. In a series of 183 patients, patients who died (11%) exhibited markedly elevated D- dimers and elevated fibrin degradation products; 15 of the patients who died met criteria for disseminated intravascular coagulation (DIC), whereas only 1 survivor developed DIC (Tang et al., 2020b). Similar derangements in hemostasis were documented in a separate case series of 94 patients (Lippi and Plebani, 2020). Development of DIC correlated with clinical deterioration.
Ischemic injury of the fingers and toes has also been reported in patients with severe COVID-19 (Li et al., 2020). In multiple large case series, elevated D-dimer is consistently associated with a higher risk of developing ARDS and death (Wu et al., 2020, Zhou et al., 2020). Reports of acute cardiovascular collapse with echocardiographic evidence of right heart strain has also been reported. In a consecutive case series of 184 COVID-19 positive patients admitted to a Dutch teaching hospital, the incidence of a composite outcome comprised of symptomatic PE, deep-vein thrombosis, ischemic stroke, myocardial infarction, or systemic arterial embolism occurred in 31% of patients (Klok et al., 2020).

The exact mechanism of coagulopathy and DIC is uncertain. SARS-CoV-2 can bind angiotensin- converting enzyme 2 (ACE2) and infect and injure endothelium, leading to tissue factor expression, endothelial activation and activation of the coagulation cascade (Zhang et al., 2020).

Endothelial dysfunction and microvascular thrombosis could explain the constellation of pulmonary findings in severe COVID-19—high dead space and impaired oxygenation in the absence of significant increase in pulmonary elastance (Liu et al., 2020). These features suggest that the pathophysiology of severe COVID-19 is quite different from typical ARDS, where shunt and dead space increase in proportion to the loss of lung volume and resulting increase in elastance. The limited autopsy data suggest a constellation of pulmonary pathological findings including thrombus in pulmonary microvessels. Endothelial dysfunction and microvascular thrombosis could also account for the high rate of cardiac injury with elevated Troponin-I and arrhythmia—both associated with poor outcome (Guo et al., 2020).

The SARS-CoV-2 spike protein has been shown to interact with UFH and LMWH. Upon binding heparin, the spike protein undergoes significant conformational change that may prevent it from binding ACE2 (https://www.biorxiv.org/content/10.1101/2020.02.29.971093v1). Heparin has been shown to prevent cellular invasion by SARS-CoV-1 (Vicenzi et al., 2004, Lang et al., 2011), and is known to inhibit attachment and entry of other enveloped viruses such as Human Immunodeficiency Virus and Herpes Simplex Virus (Moulard et al., 2000). Thus, heparin may exert a direct antiviral effect to prevent invasion of pulmonary epithelium, myocardium, and vascular endothelium, as well as potentially act to counteract complications that arise because of a hypercoagulable state.

Independent of its role as an anticoagulant, UFH has been shown to neutralize endotoxin and increase serum tumor necrosis factor binding protein-I, thus limiting both activation of coagulation and inflammation (Anastase-Ravion et al., 2003). UFH is also a known inhibitor of complement and of adhesion molecule expression in the microvasculature, which may serve to limit hemolysis and decrease neutrophil adhesion in the setting of sepsis (Lever et al., 2000). More recently, UFH has been shown to modulate HDL and reduce oxidant induced cellular damage (Wu et al., 2004), likely by abrogating histone-mediated cytotoxicity (Wildhagen et al., 2014).

There are anecdotal reports of anticoagulation with UFH being used in the treatment of COVID-19 disease in many locations. As such, it is of substantial importance that the treatment effect of UFH is established in randomized controlled trials (RCTs).

6.2.5. Evidence of effect for anticoagulation in sepsis and COVID-19 disease

Animal data suggest a benefit of heparin in models of sepsis. UFH administration reduces activation of coagulation and increases survival in endotoxin-equivalent models (including live organism infusion) of septic shock (du Toit et al., 1991). A meta-analysis of studies in animal models of sepsis found that UFH reduced the odds of death (odds ratio 0.27, 95%CI 0.16 to 0.46; n = 10 studies) (Cornet et al., 2007).

In a propensity matched retrospective cohort study of patients with septic shock therapeutic dose UFH was associated with reduced 28-day when administered within 48 hours of ICU admission (Zarychanski et al., 2008). Subgroup analyses

from 3 randomized trials studying natural anticoagulants (rhAPC, antithrombin, and tissue factor pathway inhibitor) in sepsis suggest a survival advantage associated with prophylactic dose heparin when administered as a co-intervention, independent of the study drug under investigation or whether the study drug was received (OR 0.69, 95%CI 0.56 to 0.85) (Polderman and Girbes, 2004). In a meta-analysis of RCTs conducts conducted in patients with sepsis and septic shock, compared to placebo or no intervention heparin was associated with a reduction in the odds of death (odd ratio 0.88 (95% CI, 0.77 to 1.00; I^2 = 0%) (Polderman and Girbes, 2004). Evidence of potential benefit was not dependent on the presence of DIC or coagulopathy. In a second meta-analysis that evaluated the effects of LMWH in Chinese trials that evaluated LWMH in sepsis, LMWH was associated with reduced 28-day mortality (Fan et al., 2016). In patients with septic shock, therapeutic UFH is currently being evaluated in an international phase II/III RCT (www.halointernational.org, NCT03378466).

Specific to COVID-19 disease, in an observational study of 449 hospitalized patients from Wuhan, China, among 99 patients who received heparin (primarily LMWH, but also UFH) at prophylactic doses, heparin was associated with reduced 28-day mortality in patients with sepsis-induced coagulopathy or who had d-dimers that were greater than 6-fold the upper limit of normal (Tang et al., 2020a).

High troponin has been reported to strongly be associated with poor outcomes in patients with COVID-19 disease (Inciardi et al., 2020, Wang et al., 2020b). Reports of arterial events in critically ill COVID-19 patient, including myocardial infarction and stroke occurring in COVID-19 positive patients have also been forwarded. Platelet activation is known to occur in infection, DIC and hemophagocytic syndrome (de Stoppelaar et al., 2014). While the majority of interventional trials of anti-thrombotics in sepsis have focused on parenteral anticoagulants, the role of anti-platelet agents in sepsis and in COVID-19 patients remains to be evaluated.

6.2.6. Intravenous unfractionated heparin

UFH is a naturally occurring glycosaminoglycan that exerts its anticoagulant effect by enhancing antithrombin mediated inactivation of factors Xa and IIa, but also factors IXa, XIa, and XIIa (Gans, 1975). Because its size, activity, and pharmacokinetics are variable, its anticoagulant effect requires close monitoring in hospital settings. Chains of UFH varies in length and molecular weights from 5,000

to over 40,000 Daltons.

6.2.7. Low molecular weight heparin

LMWH represent, on average, shorter chains of UFH with an average molecular weight less than 8,000 Daltons. LMWH is obtained by various methods including fractionation or depolymerization of polymeric heparin. LMWHs exert the majority of their anticoagulant effect through factor X compared to its effect on factor II (thrombin).

6.2.8. Safety of unfractionated heparin and Low molecular weight heparin

UFH and LMWH are anticoagulants and as such are associated with major and clinically relevant minor bleeding. Therapeutic anticoagulation has been studied extensively across diverse patient populations, including both critically ill and ward patients, and favorable safety data is available. Therapeutic anticoagulation is commonly used in hospitalized patients for the treatment of venous thromboembolic disease, acute coronary syndromes, and stroke prevention in patients with atrial fibrillation (Tiryaki et al., 2011). The dosing and management of both unfractionated heparin and low molecular weight heparin are very familiar to clinicians. Overall, patients receiving therapeutic anticoagulation with these agents have a 1-5% risk of major bleeding, depending on underlying risk and duration of exposure (Mismetti et al., 2005, Petersen et al., 2004, Crowther and Warkentin, 2008).

Patients with an underlying systemic hypercoagulable state (such as COVID-19), in whom therapeutic anticoagulation is being given to offset this, may intuitively have a lower risk of bleeding. For example, in cancer-associated venous thromboembolisms
– an underlying hypercoagulable state
– the estimated rate of major bleeding was reported to be 3.2% over a 6 months period (Lee et al., 2015, Li et al., 2019).

In the PROTECT trial, a multi-national thromboprophylaxis RCT comparing UFH to LMWH in critically ill patients (n=3764), the major bleeding rate was 5.6% (Group et al., 2011). In this trial, no relationship was detected between use of therapeutic heparin and the activated partial thromboplastin time (aPTT) ($p = 0.41$) (Lauzier et al., 2013).

In patients receiving therapeutic anticoagulation for the treatment of venous

thromboembolism (VTE), the rate of major hemorrhage typically reported ranges from 2-3%. Rates of major hemorrhage in patients randomized to receive UFH or LMWH appear to be similar (Dolovich et al., 2000). In patients therapeutically anticoagulated for treatment of acute coronary syndrome, rates of major hemorrhage in patients receiving UFH + a glycoprotein IIb/IIIa inhibitor is approximately 6% and similar (6%) in patients receiving LMWH (Navarese et al., 2015).

In the HALO pilot randomized trial (n = 76), where patients with septic shock were randomized to receive therapeutic dose IV UFH for the treatment of VTE or dalteparin for venous thromboprophylaxis, two patients (6%, 95%CI 1 to 11%) randomized to IV UFH and 1 patient (3%, 95%CI 1 to 7%) randomized to dalteparin experienced major bleeding. None of these bleeding events were adjudicated to contribute to morbidity or mortality.

Overall, the rate of bleeding may not be significantly different between unselected critically ill patients receiving low dose thromboprophylaxis and selected patients receiving therapeutic dose heparin or LMWH.

The incidence of heparin-induced thrombocytopenia with LMWH and UFH when administered to general medical-surgical ICU patients is approximately 0.3 to 0.6% (Group et al., 2011). Heparin- induced thrombocytopenia occurs significantly less often in patients receiving low molecular weight heparin compared with UFH (RR 0.22, 95% CI 0.06 to 0.84) (Junqueira et al., 2017). The overall incidence of HIT is 0.2–0.5%, and is higher in patients receiving therapeutic doses of UFH (0.79%) compared to those receiving prophylactic doses (<0.1%) (Creekmore et al., 2006, Smythe et al., 2007).

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of therapeutic anticoagulation for patients with acute illness due to suspected or proven pandemic infection.

We hypothesize that the probability of the occurrence of the primary endpoint specified in the relevant core protocol documents will differ based on allocation to different anticoagulation strategy. The following interventions will be available:

- Local standard venous thromboprophylaxis
- Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin

We hypothesize that the treatment effect of therapeutic anticoagulation is different depending on whether SARS-CoV-2 infection is confirmed to be present or absent.

We hypothesize that the treatment effect of therapeutic anticoagulation is different depending on the illness severity state at the time of enrollment.

We hypothesize that the treatment effect of therapeutic anticoagulation is different depending on D-dimer strata status.

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial. Treatment allocation will be based on response adaptive randomization, as described in the core protocol documents.

8.1. Population

The REMAP enrolls patients with acute illness due to suspected or proven COVID-19 admitted to hospital, including patients admitted to ICU.

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in either the REMAP-CAP Core Protocol + Pandemic Appendix or the REMAP-COVID Core Protocol. Patients eligible for the REMAP may have conditions that exclude them from this specific COVID-19 Therapeutic Anticoagulation Domain.

This domain is available for patients who have acute illness due to suspected or proven pandemic infection in both the Moderate State and the Severe State.

8.2.1. Domain inclusion criteria

Patients are eligible for this domain if:

- COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing (i.e. PISOP stratum)
- Microbiological testing for SARS-CoV-2 of upper or lower respiratory tract secretions or both has occurred or is intended to occur

8.2.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- More than 48 hours has elapsed since ICU admission (noting that this may be operationalized as more than 48 hours has elapsed since commencement of sustained organ failure support)
- Clinical or laboratory bleeding risk or both that is sufficient to contraindicate therapeutic anticoagulation, including intention to continue or commence dual anti-platelet therapy
- Therapeutic anticoagulation is already present due to prior administration of any anticoagulant agent that is known or likely to still be active or a clinical decision has been made to commence therapeutic anticoagulation
- Enrolment in a trial evaluating anticoagulation for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial
- Known or suspected previous adverse reaction to UFH or LMWH including heparin induced thrombocytopenia (HIT).
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

8.2.3. Intervention exclusion criteria

Nil.

8.3. *Anticoagulant Interventions*

8.3.1. Anticoagulation interventions

Patients will be randomly assigned to receive either of the following open-label strategies. The interventions will be commenced immediately after allocation status is revealed.

☐ Local standard venous thromboprophylaxis

☐ Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin

Administration of venous thromboprophylaxis is based on local practice and is mandatory.

8.3.2. Local standard venous thromboprophylaxis

Standard venous thromboprophylaxis that complies with local guidelines or usual practice will be administered for 14 days following randomization or until hospital discharge, whichever occurs first. The dose of agent that is chosen should not be sufficient to result in therapeutic anticoagulation.
After 14 days decisions regarding thromboprophylaxis and anticoagulation are at the discretion of the treating clinician.

8.3.2.1. *Use of therapeutic anticoagulation in patients randomized to local standard venous thromboembolism*

Any patient who develops an accepted clinical indication for anticoagulation can have this treatment commenced by the treating clinician. Such indications include, but are not limited, to proven deep venous thrombosis, proven PE, acute coronary syndrome, systemic embolic event, intermittent hemodialysis or sustained low-efficiency daily dialysis.

Systemic therapeutic anticoagulation for continuous renal replacement therapy is not permitted, unless there is an additional indication for anticoagulation. Regional citrate, heparin priming and low-dose heparin administration (without measurable systemic anticoagulation) are permitted for continuous renal replacement therapy. If regional low-dose heparin administration is used to facilitate continuous renal replacement therapy, the dose may be increased as necessary to prevent clotting of the filter, however the dose of heparin should be minimized as much as possible.

8.3.3. Therapeutic Anticoagulation

The patient will be administered either UFH or LMWH to achieve systemic anticoagulation. Either agent may be used and the same patient may be switched between UFH and LMWH at the discretion of the treating clinician

8.3.3.1. *Unfractionated heparin*

If UFH is used, this is commenced, administered, and monitored according to local hospital policy, and guidelines that are used for the treatment of VTE (i.e. not for

acute coronary syndrome). The target aPTT should typically be in the range of 1.5 to 2.5 times the upper limit of normal at the participating site. Alternately, therapeutic anti-Xa values (i.e. values targeted for the treatment of acute VTE) can be targeted based on local practice. If UFH is used, the availability of a local hospital policy that has specifies an aPTT target in this range or an anti-Xa value is a requirement. Based on an assessment of risk of administration of a loading dose, an initial bolus of UFH may be withheld at the discretion of the treating clinician.

8.3.3.2. *Low molecular weight heparin*

LMWH is commenced, administered, and monitored according to local hospital policy, practice and guidelines that pertain to treatment of VTE (i.e. not thromboprophylactic doses). The dose selected should be based on measure or estimated weight of the patient.

Adjustment for impairment of renal function should be according to local practice and policy.

8.3.3.3. *Duration of therapeutic anticoagulation*

The duration of therapeutic anticoagulation is 14 days. For patients who are discharged from hospital before 14 days, therapeutic anticoagulation should be ceased prior to hospital discharge. For patients admitted to an ICU therapeutic anticoagulation may be ceased before 14 days at the discretion of the treating clinician at ICU discharge but, during the 14 day period, all patients receiving invasive mechanical ventilation should receive therapeutic anticoagulation until at least 24 hours after cessation of mechanical ventilation.

After 14 days decisions regarding thromboprophylaxis and anticoagulation are at the discretion of the treating clinician.

8.3.4. Discontinuation of study intervention

Anticoagulation or local standard venous thromboprophylaxis should be discontinued if there is clinical bleeding or other complication sufficient to warrant cessation in the opinion of the treating clinician. Major bleeding, including death due to bleeding, is an SAE. Anticoagulation or local standard venous thromboprophylaxis may be recommenced if deemed appropriate by the treating

clinician.

Occurrence of laboratory proven HIT must result in cessation UFH or LMWH without recommencement regardless of treatment assignment. Use of an acceptable alternative agent is required in this instance as clinically indicated. Occurrence of laboratory proven HIT is an SAE.

The study interventions can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient. Temporary cessation – for the shortest period of time possible, but not longer than 24 hours - such as to allow surgical or other procedures is not a protocol deviation.

Temporary or permanent cessation of the study interventions for bleeding is not a protocol deviation.

8.3.5. COVID-19 anticoagulation strategy in patients negative for COVID-19 infection

In patients with suspected COVID-19 infection who receive an allocation status to receive active anticoagulation but who subsequently test negative for COVID-19 infection may have treatment ceased unless the treating clinician believes that doing so is not clinically appropriate. This decision should take into account the known or suspected local population incidence of COVID-19 infection among critically ill patients and sensitivity of testing for COVID-19 infection.

8.4. *Concomitant care*

Additional agents, other than those specified in the platform, that are intended to modify the patient's coagulation function as a treatment for COVID-19 infection should not be administered. A patient who receives an agent that act to inhibit platelet function as a usual medication may have this medication continued. Commencement of any new agent that inhibits platelet function is not permitted unless there is an accepted clinical indication such as an acute coronary syndrome, ischemic stroke or transient ischemic event or the agent that inhibits platelet function has been specified in another domain of this platform.

All other treatment that is not specified by assignment within the platform will be determined by the treating clinician.

8.5. *Endpoints*

8.5.1. Primary endpoint

The primary endpoint for this domain is the primary outcome specified in the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol.

8.5.2. Secondary endpoints

All secondary endpoints as specified in the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol.

The domain-specific secondary outcome measures (from randomization, during the index hospitalization, censored 90 days after enrollment) will be:

- Serial detection of SARS-CoV-2 in upper or lower respiratory tract specimens (using only specimens collected for routine clinically indicated testing)
- Confirmed deep venous thrombosis
- Confirmed pulmonary embolism
- Confirmed ischemic cerebrovascular event
- Total red cell blood cell units transfused between randomization and the end of study day 15
- Confirmed acute myocardial infarction

- Peak troponin between randomization and the end of study day 15
- Major bleeding
- Other confirmed thrombotic event including mesenteric ischemia and limb ischemia
- SAE as defined in Core Protocol and this DSA below

9. TRIAL CONDUCT

9.1. Microbiology

Microbiological testing will be performed as per local practice, including bacterial and viral testing to guide clinical care. Results of these tests will be collected but no additional testing is specified in this protocol.

Sites that are participating in this domain are encouraged to also participate in the Clinical Characterization Protocol (CCP) for patients with COVID-19 that has been established by the International Severe Acute Respiratory and Emerging

Infectious Consortium (https://isaric.tghn.org/CCP/). This protocol specifies the collection of biological samples from patients with COVID-19. Samples collected in patients who are enrolled in the CCP may be made available to REMAP-CAP investigators to evaluate aspects of host or pathogen biology associated with assignment in this domain. Ethical approval at such sites and agreement from patients to undertake the CCP will be obtained separately.

9.2. Domain-specific data collection

Additional domain-specific data will be collected.

- Baseline measures of coagulation including d-dimer
- Administration of anticoagulant agents
- Administration of agents that inhibit platelet function
- Transfusion of red cells
- Peak troponin
- Acute myocardial infarction (using fourth international definition)
- Major bleeding (using the International Society on Thrombosis and Haemostasis definition)
- Mesenteric Ischemia, limb ischemia, and other clotting events

9.3. Criteria for discontinuation

Refer to relevant core protocol documents for criteria for discontinuation of participation in the REMAP-CAP trial.

9.4. Blinding

9.4.1. Blinding

All medication will be administered on an open-label basis.

9.4.2. Unblinding

Not relevant.

10. STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

The Platform Conclusion of equivalence in this domain will not be evaluated.

Instead a Platform Conclusion of Futility will be considered. If the posterior probability of at least a 20% odds-ratio increase for therapeutic anticoagulation is less than 5% then therapeutic anticoagulation will be declared Futile as a Platform Conclusion. This rule corresponds to the one-sided equivalency region.

In all other respects the stopping rules for this domain are those outlined in the relevant core protocol documents.

10.2. Unit-of-analysis and strata

This domain is analyzed only in the pandemic statistical model and includes only patients who are in the pandemic suspected or proven stratum, as specified in the REMAP-CAP Pandemic Appendix and corresponding to the eligibility criteria specified in the REMAP-COVID Core Protocol. Within this stratum, the unit-of-analysis is defined by illness severity state at time of enrollment, defined as either Moderate State or Severe State. Unit-of-analysis may also be defined by SARS-CoV-2 infection or d-dimer strata or both. The D-dimer strata will contain 3 stratum, the breakpoints of which will be determined not later than the first interim analysis using data derived from patients enrolled in REMAP-CAP as well as any other trials that may utilize the same statistical model. Borrowing is permitted between states and strata. If the SARS-CoV-2 strata is applied in analysis, Response Adaptive Randomization will be applied to all PISOP patients, in each illness severity state, using probabilities derived from the SARS-CoV-2 confirmed stratum. Response Adaptive Randomization may also be applied according to D-dimer strata status. The decision to apply the SARS-CoV-2 and D- dimer strata will be operational.

At the time of a Platform Conclusion, results will be reported for all randomized patients, patients in whom COVID-19 infection is confirmed by microbiological testing, microbiological tests do not detect or isolate COVID-19 infection, and testing is not performed.

The shock strata will not contribute to unit-of-analysis for this domain, as this strata is not applied in the Pandemic Statistical Model.

The influenza strata will not contribute to unit-of-analysis for this domain.

10.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is

specified to be Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal if prospective agreement to participate is required for this domain (see relevant core protocol documents).

10.4. *Interactions with interventions in other domains*

An *a priori* interaction with the Antibiotic Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the Macrolide Duration Domain is not considered possible will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Influenza Antiviral Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the Corticosteroid Domain is not considered possible will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Immune Modulation Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Antiviral Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Statin Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Vitamin C Domain is either not considered possible and will not be incorporated into the statistical model used to evaluate this domain in the pandemic statistical model or is not able to be evaluated for PINSNP patients as analysis occurs in different statistical models.

No interaction is evaluable between the Ventilation Domain and this domain.

10.5. *Nesting of interventions*

Nesting is not applicable to this domain.

10.6. Threshold probability for superiority and inferiority

The threshold odds ratio delta for superiority and inferiority in this domain are those specified in the Operating Characteristics document derived from Pandemic Appendix and the REMAP-COVID Core Protocol. It is noted that the threshold for superiority and inferiority in the current model has been modified from 0.95 to 0.99 to provide adequate control of type I error, following the evaluation of simulations. It is also noted that asymmetric probabilities may be specified for harm, to allow early cessation and declaration of a Platform Conclusion for interventions that are unlikely to be effective and may be harmful. If so, this will be specified in the Operating Characteristics document which is placed in the public domain.

10.7. Threshold odds ratio delta for equivalence

The Platform Conclusion of equivalence will not be evaluated in this domain. The same odds ratio delta as specified in the relevant core protocol documents for equivalence will be used for futility. This will be applied in a one-sided analysis for futility of therapeutic anticoagulation

10.8. Informative priors

This domain will launch with priors that are not informative for main effects.

10.9. Post-trial sub-groups

Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The *a priori* patient sub-groups of interest are:

- Proven concomitant bacterial co-infection, defined as having isolation or detection of a known pathogen that causes CAP from blood, pleural fluid, or lower respiratory tract specimen
- Whether therapeutic anticoagulation is initiated with UFH or LMWH
- Shock strata
- Receiving invasive mechanical ventilation at baseline
- Baseline troponin
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

11. ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, efficacy, inferiority, or futility of different interventions with respect to the primary endpoints are possible.

The DSMB should take into account the public health, as well as clinical significance, of the analyses of this domain and are empowered to discuss results with relevant international and national public health authorities, with rapid dissemination of results to the larger community being the goal.

Safety secondary outcomes will be reported to the DSMB who are empowered to require additional analyses regarding these outcomes as required.

11.2. Potential domain-specific adverse events

For patients assigned to any intervention, occurrence of any of the following should be reported as an SAE

- Laboratory proven heparin-induced thrombocytopenia

Other SAEs should be reported only where, in the opinion of the site-investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see relevant core protocol documents).

11.3. Domain-specific consent issues

As noted in the background, and endorsed by the WHO, in the absence of evidence of effectiveness of anticoagulation for COVID-19, the use of a usual care control is both appropriate and ethical.

Both forms of anticoagulation are being used, off-trial, and typically without consent, for patients with proven or suspected COVID-19 infection. Clinicians may choose not to enroll individual patients if they feel that participation is not in patient's best interests, and safety criteria are used to exclude patients from this domain for appropriate clinical reasons.

Where all interventions that are available at a participating site and are regarded as being part of the acceptable spectrum of standard care and given the time imperative necessary to evaluate these interventions, entry to the study, for participants who are not competent to consent, is preferred to be via waiver-of-consent or some form of delayed consent.

During a pandemic, visiting by relatives of affected patients may not be possible. In such situations, alternative methods for confirming consent including electronic and telephone communication, as permitted by an appropriate ethical review body, may be acceptable methods for confirming agreement to participate in this (and other) domains of the platform.

11.4. Relationship to Antiplatelet Domain

An Antiplatelet Domain of REMAP-CAP is being planned currently. If such a domain is implemented, it is intended that the Antiplatelet Domain and the Therapeutic Anticoagulation Domain will be analyzed as a 2 x N factorial, with N interventions being available within the Antiplatelet Domain.

12. GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. This domain has not received any additional domain-specific funding but such funding, from any source, may be obtained during the life-time of the domain.

12.2. Funding of domain interventions and outcome measures

All anticoagulant agents will be provided by participating hospitals. The cost of all agents specified in this domain are known to be inexpensive.

12.3. Domain-specific declarations of interest

All investigators involved in REMAP-CAP maintain a registry of interests on the REMAP-CAP website. These are updated periodically and publicly accessible on the study website.

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14. APPENDIX 1. OVERVIEW OF DESIGN AND INITIAL RESULTS FOR THE THERAPEUTIC ANTICOAGULATION DOMAIN

14.1. Introduction

This document describes the statistical design and analysis of the testing of therapeutic anticoagulation with intravenous UFH or subcutaneous LMWH compared to local standard venous thromboprophylaxis in the COVID-19 appendix as part of the REMAP-CAP trial. Our goal is to investigate whether this is independently beneficial in increasing the number of ICU- free days for patients with COVID-19.

14.1.1. Treatment Arms

The main effect for therapeutic anticoagulation in this domain will be modeled as specified in the PAtC.

14.1.2. Primary Endpoint

The primary efficacy endpoint is as specified in the PAtC, the ordinal endpoint, ICU-free days through 21 days with the classification of in hospital death as the worst outcome.

14.2. Primary Analysis Model

The primary analysis is based on a Bayesian cumulative logistic regression assuming proportional odds for intervention effects (reference the PAtC stats document??).

14.2.1. Domain Platform Conclusions.

The Platform Conclusions of Superiority and Inferiority are as specified in the PAtC and are unchanged.

This domain substitutes a Platform Conclusion of Futility in place of Equivalence for this domain as demonstration of equivalence in not relevant but a conclusion of Futility of therapeutic anticoagulation is relevant. If the probability of at least a 20% odds ratio improvement for therapeutic anticoagulation is less than 5% then the Statistical Trigger for

Futility will have been met. This Futility trigger is the one-sided extension of the equivalence rule in PAtC. That is, Futility of therapeutic anticoagulation will be declared if $Pr(OR_1 > 1.2) < 0.05$, where OR_1 refers to the odd ratio for therapeutic anticoagulation compared to SOC for this domain.

14.3. *Simulation Details*

In this section, we outline the simulations conducted for understanding the performance of this domain. Simulations were conducted separately assuming only this domain, as there are no interactions with any other domains.

14.3.1. Standard-of-Care Rates and therapeutic anticoagulation effect assumptions

We created possible standard-of-care rates across the 23 levels of the outcome. We worked within a few clinically guided expected parameters: 20% mortality rate, 10% of patients are in the ICU 21 days, and median number of days in the ICU is 7 amongst those that did not die. Figure 1 shows the assumed rates for the ICU-free day endpoint in the left panel.

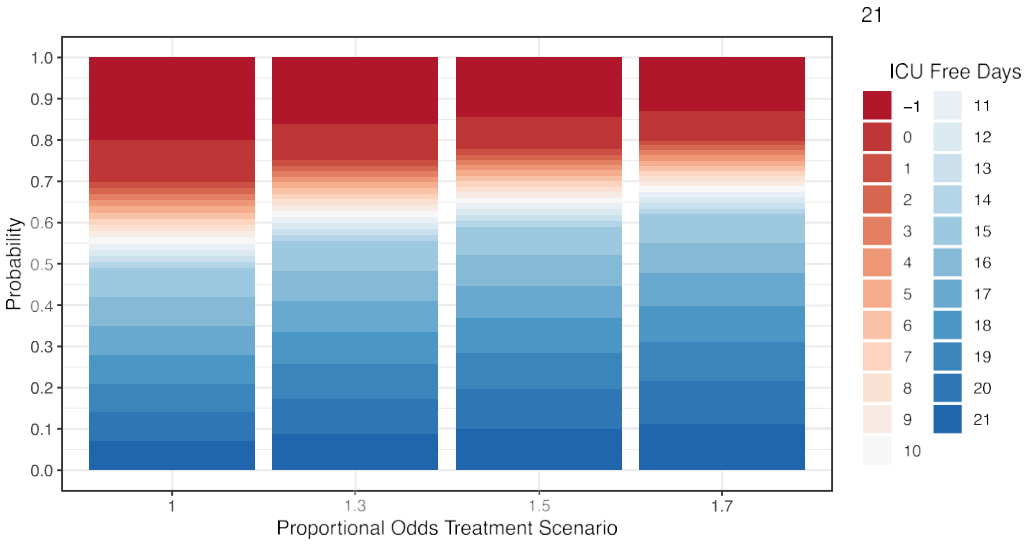


Figure 1. Control outcome probabilities for the ICU-free day end point (left panel) and then the probabilities for treatment effects of odds ratios of 1.3, 1.5, and 1.7.

For the simulations in this section interim analyses are assumed to occur at 200, 400, 600, 800, 1000, 1500, 2000, 2500, and 3000 patients enrolled in this domain.

14.4. *Operating Characteristics*

Figure 2 presents the cumulative power to determine that therapeutic anticoagulation is superior to the standard-of-care intervention as a function of the total number of patients enrolled (x-axis) and the assumed effect sizes (1.3, 1.5, and 1.7).

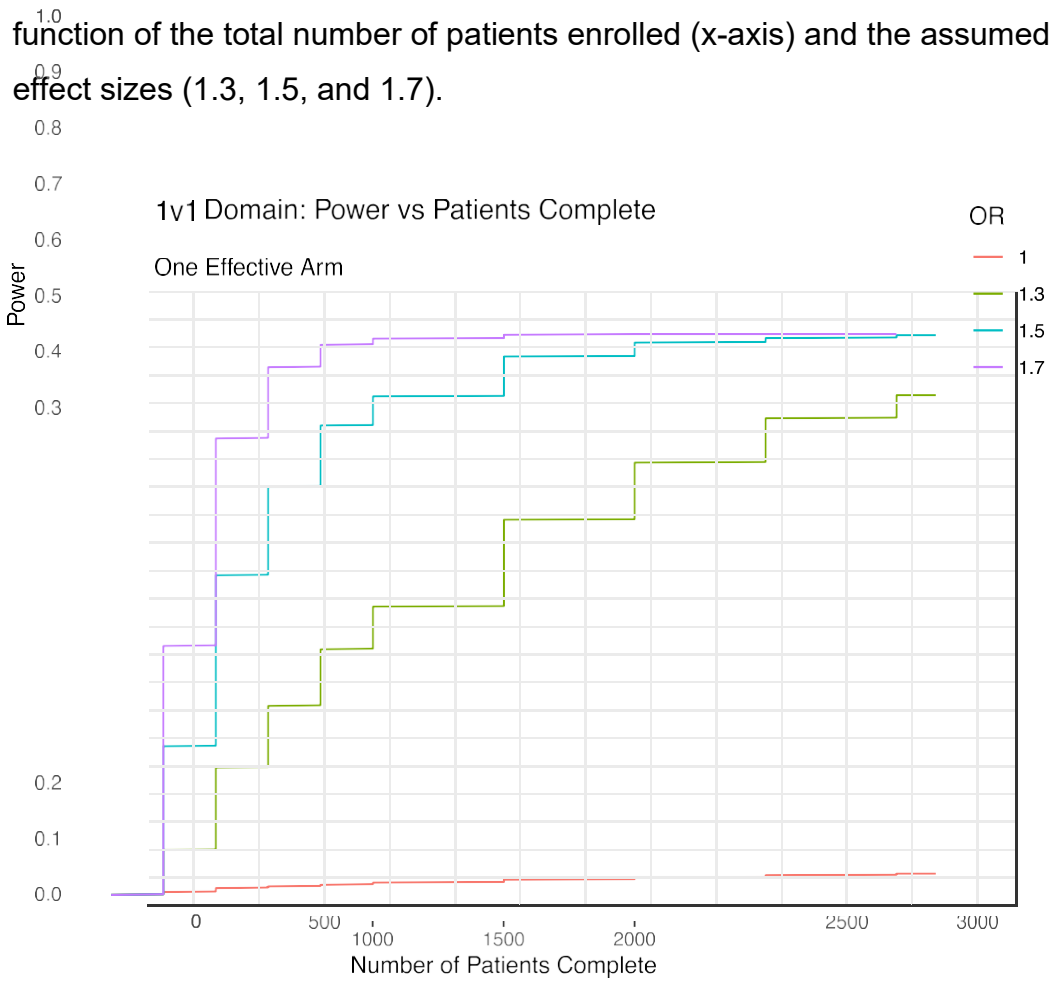
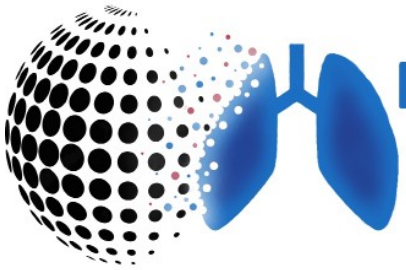


Figure 2: The cumulative power for each of the explored treatment effects (odds ratios of 1.3, 1.5, and 1.7). The cumulative type I error is shown as the red line (effect size of 1).

14.5. *Summary*

The domain is designed to provide high-level evidence. The domain has 80% power to demonstrate superiority of therapeutic anticoagulation to standard-of-care by 400 patients enrolled assuming an odds ratio effect size of 1.7. For an effect size of 1.5 the power is 80% for 800 patients enrolled. The cumulative type I error through 3000 patients is less than 5%.



Protocol Amendment to COVID-19 Therapeutic Anticoagulation Domain-Specific Appendix

Summary of changes

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

REMAP-CAP Therapeutic Anticoagulation Domain-Specific Appendix Amendment Summary Version 1 dated 24 June 2020

TABLE OF CONTENTS

1. CURRENT VERSIONS OF PROTOCOL DOCUMENTS

1.1. The current versions of Therapeutic Anticoagulation specific protocol documents:

- REMAP-CAP Core Protocol Version 3, dated 10 July 2019
- REMAP-CAP Pandemic Appendix to Core Version 2, dated 18 May 2020
- REMAP-COVID Core Protocol Version 1, dated 27 March 2020
- REMAP-CAP Therapeutic Anticoagulation Domain-Specific Appendix Version 2, dated 24 June 2020

2. AMENDMENT 1

The Therapeutic Anticoagulation Domain-Specific Appendix Protocol document underwent an amendment in June 2020. The broad objective of this amendment is to extend this domain to patients in a Moderate illness severity state. The Moderate State is defined as patients with admitted to a hospital with an acute illness due to COVID-19 who are not receiving organ support in an intensive care unit.

The REMAP-CAP COVID Core Protocol has been created as an alternative core protocol document for submission in some regions. This document removes any information from the REMAP-CAP Core Protocol that is not relevant to the COVID-19 pandemic, and integrates this information with the Pandemic Appendix to the Core Protocol into a single document. It is intended that the REMAP-COVID Core Protocol may be used by some regions as an alternative to the REMAP-CAP Core Protocol and the Pandemic Appendix to the Core Protocol. The language in this DSA has been modified to refer to either set of core protocol documents.

2.1. Summary of changes

<table>
<tr><th>Section</th><th>Original text</th><th>New Text</th><th>Reason</th></tr>
<tr><td>Front page and whole document header</td><td>REMAP-CAP Therapeutic Anticoagulation Domain-Specific Appendix Version 1 dated 20 April 2020</td><td>REMAP-CAP Therapeutic Anticoagulation Domain-Specific Appendix Version 2 dated 24 June 2020</td><td>Administrative change</td></tr>
<tr><td>Summary
Page 2</td><td>In this domain of the REMAP-CAP trial, participants meeting the platform entry criteria for REMAP-CAP admitted to participating intensive care units with suspected or microbiological testing-confirmed COVID-19 infection will be randomized to one of two interventions:
• Local standard venous thromboprophylaxis
• Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin

This domain will enroll patients only in the pandemic infection is suspected or proven (PISOP) stratum and be analyzed in the Pandemic Statistical Model as outlined from the Pandemic Appendix to Core (PAtC).</td><td>In this domain of the REMAP-CAP trial, participants meeting the platform entry criteria ~~for REMAP-CAP admitted to participating intensive care units~~ with suspected or microbiological testing-confirmed COVID-19 infection will be randomized to one of two interventions:
• Local standard venous thromboprophylaxis
• Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin

~~This domain will enroll patients only in the pandemic infection is suspected or proven (PISOP) stratum and be analyzed in the Pandemic Statistical Model as outlined from the Pandemic Appendix to Core (PAtC).~~</td><td>Text deleted to reflect that patients who are not admitted to the ICU may also be eligible.

Text removed. This information is redundant and is outlined in the body of this document.</td></tr>
<tr><td>Summary
Page 2</td><td>Blank</td><td>This DSA applies to the following states and stratum:<table><tr><th>Stratum</th><th>Pandemic infection suspected or proven (PISOP)</th><th>Pandemic infection neithersuspected nor proven (PINSNP)</th></tr></table></td><td>Addition of a standard table to outline which statistical model and</td></tr>
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<table>
<tr><td></td><td></td><td>Core protocol documents</td><td colspan="3">REMAP-CAP Core Protocol + Pandemic Appendix, or REMAP-COVID Core Protocol</td><td>REMAP-CAP Core Protocol</td><td rowspan="6">protocol document relate to this domain. This table also outlines which interventions will be submitted for ethical review in this jurisdiction; and which interventions will be offered to patients in ward and ICU settings byillness severity state.</td></tr>
<tr><td></td><td></td><td>Illness Severity State</td><td colspan="2">Moderate State</td><td>Severe State</td><td>Severe State</td></tr>
<tr><td></td><td></td><td>Interventions available in this Domain</td><td colspan="2">Local VT Therapeutic anticoagulation</td><td>Local VT Therapeutic anticoagulation</td><td>Not available</td></tr>
<tr><td></td><td></td><td>Interventions submitted for approval in this jurisdiction</td><td colspan="2">☐ Local VT
☐ Therapeutic anticoagulation</td><td>☐ Local VT
☐ Therapeutic anticoagulation</td><td>Not available</td></tr>
<tr><td></td><td></td><td rowspan="2">Interventions offered at this site</td><td>Ward</td><td>ICU</td><td>ICU</td><td>ICU</td></tr>
<tr><td></td><td></td><td>☐ Local VT
☐ Therapeutic anticoagulation</td><td>☐ Local VT
☐ Therapeutic anticoagulation</td><td>☐ Local VT
☐ Therapeutic anticoagulation</td><td>Not available</td></tr>
<tr><td>Summary table Unit of Analysis, Strata and State Page 3</td><td colspan="3">Unit of Analysis and Strata
The default unit-of-analysis for this domain will be the pandemic infection suspected or confirmed (PISOP) stratum. Analysis and Response Adaptive Randomization are applied by PISOP stratum. Unit of analysis may be modified to allow analysis to be stratified by SARS-CoV-2 infection confirmed or not confirmed with borrowing permitted. If this occurs, Response Adaptive Randomization will be applied to patients in the PISOP stratum using probabilities derived</td><td colspan="3">Unit of Analysis, Strata, and State
This domain is analyzed only in the pandemic statistical model.
The pandemic statistical model includes only patients who are in the Pandemic Infection Suspected or Proven (PISOP) stratum. Within this stratum, the unit-of-analysis is defined by illness severity state at time of enrollment, defined as either Moderate State or Severe State. Unit-of-analysis may also be defined by SARS-CoV-2 infection or d-dimer strata or both. Borrowing is permitted between states and strata. If the SARS-CoV-2</td><td>Addition of illness severity state and clarification of unit-of-analysis</td></tr>
</table>

	from SARC-CoV-2 confirmed stratum. A strata related to D-dimer level may also be applied.	strata is applied in analysis, Response Adaptive Randomization will be applied to all PISOP patients, in each illness severity state, using probabilities derived from the SARS-CoV-2 confirmed stratum. Response Adaptive Randomization may also be applied according to D-dimer strata status.	
Summary table Domain-Specific Exclusions Page 3	Patients will be excluded from this domain if they have any of the following: • More than 48 hours has elapsed since ICU admission	Patients will be excluded from this domain if they have any of the following: • More than 48 hours has elapsed since ICU admission (noting that this may be operationalized as more than 48 hours has elapsed since commencement of organ failure support)	Patients who are admitted to ICU but are not recieving organ support may be eligible in the Moderate State. This exclusion criteria may therefore be operationalised as 48 hours from the commencement of organ failure support for patients in the Severe state.
Summary table Outcome measures Page 4	Primary REMAP endpoint: as defined in an operational document specified from the Pandemic Appendix to the Core Protocol Section 7.5.1	Primary REMAP endpoint: refer to REMAP-CAP Core Protocol + Pandemic Appendix and REMAP-COVID Core Protocol	Administrative change to refer to both sets of protocol documents that are compatible with this DSA.

	Secondary REMAP endpoints: as defined in an operational document specified from Pandemic Appendix to the Core Protocol Section 7.5.2 Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment): • Serious Adverse Events (SAE) as defined in Core Protocol	Secondary REMAP endpoints: refer to REMAP-CAP Core Protocol + Pandemic Appendix and REMAP-COVID Core Protocol Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment): • Confirmed deep venous thrombosis • Confirmed pulmonary embolism • Confirmed ischemic cerebrovascular event • Total red cell blood cell units transfused between randomization and the end of study day 15 • Acute myocardial infarction • Peak troponin • Major bleeding • Other thrombotic events including mesenteric ischemia and limb ischemia • Serious Adverse Events (SAE) as defined in relevant core protocol documents and this DSA	Addition of important secondary outcomes; and addition of existing specified endpoints to this summary table.
SECTION 2 PROTOCOL APPENDIX STRUCTURE	**Original text**	**New Text**	**Reason**

Page 11	DSAs, RSAs, and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org).	The current version of the relevant Core Protocol (either REMAP-CAP Core Protocol +/- Pandemic Appendix or REMAP-COVID Core Protocol), DSAs, RSAs, and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org).	Administrative change to refer to both sets of protocol documents that are compatible with this DSA
SECTION 3 COVID-19 THERAPEUTIC ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION	**Original text**	**New Text**	**Reason**
3.1. Version history Page 12	Version 1: Approved by the COVID-19 Domain-Specific Working Group (DSWG) on 20th April 2020.	Version 1: Approved by the COVID-19 Therapeutic Anticoagulation Domain-Specific Working Group (DSWG) on 20th April 2020. Version 2: Approved by the COVID-19 Therapeutic Anticoagulation Domain-Specific Working Group (DSWG) on 9th June 2020	Administrative change
SECTION 4 COVID-19 THERAPEUTIC ANTICOAGULATION THERAPY DOMAIN GOVERNANCE	**Original text**	**New Text**	**Reason**
4.1. Domain members Page 12	Professor Derek Angus Dr. Scott Berry Dr. Shailesh Bihari Dr. Charlotte Bradbury	Prof. Derek Angus Dr. Scott Berry Dr. Shailesh Bihari Dr. Charlotte Bradbury	New memebers added *Professor* changed to *Prof.* for consistency of nomenclature

	Professor Marc Carrier Professor Dean Fergusson Professor Robert Fowler Professor Anthony Gordon Professor Anand Kumar Dr. Patrick Lawler Dr. Patrick Lawless Dr. Sylvain Lother Dr. Colin McArthur Professor John Marshall Dr. Zoe McQuilten Professor Simon StanworthDr. Alexis Turgeon Professor Steve Webb	Prof. Marc Carrier Prof. Dean Fergusson Prof. Robert Fowler A/Prof. Timothy GirardProf. Anthony Gordon A/Prof. Ghady Haidar A/Prof. Christopher Horvat Prof. David Huang Prof. Beverley Hunt Prof. Anand Kumar Prof. Mike Laffan Dr. Patrick Lawler Dr. Patrick Lawless Dr. Sylvain Lother Dr. Peter MacCallum Dr. Colin McArthur A/Prof. Bryan McVerry Prof. John Marshall Prof. Saskia MiddeldorpDr. Zoe McQuilten A/Prof. Matthew Neal Prof. Alistair Nichol Prof. John Pasi A/Prof. Christopher Seymour	

		Prof. Roger Schutgens Prof. Simon Stanworth Dr. Alexis Turgeon Prof. Steve Webb A/Prof. Alexandra Weissman	
4.3. Interaction with ATTAC trial Page 14	Blank	4.3. Interaction with ATTACC trial ATTACC is a trial that also evaluates the treatment effect of therapeutic anticoagulation in patients with COVID-19. There is overlap between the leadership of the ATTACC trial and the leadership of this domain. This domain and ATTACC have been designed to be complementary with pre-specified plans in relation to methods of analysis. It is intended that data from ATTACC will be incorporated into the pandemic statistical model of REMAP-CAP. The protocol, governance, and data management of ATTACC are separate from REMAP-CAP, but the REMAP-CAP DSMB will also serve the ATTACC trial.	The ATTACC trial has been aligned with this domain of REMAP-CAP. This addition outlines the relationship between this domain and the ATTACC trial which is planned to recruit in Canada and the United States.
SECTION 6 BACKGROUND AND RATIONALE	**Original text**	**New Text**	**Reason**

6.1. Domain definition	This is a domain within REMAP-CAP to test the effectiveness of therapeutic anticoagulation for suspected or microbiological testing-confirmed COVID-19 in patients with concomitant severe pneumonia who are admitted to an Intensive Care Unit (ICU).	This is a domain within the REMAP-CAP platform to test the effectiveness of therapeutic anticoagulation versus local venous thromboprophylaxis for patients with acute illness due to suspected or proven COVID-19.	Modification of language to reflect that this domain may include patients in the ModerateState, who may not be admitted to an ICU with severe pneumonia.
6.2.2.2 Need for evidence in patients who are critically ill as well as hospitalized patients	There is need to evaluate interventions for COVID-19 infection in patients who are critically ill. The number of current studies that are focused on patients who are critically ill is uncertain and, for those studies that are enrolling hospitalized patients, it is unclear if stratification by severity is a design feature. The need for studies that focus on patients who are critically ill arises because of the possibility of differential treatmenteffect between patients who are critically ill compared with noncritically ill patients. Among trials that evaluate interventions in patients who are critically ill it is common for the results of the trial to be different to that which was predicted based on a prior understanding of mechanism of action combined with known mechanism of disease (Landoni et al., 2015, Webb, 2015). This observation reinforces the	There is need to evaluate interventions for COVID-19 infection in patients who are critically ill or hospitalized and not critically ill, separately, because of the possibility of differential treatment effect, depending onillness severity. The number of current studies that are focused on patients who are critically ill is uncertain and, for those studies that are enrolling hospitalized patients, it is unclear if stratification by severity is a design feature. Among trials that evaluate interventions in patients who are critically ill it is common for the results of the trial to be different to that which was predicted based on a prior understanding of mechanism of action combined with known mechanism of disease (Landoni et al., 2015,Webb, 2015). This observation reinforces the importance of not necessarily relying on extrapolation	Addition to reflect the rationale for addition of the Moderate State.

	importance of not necessarily relying on extrapolation of results (both positive and negative) from patients who are not critically ill.	of results (both positive and negative) from patients who are not critically ill. It is also possible different disease mechanisms apply at different levels of illness severity and that this may also influence balance between beneficial and adverse effects of a particular intervention. This reinforces the importance of obtaining estimates of treatment effect dependent on the level of illness severity.	
6.2.8 Safety of unfractionated heparin and Low molecular weight heparin	UFH and LMWH are anticoagulants and as such are associated with major and clinically relevant minor bleeding. The rate of bleeding however is typically less than 10% and may not be significantly different between unselected critically ill patients receiving low dose thromboprophylaxis and selected patients receiving therapeutic dose heparin or LMWH. In the PROTECT trial, a multi-national thromboprophylaxis RCT comparing UFH to LMWH (n=3764), the major bleeding rate was 5.6% (Group et al., 2011). In this trial, no relationship was detected between use of therapeutic heparin and the activated partial thromboplastin time (aPTT) (p = 0.41) (Lauzier et al., 2013).	UFH and LMWH are anticoagulants and as such are associated with major and clinically relevant minor bleeding. Therapeutic anticoagulation has been studied extensively across diverse patient populations, including both critically ill and ward patients, and favorable safety data is available. Therapeutic anticoagulation is commonly used in hospitalized patients for the treatment of venous thromboembolic disease, acute coronary syndromes, and stroke prevention in patients with atrial fibrillation (Tiryaki et al., 2011). The dosing and management of both unfractionated heparin and low molecular weight heparin are very familiar to clinicians. Overall, patients receiving therapeutic anticoagulation with these agents have a 1-5% risk of major bleeding, depending on underlying risk and	Additional safety information relating to non-critically ill hospitalized patients. Additional information relating to risk of major bleeding with heparin therapy.

	In patients receiving therapeutic anticoagulation for the treatment of venous thromboembolism (VTE), the rate of major hemorrhage typically reported ranges from 2- 3%. Rates of major hemorrhage in patients randomized to receive UFH or LMWH appear to be similar (Dolovich et al., 2000). In patients therapeutically anticoagulated for treatment of acute coronary syndrome, rates of major hemorrhage in patients receiving UFH + a glycoprotein IIb/IIIa inhibitor is approximately 6% and similar (6%) in patients receiving LMWH (Navarese et al.,2015). In the HALO pilot randomized trial (n = 76), where patients with septic shock were randomized to receive therapeutic dose IV UFH for the treatment of VTE or dalteparin for venous thromboprophylaxis, two patients (6%, 95%CI 1 to 11%) randomized to IV UFH and 1 patient (3%, 95%CI 1 to 7%) randomized to dalteparin experienced major bleeding. None of these bleeding events were adjudicated to contribute to morbidity or mortality. The incidence of heparin-induced thrombocytopenia with LMWH and UFH when administered to general	duration of exposure (Mismetti et al., 2005, Petersen etal., 2004, Crowther and Warkentin, 2008). Patients with an underlying systemic hypercoagulable state (such as COVID-19), in whom therapeutic anticoagulation is being given to offset this, may intuitively have a lower risk of bleeding. For example, in cancer-associated venous thromboembolisms – an underlying hypercoagulable state – the estimated rate of major bleeding was reported to be 3.2% over a 6 months period (Lee et al., 2015, Li et al., 2019). In the PROTECT trial, a multi-national thromboprophylaxis RCT comparing UFH to LMWH in critically ill patients (n=3764), the major bleeding rate was 5.6% (Group et al., 2011). In this trial, no relationship was detected between use of therapeutic heparin and the activated partial thromboplastin time (aPTT) (p = 0.41) (Lauzier et al., 2013). In patients receiving therapeutic anticoagulation for the treatment of venous thromboembolism (VTE), the rate of major hemorrhage typically reported ranges from 2-3%. Rates of major hemorrhage in patients randomized	

	medical-surgical ICU patients is approximately 0.3 to 0.6% (Group et al., 2011). Heparin-induced thrombocytopenia occurs significantly less often in patients receiving low molecular weight heparin compared with UFH (RR 0.22, 95% CI 0.06 to 0.84) (Junqueira et al., 2017). The overall incidence of HIT is 0.2–0.5%, and is higher in patients receiving therapeutic doses of UFH (0.79%) compared to those receiving prophylactic doses (<0.1%) (Creekmore et al., 2006, Smythe et al., 2007).	to receive UFH or LMWH appear to be similar (Dolovich et al., 2000). In patients therapeutically anticoagulated for treatment of acute coronary syndrome, rates of major hemorrhage in patients receiving UFH + a glycoprotein IIb/IIIa inhibitor is approximately 6% and similar (6%) in patients receiving LMWH (Navarese et al.,2015). In the HALO pilot randomized trial (n = 76), where patients with septic shock were randomized to receive therapeutic dose IV UFH for the treatment of VTE or dalteparin for venous thromboprophylaxis, two patients (6%, 95%CI 1 to 11%) randomized to IV UFH and 1 patient (3%, 95%CI 1 to 7%) randomized to dalteparin experienced major bleeding. None of these bleeding events were adjudicated to contribute to morbidity or mortality. Overall, the rate of bleeding may not be significantly different between unselected critically ill patients receiving low dose thromboprophylaxis and selected patients receiving therapeutic dose heparin or LMWH. The incidence of heparin-induced thrombocytopenia with LMWH and UFH when administered to general	

		medical-surgical ICU patients is approximately 0.3 to 0.6% (Group et al., 2011). Heparin-induced thrombocytopenia occurs significantly less often in patients receiving low molecular weight heparin compared with UFH (RR 0.22, 95% CI 0.06 to 0.84) (Junqueira et al., 2017). The overall incidence of HIT is 0.2–0.5%, and is higher in patients receiving therapeutic doses of UFH (0.79%) compared to those receiving prophylactic doses (<0.1%) (Creekmore et al., 2006, Smythe et al., 2007).	
SECTION 7 DOMAIN OBJECTIVES	**Original text**	**New Text**	**Reason**
	The objective of this domain is to determine the effectiveness of therapeutic anticoagulation for patients with severe pneumonia who have suspected or microbiological testing-confirmed COVID-19 infection. We hypothesize that the probability of the occurrence of the primary endpoint specified from the PAtC will differ based on the allocated anticoagulation strategy. The following interventions will be available: • Local standard venous thromboprophylaxis	The objective of this domain is to determine the effectiveness of therapeutic anticoagulation for patients with acute illness due to suspected or proven pandemic infection. We hypothesize that the probability of the occurrence of the primary endpoint specified in the relevant core protocol documents will differ based on allocation to different anticoagulation strategy. The following interventions will be available: • Local standard venous thromboprophylaxis	Modification of language to reflect that patients in the Moderate State may be eligible with acute illnes due to COVID, and do not require severe pneumonia for eligibility. Administrative change to refer to both sets of protocol documents that

	• Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin We hypothesize that the treatment effect of therapeutic anticoagulation is different depending on whether COVID-19 infection is confirmed to be present or absent.	• Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin We hypothesize that the treatment effect of therapeutic anticoagulation is different depending on whether SARS-CoV-2 infection is confirmed to be present or absent. We hypothesize that the treatment effect of therapeutic anticoagulation is different depending on the illness severity state at the time of enrollment.	are compatible with this DSA Addition of a hypothesis relating to illness severity state.
SECTION 8 TRIAL DESIGN	**Original text**	**New Text**	**Reason**
	This domain will be conducted as part of the REMAP-CAP trial (see Core Protocol Section 7). Treatment allocation will be based on response adaptive randomization, as described in the Core Protocol Section 7.5.2 and from the PAtC.	This domain will be conducted as part of the REMAP-CAP trial. Treatment allocation will be based on response adaptive randomization, as described in the core protocol documents.	Administrative change to refer to both sets of protocol documents that are compatible with this DSA
8.1 Population	The REMAP enrolls patients with severe pneumonia admitted to ICU (see Core Protocol Section 7.3).	The REMAP enrolls patients with acute illness due to suspected or proven COVID-19 admitted to hospital, including patients admitted to ICU.	Modification of language to reflect that patients in the Moderate State may be eligible without being

			admitted to ICU with severe pneumonia
8.2 Eligibility criteria	Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria (see Core Protocol Section 7.4 and PAtC). Patients eligible for the REMAP may have conditions that exclude them from this specific COVID-19 Therapeutic Anticoagulation Domain.	Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in either the REMAP-CAP Core Protocol + Pandemic Appendix or the REMAP-COVID Core Protocol. Patients eligible for the REMAP may have conditions that exclude them from this specific COVID-19 Therapeutic Anticoagulation Domain. This domain is available for patients who have acute illness due to suspected or proven pandemic infection inboth the Moderate State and the Severe State.	Administrative change to refer to both sets of protocol documents that are compatible with this DSA Specification that this domain is available to patients in both the Moderate and Severe illness severity state
8.2.2 Domain exclusion criteria	• More than 48 hours has elapsed since ICU admission	• More than 48 hours has elapsed since ICU admission (noting that this may be operationalized as more than 48 hours has elapsed since commencement of sustained organ failure support)	Patients who are admitted to ICU but are not recieving organ support may be eligible in the Moderate State. This exclusion criteria may therefore be operationalised as 48 hours from the commencement of organ

			failure support for patients in the Severe state.
8.3.2 Local standard venous thromoprophylaxis	Standard venous thromboprophylaxis that complieswith local guidelines or usual practice will be administered for 14 days following randomization.	Standard venous thromboprophylaxis that complies with local guidelines or usual practice will be administered for 14 days following randomization or until hospital discharge, whichever occurs first.	Modification of duration of intervention to reflect that the intervention should not be continued after hospital discharge.
8.3.2.1 Use of therapeutic anticoagulation in patients randomized to local standard venous thromboembolism	Systemic therapeutic anticoagulation for continuous renal replacement therapy is not permitted, unless there is an additional indication for anticoagulation. Regional citrate, heparin priming and low-dose heparin administration (without measurable systemic anticoagulation) are permitted for continuous renal replacement therapy.	Systemic therapeutic anticoagulation for continuous renal replacement therapy is not permitted, unless there is an additional indication for anticoagulation. Regional citrate, heparin priming and low-dose heparin administration (without measurable systemic anticoagulation) are permitted for continuous renal replacement therapy. If regional low-dose heparin administration is used to facilitate continuous renal replacement therapy, the dose may be increased as necessary to prevent clotting of the filter, however the dose of heparin should be minimized as much as possible.	Clarification of delivery of intervention for patients requiring renal replacement therapy
8.3.3.3 Duration of therapeutic anticoagulation	The duration of therapeutic anticoagulation is 14 days. Therapeutic anticoagulation should be continued for any period of time that the patient is receiving invasive mechanical ventilation. Anticoagulation may be ceased	The duration of therapeutic anticoagulation is 14 days. For patients who are discharged from hospital before 14 days, therapeutic anticoagulation should be ceased prior to hospital discharge. For patients admitted to an	Clarification that the intervention should not be continued after hospital discharge.

	24 hours after cessation of mechanical ventilation or at ICU discharge as determined by the treating clinician. For patients not receiving invasive mechanical ventilation the heparin infusion may be ceased at ICU discharge. After 14 days decisions regarding thromboprophylaxis and anticoagulation are at the discretion of the treating clinician.	ICU therapeutic anticoagulation may be ceased before 14 days at the discretion of the treating clinician at ICU discharge but, during the 14 day period, all patients receiving invasive mechanical ventilation should receive therapeutic anticoagulation until at least 24 hours after cessation of mechanical ventilation. After 14 days decisions regarding thromboprophylaxis and anticoagulation are at the discretion of the treating clinician.	The intervention may also be ceased prior to 14 days at the discretion of the treating clinician, ifthe patient is discharged from ICU.
8.3.4 Discontinuation of study intervention	Occurrence of HIT must result in cessation UFH or LMWH without recommencement regardless of treatment assignment. Use of an acceptable alternative agent is required in this instance as clinically indicated. Occurrence of HIT is an SAE.	Occurrence of laboratory proven HIT must result in cessation UFH or LMWH without recommencement regardless of treatment assignment. Use of an acceptable alternative agent is required in this instance as clinically indicated. Occurrence of laboratory proven HIT is an SAE.	Clarification that HIT should be laboratory proven.
8.4 Concomitant care	Additional agents, other than those specified in the platform, that are intended to modify the patient's coagulation function as a treatment for COVID-19 infection should not be administered. A patient who receives one or more agents that act to inhibit platelet function as a usual medication may have this medication continued. Commencement of any new agent that inhibits platelet function is not permitted unless there is	Additional agents, other than those specified in the platform, that are intended to modify the patient's coagulation function as a treatment for COVID-19 infection should not be administered. A patient who receives an agent that act to inhibit platelet function as a usual medication may have this medication continued. Commencement of any new agent that inhibits platelet function is not permitted unless there is an accepted	Addition to reflect a potential anti-platelet domain which may be added to the platform.

	an accepted clinical indication such as an acute coronary syndrome, ischemic stroke or transient ischemic event.	clinical indication such as an acute coronary syndrome, ischemic stroke or transient ischemic event or the agent that inhibits platelet function has been specified in another domain of this platform.	
8.5.1 Primary endpoint	The primary endpoint for this domain is the primary outcome specified in an operational document from within the options specified from the PAtC.	The primary endpoint for this domain is the primary outcome specified the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol.	Administrative change to refer to both sets of protocol documents that are compatible with this DSA.
8.5.2 Secondary endpoints	All secondary endpoints as specified from the PAtC Section 7.5.2. The domain-specific secondary outcome measures (from randomization, during the index hospitalization, censored 90 days after enrollment) will be: • Serial detection of SARS-CoV-2 in upper or lower respiratory tract specimens (using only specimens collected for routine clinically indicated testing) • Confirmed deep venous thrombosis • Confirmed pulmonary embolism • Total red cell blood cell units transfused between randomization and the end of study day 15 • SAE as defined in Core Protocol and this DSA below	All secondary endpoints as specified in the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol The domain-specific secondary outcome measures (from randomization, during the index hospitalization, censored 90 days after enrollment) will be: • Serial detection of SARS-CoV-2 in upper or lower respiratory tract specimens (using only specimens collected for routine clinically indicated testing) • Confirmed deep venous thrombosis • Confirmed pulmonary embolism • Confirmed ischemic cerebrovascular event • Total red cell blood cell units transfused between randomization and the end of study day 15	Administrative change to refer to both sets of protocol documents that are compatible with this DSA Addition of important secondary endpoints.

		• Confirmed myocardial infarction • Peak troponin between randomization and the end of study day 15 • Major bleeding • Other confirmed thrombotic event including mesenteric ischemia and limb ischemia • SAE as defined in Core Protocol and this DSA below	
SECTION 9 TRIAL CONDUCT	**Original text**	**New Text**	**Reason**
9.2 Domain-specific data collection	• Baseline measures of coagulation including d-dimer • Administration of anticoagulant agents • Administration of agents that inhibit platelet function • Transfusion of red cells	• Baseline measures of coagulation including d-dimer • Administration of anticoagulant agents • Administration of agents that inhibit platelet function • Transfusion of red cells • Peak troponin • Acute myocardial Infarction (using fourth international definition) • Major bleeding (using the International Society on Thrombosis and Haemostasis definition) • Mesenteric ischemia, limb ischemia, and other clotting events	Specification of additional domain-specific data points required for collection of secondary outcomes.

9.3 Criteria for discontinuation	Refer to Core Protocol Section 7.3 for criteria for discontinuation of participation in the REMAP-CAP trial.	Refer to relevant core protocol documents for criteria for discontinuation of participation in the REMAP-CAP trial.	Administrative change to refer to both sets of protocol documents that are compatible with this DSA.
SECTION 10 STATISTICAL CONSIDERATIONS	**Original text**	**New Text**	**Reason**
10.1 Domain-specific stopping rules	In all other respects the stopping rules for this domain are those outlined in the Core Protocol Section and from the PAtC.	In all other respects the stopping rules for this domain are those outlined in the relevant core protocol documents.	Administrative change to refer to both sets of protocol documents that are compatible with this DSA.
10.2 Unit-of-analysis and strata	The default unit-of-analysis, for both analysis of treatment effect and the Response Adaptive Randomization, will be the PISOP stratum, as specified from the PAtC. As determined by the ITSC, and based on an understanding of the sensitivity and availability of testing for COVID-19 infection, the unit-of analysis may be modified to allow separate analysis of the COVID-19 infection confirmed and not confirmed stratum. This will be an operational decision. At the time of a Platform Conclusion, results will be reported for all randomized patients, patients in whom	This domain is analyzed only in the pandemic statistical model and includes only patients who are in the pandemic suspected or proven stratum, as specified in the REMAP-CAP Pandemic Appendix and corresponding to the eligibility criteria specified in the REMAP-COVID Core Protocol. Within this stratum, the unit-of-analysis is defined by illness severity state at time of enrollment, defined as either Moderate State or Severe State. Unit-of-analysis may also be defined by SARS-CoV-2 infection or d-dimer strata or both. The D-dimer strata will contain 3 stratum, the breakpoints of which will be determined not later than the first interim analysis using	Updated text to provide more clarity regarding unit of analysis plus standardize text across all DSAs. Addition of illness severity state.

	COVID-19 infection is confirmed by microbiological testing, microbiological tests do not detect or isolate COVID-19 infection, and testing is not performed. An additional strata may be applied to the unit-of-analysis which will determined by status with respect to the D-dimer collected closest to but before randomization. This strata will contain 2 or 3 stratum, the breakpoints of which will be determined not later than the first interim analysis using data derived from patients enrolled in REMAP-CAP as well as any other trials that may utilize the same statistical model. The shock strata will not contribute to unit-of-analysis for this domain, as this strata is not applied in the Pandemic Statistical Model. The influenza strata will not contribute to unit-of-analysis for this domain.	data derived from patients enrolled in REMAP-CAP as well as any other trials that may utilize the same statistical model. Borrowing is permitted between states and strata. If the SARS-CoV-2 strata is applied in analysis, Response Adaptive Randomization will be applied to all PISOP patients, in each illness severity state, using probabilities derived from the SARS-CoV-2 confirmed stratum. Response Adaptive Randomization may also be applied according to D-dimer strata status. The decision to apply the SARS-CoV-2 and D-dimer strata will be operational. At the time of a Platform Conclusion, results will be reported for all randomized patients, patients in whom COVID-19 infection is confirmed by microbiological testing, microbiological tests do not detect or isolate COVID-19 infection, and testing is not performed. The shock strata will not contribute to unit-of-analysis for this domain, as this strata is not applied in the Pandemic Statistical Model. The influenza strata will not contribute to unit-of-analysis for this domain.	

10.3 Timing of revealing of randomization status	The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal if prospective agreement to participate is required for this domain (see section 7.8.3.6 in Core Protocol).	The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal if prospective agreement to participate is required for this domain (see relevant core protocol documents).	Administrative change to refer to both sets of protocol documents that are compatible with this DSA.
10.4 Interactions with interventions from other domains	An a priori interaction with the Antiviral Domain is not able to be evaluated as analysis occurs in different statistical models.	An a priori interaction with the Influenza Antiviral Domain is not able to be evaluated as analysis occurs in different statistical models.	Clarification that this interaction relates to the influenza Antiviral Domain, as opposed to the COVID-19 Antiviral Domain
10.4 Interactions with interventions from other domains	N/A	An *a priori* interaction with the COVID-19 Statin Domainis not considered possible and will not be incorporated into the statistical models used to analyze this domain. An *a priori* interaction with the Vitamin C Domain is either not considered possible and will not be incorporated into the statistical model used to evaluate this domain in the pandemic statistical model or is not able to be evaluated for PINSNP patients as analysis occurs in different statistical models.	Addition to reflect potential interactions with other new domains that have been added to the platform since the previous version of this DSA.
10.5 Nesting of interventions	Nesting is not applicable in this domain.	Nesting is not applicable to this domain.	Correction of grammar.

10.6 Threshold probability for superiority and inferiority	The threshold odds ratio delta for superiority and inferiority in this domain are those specified in the Operating Characteristics document derived from PAtC.	The threshold odds ratio delta for superiority and inferiority in this domain are those specified in the Operating Characteristics document derived from Pandemic Appendix and the REMAP-COVID Core Protocol.	Administrative change to refer to both sets of protocol documents that are compatible with this DSA. It is noted that the probability threshold is increased from 0.95 to 0.99, a change that has occurred because of simulations indicating that the more stringent threshold was needed to provide adequate control of type I error.
10.7 Threshold odds ratio delta for equivalence	The Platform Conclusion of equivalence will not be evaluated in this domain. The same odds ratio delta as specified in the PAtC (Section 7.8.8) for equivalence will be used for futility. This will be applied in a one-sided analysis for futility of therapeutic anticoagulation	The Platform Conclusion of equivalence will not be evaluated in this domain. The same odds ratio delta as specified in the relevant core protocol documents for equivalence will be used for futility. This will be applied in a one-sided analysis for futility of therapeutic anticoagulation	Administrative change to refer to both sets of protocol documents that are compatible with this DSA.
SECTION 11 ETHICAL CONSIDERATIONS	**Original text**	**New Text**	**Reason**

11.1 Data Safety and Monitoring Board	The DSMB should be aware that the superiority, inferiority, or futility of different interventions with respect to the primary endpoint is possible. The DSMB should take into account the public health, as well as clinical significance, of the analyses of this domain and are empowered to discuss results with relevant international and national public health authorities, with rapid dissemination of results to the larger community being the goal.	The DSMB should be aware that the superiority, efficacy, inferiority, or futility of different interventions with respect to the primary endpoints are possible. The DSMB should take into account the public health, as well as clinical significance, of the analyses of this domain and are empowered to discuss results with relevant international and national public health authorities, with rapid dissemination of results to the larger community being the goal. Safety secondary outcomes will be reported to the DSMB who are empowered to require additional analyses regarding these outcomes as required.	Modification to reflect that efficacy outcomes may also be evaluated in some domains. Clarification that safety outcomes will be reported to the DSMB.
11.2 Potential domain-specific adverse events	For patients assigned to any intervention, occurrence of any of the following should be reported as an SAE • Major bleeding, including death due to bleeding • Heparin-induced thrombocytopenia Other SAEs should be reported only where, in the opinion of the site-investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see Core Protocol Section 8.13).	For patients assigned to any intervention, occurrence of any of the following should be reported as an SAE • Laboratory proven heparin-induced thrombocytopenia Other SAEs should be reported only where, in the opinion of the site-investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see relevant core protocol documents).	Major bleeding removed as an SAE as it is now specified as a secondary endpoint. Administrative change to refer to both sets of protocol documents that are compatible with this DSA.

11.4 Relationship to Antiplatelet Domain	N/A	An Antiplatelet Domain of REMAP-CAP is being planned currently. If such a domain is implemented, it is intended that the Antiplatelet Domain and the Therapeutic Anticoagulation domain will be analyzed as a 2 x N factorial, with N interventions being available within the Antiplatelet Domain

REMAP-CAP Anticoagulation Domain

Summary of changes in REMAP-CAP Anticoagulation Domain-Specific Appendix (v2.1)

Implemented December 9th, 2020.

Section	Original Text	New Text	Reason
Front page and whole document header	Version 2.0 dated 24th June 2020	Version 2.10 dated 9th December, 2020	Administrative change to track versions
Domain membership (page 11)	Removed A/Prof. Timothy Girard, A/Prof Ghady Haidar, Dr. Patrick Lawless, Dr. Peter MacCallum, Prof. John Pasi, A/Prof Alexandra Weissman	Added Dr Diptesh Aryal, Dr Deva Jayakumar	Clarification of list of investigators actively contributing to domain oversight
Section 4.3 – Interaction with ATTACC and ACTIV-IV platform trials	Originally described interaction with the ATTACC trial. ATTACC is a trial that also evaluates the treatment effect of therapeutic anticoagulation in patients with COVID-19. There is overlap between the leadership of the ATTACC trial and the leadership of this domain. This domain and ATTACC have been designed to be complementary with pre-specified plans in relation to methods of analysis. It is intended that data from ATTACC will be incorporated into the pandemic statistical model of REMAP-CAP. The protocol, governance, and data management of ATTACC and ACTIV-IV are separate from REMAP-	Both ATTACC and ACTIV-IV are platform trials that are also evaluating the treatment effect of therapeutic anticoagulation in patients with COVID-19. There is overlap between the leadership of the ATTACC trial and ACTIV-IV (inpatient) and the leadership of this domain. This domain and, ATTACC and ACTIV-IV have been designed to be complementary with pre-specified plans in relation to methods of analysis. It is intended that data from ATTACC and ACTIV-IV will be incorporated into the pandemic statistical model of REMAP-CAP. The protocol, governance, and data management of ATTACC and ACTIV-IV are separate from REMAP-	Clarification of relationships between ATTACC and ACTIV-IV.

	CAP, but the. REMAP-CAP DSMB will also serve the ATTACC trial.	CAP. REMAP-CAP DSMB will also serve the ATTACC trial; ACTIV-IV functions with a separate independent DSMB. All three trial platforms forward interim data pertaining to the primary outcome to Berry Consultants to effectively form a single multi-platform randomized controlled trial. Agreed upon pre-defined stopping rules related to the primary outcome guide trial conclusions based on efficacy or futility. (See Appendix 1: 14.2.1)	
Section 10.9. Post-trial subgroups	None	"Concomitant administration of an antiplatelet at baseline" added as a pre-specified subgroup analysis	Additional subgroup pre-specified for analysis.

Original ATTACC Protocol Version 1.0

ANTITHROMBOTIC THERAPY TO AMELIORATE COMPLICATIONS OF COVID-19 (ATTACC)

Protocol Version #: 1.0

Protocol Date: 27-APR-2020

Study Number: OZM-113

Sponsor: Dr. Ryan Zarychanski, University of Manitoba

Sponsor's Address: ON 2051 – 675 McDermot Avenue
Winnipeg, Manitoba, Canada R3E 0V9Tel: 204-787-2293
Fax: 204-235-3309
Email: rzarychanski@cancercare.mb.ca

Co-Principal Investigators: Ryan Zarychanski, MD MSc
Patrick R. Lawler, MD MPHEwan Goligher, MD PhD

Co-investigators: Charlotte Bradbury, MD
Marc Carrier, MD, MSc Vlad Dzavik, MD Michael
Farkouh, MD
Dean Fergusson, PhD MHARobert Fowler, MD MSc
Emily Gibson McDonald, MD MScPeter Gross, MD MSc
Brett L Houston, MD Mansoor Husain, MD Susan Kahn,
MD MSc Anand Kumar, MD John Marshall, MD Srinivas
Murthy, MD Arthur Slutsky, MD MScAlexis Turgeon, MD

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Original: Version 1.0; dated 27-APR-2020

Clinical Trial Management/Clinical Trials Specialist

Lindsay Bond
Ozmosis Research Inc. 65 Queen Street West Suite 2020, Toronto, ONM5H 2M5
Main Line: 416-634-8318
Fax: 416-598-4382
Email: Lindsay.bond@ozmosisresearch.ca

Investigator Initiated Sponsor's Agreement to Protocol Version 1.0, 27-Apr-2020

Name of Authorized Personnel (Print) _____

Title of Authorized Personnel (Print) _____

Signature of Authorized Personnel: _____

Date of Approval: _____
DD-MMM-YYYY

1 SYNOPSIS

Study Title:	**A**nti**T**hrombotic **T**herapy to **A**meliorate **C**omplicationsof **C**OVID-19 (**ATTACC**)
Primary Objective/ Endpoint:	To establish whether therapeutic-dose parenteral anticoagulation improves outcomes (reduces intubation or mortality) by 30 days after randomization. The primary endpoint in the trial is an ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 30 following randomization: no invasive mechanical ventilation, invasive mechanical ventilation, or death.
Secondary Objectives:	Secondary Efficacy Endpoints: • Mortality assessed at 30 and 90 days following randomization • Intubation assessed at 30 days following randomization • Organ support-free days at day 21 • ICU-free days assessed at 30 days following randomization • Use of non-invasive mechanical ventilation or high flow nasal cannula • Ventilator free days (days alive not on a ventilator) assessed at 30 days following randomization • Hospital-free days (days alive outside hospital assessed at 30 days following randomization) • Symptomatic proximal venous thromboembolism (DVT or PE) assessed at 30 and 90 days following randomization • Myocardial infarction assessed at 30 and 90 days following randomization • Ischaemic stroke assessed at 30 and 90 days following randomization Secondary Safety Endpoints: • Laboratory confirmed heparin induced thrombocytopenia (HIT) • **Major bleeding**, defined according to the International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) definitions

	and bleeding assessment tool in non-surgical patients (Schulman *J Thromb Haemost* 2005): ○ fatal bleeding; and/or ○ symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; and/or ○ bleeding causing a fall in hemoglobin level of ≥20 g/L, or leading to transfusion of 2 or more units of whole blood or red cells.
Study Design:	A prospective, open-label, randomized, multicentre, adaptive clinical trial.
Duration:	The duration of this study will be ongoing in nature during the COVID-19 pandemic following outcomes up to a maximum of 90 days.
Planned Total Sample Size:	The trial is a Bayesian adaptive design and as such is not predicated on a fixed *a priori* sample size. This design was chosen given uncertainty regarding anticipated event rates and potential treatment effect sizes. Approximately 350 to a maximum of 3000 evaluable patients are anticipated to be enrolled in this adaptive trial, with anticipated reprioritization of key subgroups (including D-dimer defined) as the trial is undertaken.
Drug Administration:	Participants randomized to the investigational arm will receive therapeutic anticoagulation for 14 days (or until hospital discharge or liberation from the need for supplemental oxygen, whichever comes first) with preference for low-molecular weight heparin (LMWH), or alternative unfractionated heparin (UFH) Participants randomized to the control arm will receive usual care, which is anticipated to include thromboprophylactic dose anticoagulation according to local practice.
Inclusion/Exclusion Criteria:	Inclusions: 1. Patients ≥18 years of age providing (possibly through a substitute decision maker) informed

	consent who require hospitalization anticipated to last ≥72 hours, with microbiologically- confirmed COVID-19, enrolled < 72 hours of hospital admission or of COVID-19 confirmation Exclusions: 1. Receiving invasive mechanical ventilation 2. Patients for whom the intent is to not use pharmacologic thromboprophylaxis 3. Active bleeding 4. Risk factors for bleeding, including: a. intracranial surgery or stroke within 3 months; b. history of intracerebral arteriovenous malformation; c. cerebral aneurysm or mass lesions of the central nervous system; d. intracranial malignancy e. history of intracranial bleeding f. history of bleeding diatheses (e.g., hemophilia) g. history of gastrointestinal bleeding within previous 3 months h. thrombolysis within the previous 7 days i. presence of an epidural or spinal catheter j. recent major surgery <14 days k. uncontrolled hypertension (sBP >200 mmHg, dBP >120 mmHg) l. other physician-perceived contraindications to anticoagulation 5. Platelet count <50 x10^9/L, INR >2.0, or baseline aPTT >50 6. Hemoglobin <80 g/L (to minimize the likelihood of requiring red blood cell transfusion if potential bleeding were to occur) 7. Acute or subacute bacterial endocarditis 8. History of heparin induced thrombocytopenia (HIT) or other heparin allergy including hypersensitivity 9. Current use of dual antiplatelet therapy 10. Patients with an independent indication for therapeutic anticoagulation

	11. Patients in whom imminent demise is anticipated and there is no commitment to active ongoing intervention 12. Pregnancy 13. Anticipated transfer to another hospital that is not a study site within 72 hours 14. Enrollment in other trials related to anticoagulation or antiplatelet therapy
Study Assessments:	Study assessments are depicted in the study schedule
Safety Variables & Analysis:	The safety of therapeutic anticoagulation with LWMH or intravenous UFH infusion will be evaluated by AE reports. Treatment-related AEs include bleeding and HIT.
Efficacy Assessments & Analysis	The efficacy of therapeutic-dose parenteral anticoagulation with subcutaneous LMWH or intravenous UFH will be evaluated in comparison to usual care
Reasons for premature discontinuation of therapy:	Treatment will continue until any of the followingoccurs: • Heparin induced thrombocytopenia or other heparin allergy/hypersensitivity • Thrombocytopenia (platelet count <50 x10^9/L) • Major bleeding, defined based closely on the International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) definitions and bleeding assessment tool in non-surgical patients • Coagulopathy associated with an elevated INR (e.g., >2.0) or hypofibrinogemia • Following Invasive procedures where heparin is deemed unsafe to re-institute • Patients requiring systemic fibrinolytic therapy • Treating physician discretion Temporary interruptions in therapy ≤24 hours (e.g., to facilitate invasive procedures) will not be considered a premature treatment discontinuation or a protocol violation.

	Change in choice of anticoagulant or dose will not be considered discontinuation of therapy or a protocol violation. Time on unfractionated heparin will be determined as the time during which the infusion was administered, not determined by aPTT level. Occurrence of HIT must result in cessation UFH or LMWH without recommencement regardless of treatment assignment. Use of an acceptable alternative agent is required in this instance as clinically indicated. Occurrence of HIT is an SAE.
Sample Size Determination:	This is an adaptive randomized trial. The trial will be discontinued when pre-specified criteria for superiority or futility are met according to regular interim analyses. The trial will be capable of enrolling a maximum of 3,000 patients, although most scenarios will achieve 90% power to detect an odds ratio ≥ 1.5 for avoiding intubation or death at appreciably lower sample sizes.
Statistical Analysis:	Data will be analyzed by an intention to treat analysis for the primary analysis; a per-protocol analysis will also be completed as a secondary analysis. Patients who receive at least one dose of drug will be evaluablefor safety and efficacy. Response-adaptive randomization based on D-dimer subgroups is embedded.

Table of Contents

2 LIST OF ABBREVIATIONS

Ensure all abbreviations used within the protocol are listed hereAE

	Adverse Event
aPTT	activated partial thromboplastin time
CCC	Clinical Coordinating Centre
CRF	Case Report Form
CRO	Clinical Research Organization
CTA	Clinical Trial Application
dBP	diastolic Blood Pressure
DCC	Data Coordinating Centre
DIC	Disseminated Intravascular Coagulation
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FiO_2	Fraction of Inspired Ozygen
GCP	Good Clinical Practice
HIT	Heparin-Induced Thrombocytopenia
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IL-6	Interlukin-6
INR	International Normalized Ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
LAR	Legally Acceptable Representative
LMWH	Low-Molecular Weight Heparin
PE	Pulmonary Embolus

REB	Regulatory Ethics Board
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
sBP	systolic Blood Pressure
SpO_2	Oxygen Saturation
SSC	Scientific and Standardization Committee
UFH	Unfractionated Heparin
VTE	Venous Thromboemboembolism
WHO	World Health Organization

3 BACKGROUND

At the end of 2019, an outbreak of severe respiratory infection has surged in Wuhan, China and, since then, it has rapidly spread across the globe. A novel coronavirus wasidentified as the cause of this outbreak (Zhu *N Engl J Med* 2020). The World Health Organization declared this new infection a global pandemic on March 11, 2020. This disease has since been known as COVID-19 and the virus that causes COVID-19 wasnamed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Zhu *N Engl JMed* 2020; Guan *N Engl J Med* 2020). As of the beginning of April 2020, more than 2 million people have been diagnosed with COVID-19 and more than 140,000 have died.Currently in Canada, >30,000 patients have been infected and >1,100 have died thus far (Government of Canada 2020).

The clinical spectrum of COVID-19 is extremely variable and not yet completely understood. The incubation period is thought to be within 14 days after exposure, mostcommonly in the first 5 days (Guan *N Engl J Med* 2020; Wu *JAMA* 2020). Most infections are mild, and a large proportion of infected people likely develop no or very mild symptoms. Approximately 15% of symptomatic patients progress to severe pneumonia, with the need for hospitalization, and 5% develop respiratory failure, shockand multi-organ dysfunction (Wu *JAMA* 2020; Wu *JAMA Inter Med* 2020; Yang *Lancet Respir Med* 2020). The case fatality rate is extremely variable, most likely a function of differences in population demographics and density, diagnostic screening criteria, and death reports among countries (Spychalski *Lancet Infect Dis* 2020). In Wuhan, the case-fatality rate was approximately 5.8%. In Italy, the estimated case-fatality rate in March was 7.2%, while in South Korea it is currently 1.73% (WHO-China 2020; Onder *JAMA* 2020; Korea Centers for Disease Control and Prevention 2020).

There are no proven effective treatments for COVID-19 and current management is supportive (Alhazzani *Crit Care Med* 2020). A number of therapies are currently underinvestigation and have been used anecdotally in clinical practice, particularly in those with severe forms of COVID-19. Examples are antiviral drugs (e.g., remdesivir), antimalarials (e.g., chloroquine and hydroxychloroquine), alone or in combination withazithromycin, and IL-6 inhibitors (e.g., tocilizumab) (Alhazzani *Crit Care Med* 2020) – these therapies are now being studied in trials. To date, however, there remains a strong unmet clinical need for effective therapeutic approaches.

4 STUDY RATIONALE

ATTACC Trial Rationale Overview

Several lines of evidence support the potential efficacy of therapeutic parenteral anticoagulation with heparin for the treatment of COVID-19. First, COVID-19 can be associated with a hypercoagulable state, and many patients may experience significantcardiac and pulmonary macro-and micro-vascular thrombotic complications contributingto clinical deterioration. COVID-19 is associated with an unusually high incidence of venous thromboembolic events (Klok et al. *Thrombosis Research* 2020; Cui *J Thromb Haemost* 2020). Second, heparin directly induces conformation changes in the SARS- CoV-2 receptor spike protein, and may limit cellular invasion into the pulmonary epithelium, myocardium, and vascular endothelium (MyCroft-West bioRxiv pre-print).
Third, heparin has direct anti-inflammatory effects that may reduce the severity of organinjury and hemodynamic collapse. Given its ubiquitous availability, heparin may be rapidly translatable to clinical care globally if found to be effective (Thachil *J Thromb Haemost* 2020), at a time when immediately implementable solutions are urgently needed. Nonetheless bleeding concerns are present. D-dimer identifies higher risk COVID-19 patients and may be both a prognostic and predictive enrichment marker, possibly stratifying the benefit of heparin. For example, a recent observational study from Wuhan observed that when D-dimer exceeded 3.0 ug/mL, prophylactic-dose heparin use was associated with an approximately 20% absolute risk reduction in 28- day mortality (32.8% vs 52.4%, p=0.017) (Tang *J Thromb Haemo* 2020), although mortality remained high. More intensive anticoagulation strategies may provide even further event reduction. The present study therefore aims to evaluate the efficacy of therapeutic-dose parenteral heparin versus usual care in hospitalized COVID-19. Giventhat D-dimer may stratify the benefit of heparin, response adaptive randomization is implemented based on D-dimer cut points, enabling the trial to determine where therapeutic benefit exists across a range of D-dimer levels. The adaptive design is also appropriate for the pandemic, as information to guide sample size estimations is limited.

Risk Stratification in Patients with COVID-19

Advanced age and underlying comorbidities have been associated with increased likelihood of severe illness (Zhou *Lancet* 2020). Patients with cardiovascular disease or known cardiovascular disease risk factors, such as diabetes and hypertension, are at a particularly high risk of an unfavorable disease course (Wu *JAMA* 2020). Biomarkers are also associated with worse prognosis, including D-dimer and troponin (Zhou *Lancet* 2020). In a retrospective cohort from Wuhan, Shi and collaborators reported that, among 416 consecutive hospitalized patients with COVID-19, 20% had elevated troponin at hospital admission (Shi *JAMA Cardiol* 2020; Figure 1). Compared to patientswith normal troponin, these patients had a markedly increased risk of complications, including acute respiratory distress syndrome (ARDS), acute kidney injury and in-

hospital mortality (adjusted HR for mortality: 3.41; 95% CI: 1.62 to 7.16; p=0.001), with 50% of these troponin-positive patients dying (Shi *JAMA Cardiol* 2020). In another observational study, Zhou and collaborators included 191 COVID-19 patients from two hospitals in Wuhan. In unpublished analyses, we have observed that most patients withelevated troponin also have elevated D-dimer, which may mark an upstream coagulopathy producing end-organ injury. Indeed, patients with **D-dimer** greater than 1mcg/mL at admission were at increased risk of in-hospital death (adjusted OR: 18.42; 95% CI: 2.64 to 128.55; p=0.0033). When comparing 113 patients with COVID-19 who died versus 161 who survived, Chen and colleagues found that troponin I and D-dimer levels were markedly higher in deceased patients (median troponin I levels: 40.8 pg/mL(IQR: 14.7-157.8) vs. 3.3 (IQR: 1.9-7.0); median d-dimer levels: 4.6 mcg/mL (IQR: 1.3-
21.0) vs. 0.6 (IQR: 0.3-1.3) (Chen *BMJ* 2020). These results are consistent with emerging U.S. reports (Petrilli *bioRxiv* 2020). These biomarkers may be a valuable aid to risk stratification and guidance on resource allocation among hospitalized patients and have been routinely recommended in some institutional protocols (e.g., www.covidprotocols.org). These observations highlight the potential use of biomarkers to guide treatment decision-making both as **prognostic** and **predictive risk markers**. However, more work is needed to understand the optimal biomarker cut-offs that align treatment with benefit. Furthermore, biomarkers that reflect downstream processes maybe later markers, and treatment benefit may be realized with earlier intervention. An adaptive clinical trial with pre-defined biomarker subgroups based on D-dimer level, could address these questions while evaluating therapeutic efficacy.

Hypercoagulability in Patients with COVID-19

Severe illness from COVID-19 is associated with important derangements in coagulation resulting in a hypercoagulable state. These derangements are strongly associated with poor clinical outcomes and various lines of evidence suggest that the prothrombotic state may be causally related to poor outcomes. Elevated D-dimers may be a biomarker of this pathway (Zhou *Lancet* 2020). In a series of 183 patients, those who died 11% exhibited markedly elevated D-dimers and fibrin degradation products; 15 of the patients who died met the criteria for disseminated intravascular coagulation (DIC), whereas only 1 survivor developed DIC (Tang *J Thromb Haemost* 2020). Similarderangements in hemostasis were documented in a separate case series of 94 patients(Lippi *Clin Chem Lab Med* 2020). Markers of DIC correlate with clinical deterioration including ischemic injury in the fingers and toes (Li *Emerg Microbes Infect* 2020).
Macrovascular embolic events seem frequent. In a case series, pulmonary embolism was identified in 10 of the 25 patients who underwent CT pulmonary angiography (pre-print data, SSRN id: 3548771). The limited autopsy data suggest a constellation of pathological findings including thrombus in pulmonary microvessels (Fox *bioRxiv* 2020;Yao *Chin J Pathol* 2020).

The specific drivers of coagulopathy and DIC in COVID-19 disease are uncertain. SARS-CoV-2 can bind ACE2 and infect and injure endothelium, leading to tissue factor expression, endothelial activation and activation of the coagulation cascade (endotheliopathy). Strikingly, respiratory mechanics in patients requiring mechanical ventilation markedly differs from conventional mechanics seen in ARDS, and in COVID-19 is characterized by high dead space and impaired oxygenation in the absence of significant increase in pulmonary elastance, suggestive of pulmonary vascular occlusion. Similarly, reports of rapid deterioration in left ventricular systolic function alsosupport both coronary and cardiac micro-thrombotic occlusive processed. Coronary events are well known to be increased early in patients with other forms of viral pneumonia, and this may explain the 3 to 4 fold increased in mortality hazard in patients with elevated troponin.

Managing Hypercoagulability in Patients with COVID-19

Many institutional guidelines, as well as the International Society of Thrombosis and Hemostasis (ISTH), recommend routine venous thromboprophylaxis in patients hospitalized with COVID-19 (e.g., www.covidprotocols.org; Thachil *J Thromb Haemost* 2020). However, based on the above there is a compelling rationale to administer therapeutic heparin earlier in the disease course, which may also have pleiotropic benefit. In a recently published case-control study from Wuhan, 99 out of 449 consecutive patients received heparin (primarily thromboprophylactic dose heparin) for 7 days or longer (Tang *J Thromb Haemost* 2020). Although no difference in 28-day mortality was observed between patients receiving (or not) heparin (adjusted OR: 1.65; 95% CI: 0.93 to 2.92; p=0.088), among patients with elevated D-dimer, those treated with heparin, compared to those not treated with heparin, experienced lower 28-day mortality (OR for D-dimer> 3mcg/mL: 0.44; 95% CI: 0.27 to 0.87; p=0.017) (Tang *J Thromb Haemost* 2020). Based on clinical experience, an increasing understanding of the pathobiology of COVID-19, and emerging observational evidence, administering therapeutic anticoagulation in patients with COVID-19 has become the practice in some centers who have cared for a large number of these patients, but equipoise remains andcurrently this is not part of standard of care. At the time of writing, only one trial of 491 registered trials on www.covid19-trials.org is testing therapeutic enoxaparin, with a planned sample size of 60 patients and a primary endpoint of time to virus eradication (http://www.chictr.org.cn/showproj.aspx?proj=50795).

Other Potential Therapeutic Benefits of Heparin in COVID-19: Anti-viral and Anti-inflammatory Effects

In addition to its antithrombotic benefit, heparin has two additional potential beneficial effects in COVID-19: anti-viral effects that may limit viral invasion and anti-inflammatoryeffects. Very recently, the SARS-CoV-2 spike protein has been shown to interact with heparin. Upon binding heparin, the spike protein undergoes significant conformational

changes that may prevent it from binding ACE2 (Mycroft-West *bioRxiv* 2020). We have discussed these data with the investigators in the U.K., and these anti-viral effects are present for both unfractionated heparin and some low molecular weight heparins.
Heparin had previously also been shown to prevent cellular invasion by SARS-CoV-1 (Vicenzi *Emerg Infect Dis* 2004; De Haan *J Virology 2005*), and is known to inhibit attachment and entry of other enveloped viruses such as HIV and HSV (Moulard *J Virol*2000). Thus, heparin may exert a direct antiviral effect to prevent viral invasion of pulmonary epithelium, myocardium, and vascular endothelium.

Unfractionated heparin (UFH) also has potentially beneficial anti-inflammatory effects. UFH is a known inhibitor of complement and adhesion molecule expression in the microvasculature (Lever *Br J Pharmacol* 2000). UFH administration prevents acute lunginjury and increases survival in various models of septic shock (Gans *Surgery* 1975). Ina propensity-matched retrospective cohort study of patients with septic shock, heparin was associated with reduced 28-day mortality (Zarychanski *Crit Care Med* 2008). In a systematic review and meta-analysis of 6 randomized trials of heparin enrolling 2,477 patients with sepsis, the pooled odds ratio for mortality was 0.88 (95% CI: 0.77 to 1.00; I2 = 0%) (Zarychanski *Crit Care Med* 2015).

Safety of Heparin

The most frequent complication of anticoagulation use is bleeding. However, anticoagulation with parenteral anticoagulation (low molecular weight heparin or unfractionated) has been studied extensively across diverse patient populations and favourable safety data is available. Therapeutic parenteral anticoagulation is commonlyused in hospitalized patients for the prevention and treatment of venous thromboembolic disease, acute coronary syndromes, and stroke prevention in patients with atrial fibrillation (Tiryaki AmJ Heal Pharm 2011). Its dosing and management of heparin is thus very familiar to clinicians. Overall, patients receiving therapeutic heparinhave a 1-5% risk of major bleeding, depending on underlying risk and duration of exposure (Mismetti Chest 2005; Petersen JAMA 2004; Crowther Blood 2008).

When explored as an intervention for reducing mortality in patients with septic shock requiring intensive care unit admission, unfractionated compared to placebo or usual care demonstrated no significant differences in bleeding (gastrointestinal, central nervous system, epistaxis, hematuria) or need for blood product transfusion (Jaimes Crit Care Med 2009; Zarychanski Crit Care Med 2008). Subsequent meta-analysis of studies comparing UFH or LMWH with placebo or usual care in patients with sepsis admitted to the ICU suggests no increase the risk of major hemorrhage (RR 0.79, 95% CI 0.53–1.17), although its use is associated with a modest increase in minor hemorrhage (RR 1.49, 95% CI 1.07–2.07) (Zarychanski Crit Care Med 2015). In critically-ill patients, increased doses of UFH are not associated with increased clinicallysignificant bleeding (0.2% with higher UFH dosing compared to 0.3% with standard unfractionated dosing, p=0.059) (Reynolds J Hum Pharmacol Drug Ther 2019). When

compared to unfractionated, low molecular weight heparin — the preferred anticoagulant of choice in this study in the absence of any clinical contraindications — may exhibit a reduced risk of bleeding (OR 0.43; 95% CI 0.22 to 0.83; p=0.01) (Alikhan Cochrane Database Syst Rev 2014). In a randomized-controlled trial, no difference in bleeding has been observed with enoxaparin 1.5 mg/kg subcutaneous once daily versus 1 mg/kg twice daily (Merli Annals Internal Med 2001). In this trial of 900 patients with venous thromboembolic disease, the incidence of major haemorrhage did not differamong those receiving unfractionated heparin (2.1%) once-daily enoxaparin (1.7%) or twice-daily enoxaparin group (1.3%).

Patients with an underlying systemic hypercoagulable state, in whom heparin is being given to offset this, may intuitively have a lower risk of bleeding. For example, in cancer-associated venous thromboembolisms (VTEs) – an underlying hypercoagulable state – with an estimated rate of major bleeding of 3.2% over 6 months' follow-up (Lee JAMA 2015; Li Thromb Res 2019).

Major bleeding will be a secondary safety endpoint and will be monitored by the DSMB in frequent interim analyses. Premature discontinuation of therapy related to bleeding, need for procedures requiring >48 hours of interruption, or physician discretion will alsobe monitored. A minimum hemoglobin cut-off of 80 g/L will be applied to reduce the riskof requiring blood transfusion in patients who experience bleeding.

Heparin-induced thrombocytopenia is another adverse event which can accompany heparin therapy, occurring significantly less often in patients receiving low molecular weight heparin compared with UFH (RR 0.22, 95% CI 0.06 to 0.84) (Junqueira Cochrane Database Syst Rev 2017). The overall incidence of HIT is 0.2–0.5%, and ishigher in patients receiving therapeutic doses of UFH (0.79%) compared to those receiving prophylactic doses (<0.1%). (Creekmore J Hum Pharmacol Drug Ther 2006;Smythe Chest 2007).

Injection site adverse effects may include pain, mild local irritation, hard inflammatorynodules and injection site hematomas may follow the subcutaneous injection of a lowmolecular weight heparin.

Other rare adverse reactions reported with the use of unfractionated heparin and LMWHare hypersensitivity and allergic reactions, hepatic enzymes increase, hypercalcemia, urticaria, pruritus, erythema.

Background Summary

Taken together, these observations provide a compelling rationale for the use of therapeutic dose heparin in patients with COVID-19. These beneficial effects reflect antithrombotic properties, direct SARS-CoV2 antiviral properties, and anti-inflammatoryproperties (**Figure 1**). Risks of bleeding from prior studies are small. Risk/benefit may be best aligned using D-dimers. The clinical trial proposed herein looks to prevent

clinical deterioration and improve survival in patients hospitalized with COVID-19 with therapeutic-dose heparin treatment, using an adaptive design that allows various D- dimer cut-offs to be studied objectively.

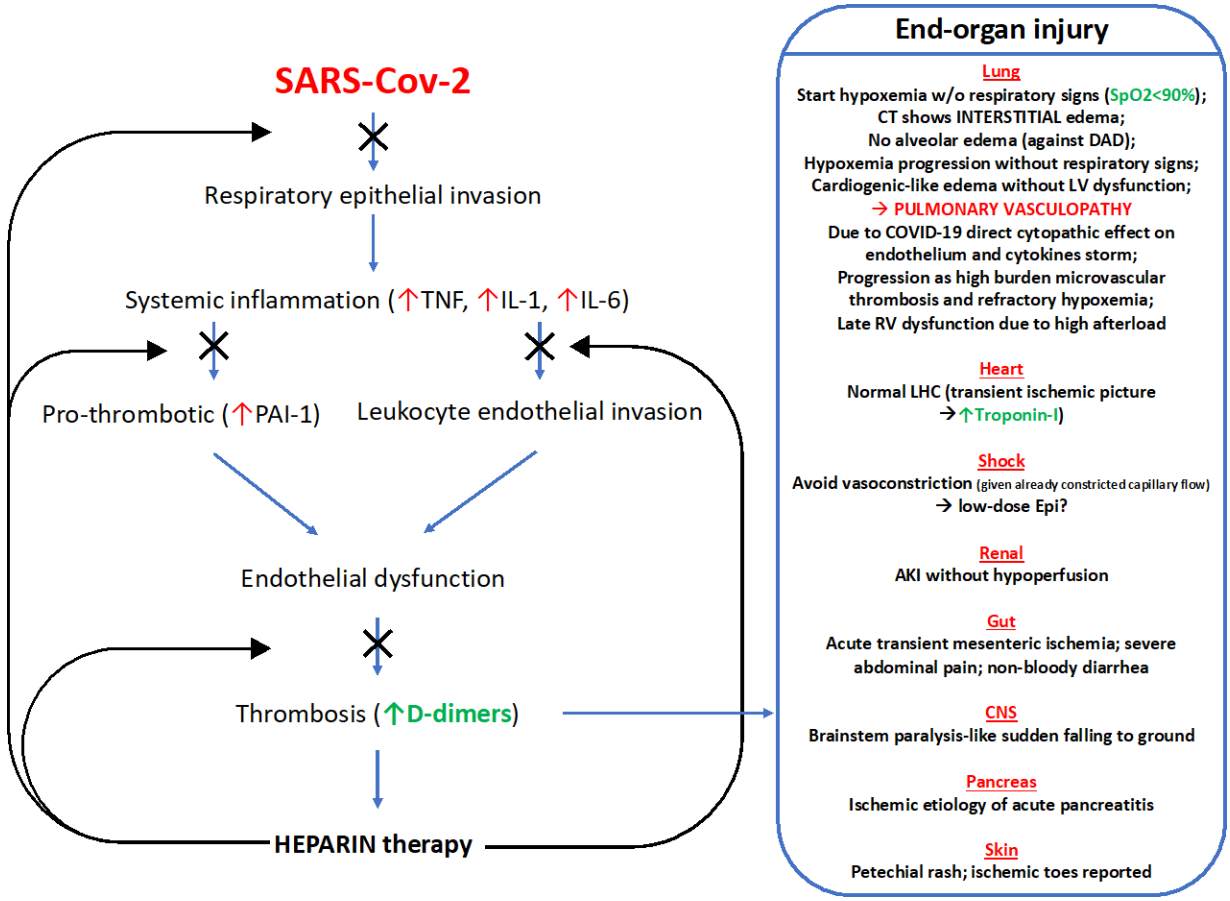

Figure 1: Proposed pathophysiologic pathways in COVID-19 upon which heparin may act.

5 STUDY DESIGN

The duration of this study will be ongoing in nature during the COVID-19 pandemicfollowing outcomes up to a maximum of 90 days.

Patient Population

Participants with laboratory confirmed COVID-19 requiring hospitalization anticipated to last ≥72 hours, but prior to intubation, will be enrolled into this study.

Primary Objective

To establish whether therapeutic-dose parenteral anticoagulation improves outcomes(reduces intubation or mortality) by 30 days following randomization.

Primary Endpoint

The primary endpoint in the trial is an ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 30 following randomization: no invasive mechanical ventilation, invasive mechanical ventilation, or death.

Secondary Objectives

- To determine safety of therapeutic-dose parenteral anticoagulation
- To evaluate efficacy of therapeutic dose parenteral anticoagulation

Secondary Endpoints

Secondary safety endpoints: (determined to occur after enrollment)

- Laboratory confirmed Heparin induced thrombocytopenia **(HIT)**
- **Major bleeding**, defined according to the International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) definitions and bleeding assessment tool in non-surgical patients (Schulman *J Thromb Haemost* 2005):
    - fatal bleeding; and/or
    - symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; and/or
    - bleeding causing a fall in hemoglobin level of ≥20 g/L, or leading to transfusion of 2 or more units of whole blood or red cells.

Secondary efficacy endpoints:

- Mortality assessed at 30 and 90 days following randomization
- Intubation assessed at 30 days following randomization

- Organ support-free days at day 21

- ICU-free days assessed at 30 days following randomization
- Use of non-invasive mechanical ventilation or high flow nasal cannula
- Ventilator free days (days alive not on a ventilator) assessed at 30 days following randomization
- Hospital-free days (days alive outside hospital assessed at 30 days following randomization)
- Myocardial infarction assessed at 30 days and 90 days following randomization
- Ischaemic stroke assessed at 30 and 90 days following randomization

6 PATIENT ELIGIBILITY

This trial will be conducted in compliance with the protocol and GCP. Any questions about eligibility criteria must be addressed prior to patient registration. Patients will beenrolled within 72 hours of admission.

Inclusion Criteria

1. Patients ≥18 years of age providing (possibly through a substitute decision maker) informed consent who require hospitalization anticipated to last ≥72hours, with microbiologically-confirmed COVID-19, enrolled < 72 hours of hospital admission or of COVID-19 confirmation

Exclusion Criteria

1. Receiving invasive mechanical ventilation
2. Patients for whom the intent is to not use pharmacologic thromboprophylaxis
3. Active bleeding
4. Risk factors for bleeding, including:
    a. intracranial surgery or stroke within 3 months;
    b. history of intracerebral arteriovenous malformation;
    c. cerebral aneurysm or mass lesions of the central nervous system;
    d. intracranial malignancy
    e. history of intracranial bleeding
    f. history of bleeding diatheses (e.g., hemophilia)
    g. history of gastrointestinal bleeding within previous 3 months
    h. thrombolysis within the previous 7 days
    i. presence of an epidural or spinal catheter
    j. recent major surgery <14 days
    k. uncontrolled hypertension (sBP >200 mmHg, dBP >120 mmHg)
    l. other physician-perceived contraindications to anticoagulation
5. Platelet count <50 $x10^9$/L, INR >2.0, or baseline aPTT >50
6. Hemoglobin <80 g/L (to minimize the likelihood of requiring red blood cell transfusion if potential bleeding were to occur)
7. Acute or subacute bacterial endocarditis

8. History of heparin induced thrombocytopenia (HIT) or other heparin allergy including hypersensitivity
9. Current use of dual antiplatelet therapy
10. Patients with an independent indication for therapeutic anticoagulation
11. Patients in whom imminent demise is anticipated and there is no commitment to active ongoing intervention
12. Pregnancy
13. Anticipated transfer to another hospital that is not a study site within 72 hours
14. Enrollment in other trials related to anticoagulation or antiplatelet therapy

Patient Consent

Sample English consent forms for the trial will be provided. A copy of the initial full board REB/IRB approval and approved consent form must be sent to Ozmosis Research. The subject/LAR must sign consent prior to registration or may provide consent as per FDA guidance document Coronavirus (COVID-19) Update: FDA IssuesGuidance for Conducting Clinical Trials (Appendix A) or REB/IRB recommendations.

Patients admitted to hospital that are confirmed to have microbiologically-confirmed SARS-CoV-2 will be assessed for eligibility. Screening will include a review of inclusionand exclusion criteria. Study staff will discuss with the treating clinical team a potential subject's suitability to be approached for the trial. Information about the study will be presented to potential subjects (or legally authorized representative, which can includea substitute decision-maker in cases of incapacity). Given the potential for viral transmission and the nature of the studied intervention, consent will be obtained as perthe REB/IRB recommendations or FDA Guidance (Appendix A). This is anticipated to include verbal consent and consent by telephone.

Patient Registration

The randomization and registration process will be provided to the sites at site start-upphase.

7 STUDY PLAN

Study Schedule

Participants will be given therapeutic-dose parenteral anticoagulation daily, up to 14 days or until *recovery*, defined as hospital discharge or liberation from supplemental oxygen >24 hours (provided supplemental oxygen was originally required), whichever comes first. Subjects will be followed until hospital discharge, after which time telephonecontact will be undertaken to ascertain vital status following hospital discharged. (Schedule days refer to post-randomization days.) All post-discharge follow-up is telephone-/remote.

Investigations	Pre-Treatment (Baseline)	Day 1	Day 3	Day 7	Day 14	Day 21	Day 30	Day 90

Windows		+/- 3 days					+/- 3 days	+/- 7 days
Consent & Registration	X							
Demographics	X							
Medical History	X							
Weight	X							
SOC Vitals documented (SpO2 and FiO2, heart rate, blood pressure, respiratory rate, temperature)[1]	X	X	X	X	X			
Hematology bloodwork (SOC)[1]	X	X	X	X	X			
Biochemistry bloodwork (SOC)[1]	X	X	X	X	X			
Troponin (SOC)[1]	X	X	X	X	X			
D-dimer (SOC)[1]	X	X	X	X	X			
Anticoagulant Administration[2]		X[2]	X[2]	X[2]	X[2]			
Organ-free support outcome						X		
Primary and secondary outcomes[3, 4]						X		
Mortality, DVT, PE, MI (by phone)[3]								X
Adverse events[5]				X				
Concomitant medications[5]				X				

Footnotes:

[1]as per routine standard of care, collected while on therapy (until discharge or up to 14dor recovery); record the “worst” value observed during internal since last assessment;

[2] Participants randomized to the investigational arm will receive therapeutic anticoagulation for 14 days (or until hospital discharge or liberation from supplemental oxygen >24 hours if previously required, whichever comes first) with heparin, with preference for subcutaneous low molecular weight heparin (enoxaparin preferred, although dalteparin or tinzaparin are also acceptable, as available) if no contraindicationis present; alternatively, intravenous unfractionated heparin infusion may be used.

Participants randomized to the control arm will receive usual care, which is anticipatedto include thromboprophylactic dose anticoagulation according to local practice.

[3]all post-discharge follow-up is telephone-/remote.

[4]Primary and secondary outcomes to be collected include:

Primary outcome:

- an ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 30 following randomization: no invasive mechanical ventilation, invasive mechanical ventilation, or death.

Secondary outcomes:

- Laboratory confirmed Heparin induced thrombocytopenia (**HIT)**
- **Major bleeding**, defined according to the International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) definitions and bleeding assessment tool in non-surgical patients (Schulman *J Thromb Haemost* 2005):
    - fatal bleeding; and/or
    - symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; and/or
    - bleeding causing a fall in hemoglobin level of ≥20 g/L, or leading to transfusion of 2 or more units of whole blood or red cells.
- Organ support-free days at day 21
- Intubation assessed at 30 days following randomization
- ICU-free days assessed at 30 days following randomization
- Use of non-invasive mechanical ventilation or high flow nasal cannula
- Ventilator free days (days alive not on a ventilator) assessed at 30 days following randomization
- Hospital-free days (days alive outside hospital assessed at 30 days following randomization)
- Symptomatic proximal venous thromboembolism (DVT or PE) assessed at 30 and 90 days following randomization
- Myocardial infarction assessed at 30 and 90 days following randomization
- Ischaemic stroke assessed at day 30 and 90 days following randomization
- Mortality assessed at 30 and 90 days following randomization

[5]Treatment-related adverse events and concomitant medications assessed only whileon therapy.

8 CONCOMITANT MEDICATIONS

Concomitant medications representing experimental COVID-19 treatments (as long asnot related to anticoagulation) and anti-platelet agents, will be collected for the study from time of consent to 14 days or time of pre-defined treatment discontinuation (whichever comes first).

Potential Drug Interactions: refer to the next section and to the current productmonographs for up to date interactions.

Drug Interactions

Heparin should be used with caution in patients receiving non-steroidal anti- inflammatory drugs, thrombolytic agents, glycoprotein IIb/IIIa antagonists, acetylsalicylicacid, platelet inhibitors, vitamin K antagonists, activated protein C, direct factor Xa and IIa inhibitors because of increased risk of bleeding.

9 MEDICINAL PRODUCT

Characterization of Investigation Medicinal Product

For patients randomized to the intervention arm, patients will recieve therapeutic-dose parenteral anticoagulation, with preference for subcutaneous low molecular weight heparin, given ease of administration and resultant reductions in the need for clinical staff-patient interactions, if no contraindication is present. Enoxaparin is the preferred low molecular weight heparin given emerging data supporting potential viral inhibitory properties (Mycroft-West bioRvix preprint and Mark Skidmore, Keele University, personal communication), although tinzaparin or dalteparin are also acceptable, if available. **Alternatively**, intravenous unfractionated heparin infusion may be also used.The therapy may be switched within a subject during the course of the trial at the discretion of the treating physician.

Study Drug Administration

Anticoagulants used in the trial, whether as part of the intervention arm or as part of usual care/control arm, will be sourced, stored and dispensed by participating hospitalsaccording to current practice and local policy.

This is a pragmatic trial of therapeutic anticoagulation, and hence the treating physicianshould determine what is the most appropriate parenteral anticoagulant for the patientsto receive.

<u>Low molecular weight heparin (LMWH)</u>

LMWH is commenced, administered, and monitored according to local hospital policy,practice and guidelines that pertain to treatment of venous thromboembolism (i.e. not thromboprophylactic doses). The dose selected should be based on measure or estimated weight of the patient.

Adjustment for impairment of renal function should be according to local practice andpolicy

The *preferred therapeutic anticoagulant* is enoxaparin. Generally accepted dosing regimens for enoxaparin include: 1.5 mg/kg subcutaneous once daily or 1 mg/kg subcutaneous twice daily, assuming no dose adjustment is required. Alternatively, othersubcutaneous low molecular weight heparins may be used, including tinzaparin, if available, (generally given at a dose of 175 anti-Xa IU/kg subcutaneous once daily if nodose adjustment is required) or dalteparin (200 IU/kg subcutaneous once daily or 100 IU/kg subcutaneous twice a day if no dose adjustment is required), as available.

Unfractionated heparin (UFH)

If UFH is used, this is commenced, administered, and monitored according to local hospital policy, and guidelines that are used for the treatment of venous thromboembolism (i.e. not for acute coronary syndrome). Intravenous infusion of unfractionated heparin, is typically dosed according to total body weight and pragmatically adjusted according to local institutional policy to achieve an activated partial thromboplastin time (aPTT) of 1.5-2.5x the reference value. If UFH is used, the availability of a local hospital policy that has specifies an aPTT target in this range or ananti-Xa value is a requirement.

Accountability and Destruction

This standard-of-care study drug for thromboprophylaxis will be provided from standard hospital supply and dosed according to local policy and practice. Sites will be responsible for assuring adequate local supply in coordination with local pharmacy.

Dose Adjustments

Dosing and dose adjustment of anticoagulants used for therapeutic anticoagulationshould conform to local practices and policies. Examples are provided below.

Renal Impairment: In patients with acute or chronic severe renal impairment (creatinine clearance <30 mL/min), dose-adjustments or changes in therapy in patients receiving therapeutic dose LMWH) is typically required. Dose adjustments and continued use of LMWH in this setting (vs. switching to UFH) is at the discretion of the treating medical team.

Liver Impairment: Low molecular weight heparin should be used with caution in patientswith hepatic insufficiency.

Subject Compliance

Daily drug administration including name of drug, dose, and route of administration willbe recorded in the source documents and captured into an eCRF.

Premature Withdrawal/ Discontinuation Criteria

Treating physicians may choose to discontinue therapy at their discretion. A premature discontinuation of treatment will be defined as an interruption in study drug for >24 hours. Temporary, shorter interruptions, for example to safely facilitate invasive procedures, are not

considered interruptions or discontinuations in therapy provided theinterruption does not exceed 48 hours. Reasons for treatment discontinuation may include but is not limited to:

- Heparin induced thrombocytopenia or other heparin allergy/hypersensitivity
- Thrombocytopenia if platelet count <50x10^9/L
- Major Bleeding, defined based closely on the ISTH/SSC definitions and bleeding assessment tool in non-surgical patients (below)
- Coagulopathy associated with an elevated INR (e.g. >2.0) or hypofibrinogemia
- Following invasive procedures where heparin is deemed unsafe to re-institute
- Patients requiring systemic fibrinolytic therapy
- Treating physician discretion

Temporary interruptions in therapy for ≤24 hours (e.g., to facilitate invasive procedures) will not be considered a premature treatment discontinuation or a protocol violation

Change in choice of anticoagulant or dose will not be considered discontinuation of therapy or a protocol violation. Time on unfractionated heparin will be determined as thetime during which the infusion was administered, not determined by aPTT level.

Occurrence of HIT must result in cessation UFH or LMWH without recommencement regardless of treatment assignment. Use of an acceptable alternative agent is requiredin this instance as clinically indicated. Occurrence of HIT is an SAE.

10 SAFETY AND REPORTING REQUIREMENT

Adverse Event (ONLY study drug related AEs will be reported)

As an open label trial of UFH or LMWH, adverse events captured in this trial are eventsthat are **plausibly related** to the investigational agent. Adverse events **plausibly related** to heparin or low molecular weight heparin include major bleeding and HIT.

Adverse Event Documentation

Treatment-related AEs must be recorded in the eCRFs. Documentation must be supported by an entry in the subject's file.

Serious Adverse Event (SAE) due to the study drug

SAEs must be serious events that are believed to be **plausibly related** to the studydrug and will include:

- Major bleeding (outlined the definition here of the ISTH)
- Laboratory confirmed heparin-induced thrombocytopenia

As per ICH guidelines, a **Serious Adverse Event** is any AE occurring at any dose that **(we will only report study drug related SAEs)**:

- Results in death
- Is life-threatening
- Requires prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

Is a congenital anomaly / birth defect

Life-threatening: The term “life-threatening” in the definition of “serious” refers to an adverse event in which the subject was at risk of death at the time of the event. It doesnot refer to an adverse event that hypothetically might have caused death if it were more severe.

Disability means a substantial disruption of a person’s ability to conduct normal life’sfunctions.

Important medical event: Any adverse event may be considered serious because itmay jeopardize the subject and may require intervention to prevent another serious condition.

Any death (regardless of cause) that occurs from the time of administration of the firstdose of study therapy until 28 days after the final administration of the study drug, andany death occurring after this time that is judged at least possibly related to prior treatment with the study drug, will be promptly reported

Reporting Serious Adverse Events (Only Study Drug Related SAEs will be reported)

All serious adverse events (SAE) defined as per ICH guidelines (see above) and other adverse events that are **related** to the study drug must be recorded on case report forms. In addition, all serious adverse events that are **related** to the study drug must bereported by using the SAE form and must be submitted to Ozmosis. **Related** SAEs should be reported within 24 hours of becoming aware of the event.

Serious Adverse Event Reporting Instructions

All serious adverse events that are related to study drug must be reported as follows:

Within 24 hours: Report initial information (on trial specific SAE report form) by fax or e-mail to:

Ozmosis Research IncPhone: 416-634-8300

Fax: 416-598-4382
E-mail: ozmsafety@ozmosisresearch.caThe initial information should

always contain:

- Name of Reporter/Investigator,
- Subject Identification,
- Adverse Event Term,
- Study Drug Dose and Start/Stop Dates

On the next working day: Fax completed trial-specific Serious Adverse Event form

Procedure for Expedited Reporting

Responsibility for Reporting Serious Adverse Events to Health Canada

Ozmosis Research will provide expedited reports of SAEs to Health Canada according to applicable guidelines and regulations (including the 7-day notification for death and life-threatening events), i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

Responsibility for Reporting Serious Adverse Events to Sponsor

Ozmosis Research will be responsible for submitting SAE reports (Initial and/or Follow-up reports) received from the sites, to the Sponsor within 24hrs after receipt of the SAEform at Ozmosis Research.

Reporting Serious Adverse Events to Local Research Ethics Boards

Ozmosis Research will notify all Investigators on this study of all Serious Adverse Eventsthat are reportable to regulatory authorities in Canada. This includes all serious events that are unexpected and related to protocol treatment. Investigators must notify their Research Ethics Boards (REB/IRBs) and file the report with their Investigator Site File. Documentation that serious adverse events (SAEs) have been reported to REB/IRBs must be kept on file at Ozmosis Research.
Documentation can be any of the following:

- letter from the REB/IRB acknowledging receipt
- stamp from the REB/IRB, signed and dated by REB/IRB chair, acknowledging receipt
- letter demonstrating the SAE was sent to the board

All expedited serious adverse events occurring within a centre should also be reportedto local REB/IRBs.

Study Management and Governance

Clinical Coordination Centre

The Clinical Coordinating Centre (CCC) will be Ozmosis Research who will beresponsible for overall study management.

Data Coordinating Centre

The Data Coordinating Centre (DCC) is at SOCAR Research in Switzerland. SOCAR will receive statistical support from Berry Consultants, who will perform interim analysis based on shared limited datasets from SOCAR to Berry. Data may also be shared with external research consortia (including other trials) to facilitate pooled analyses and morerapid/timely dissemination of results.

Executive Committee and Steering Committee

The Executive Committee will consist of the Principal Investigators, as well as representatives from the CCC and SOCAR. The Executive Committee is responsible forthe execution of the trial according the study protocol. A Steering Committee will be responsible for providing clinical and methodological guidance, including overall study design, execution, analysis, and publication of the main study results. The Steering Committee will oversee the management of the clinical trial sites and will also act as thePublication Committee. While the study is ongoing, the Committee will approve any protocol amendment that may become necessary and is responsible for maintaining the scientific integrity of the study.

11 STATISTICAL ANALYSIS

Study Population

The adaptive design does not require specification of a sample size a priori. This designwas chosen given uncertainty about effect sizes and event rates given the lack of historical data amidst the emerging pandemic. The study population is anticipated to be 350-3000 patients. Simulations below outline the anticipated sample sizes in detail. Thetrial will be discontinued when pre-specified criteria for superiority or futility are met according to regular interim analyses, including in subgroups of the overall trial (definedbased on biomarkers and clinical parameters). We anticipate enrolling between 350 and2,000 patients, which gives 90% power to detect an odds ratio ≥ 1.5 for avoiding intubation or death. Data will be analyzed primarily with intention-to-treat.

Evaluation of Safety

The safety of therapeutic anticoagulation will be evaluated by means of AE reports.

Trial Design Introduction

The trial design is an adaptive trial comparing therapeutic anticoagulation with UFH or LMWH vs. usual care. The effect of therapeutic anticoagulation is modeled as potentially different within prespecified patient subgroups based on the baseline d-dimerlevels. Each patient is classified by their baseline D-dimer levels as high (top quartile), medium (3rd quartile), and low (less than median).

The effect of therapeutic anticoagulation is modeled as potentially a function of thepatient D-dimer subgroup. Each conclusion for therapeutic anticoagulation is by subgroup with a statistical model that borrows the effect across subgroups.

The adaptive aspects of the trial include response adaptive randomization within each of the 3 subgroups as well as any potential conclusions (superiority, futility) for the effectof therapeutic anticoagulation within each of these 3 subgroups.

Interim analyses will be conducted periodically (starting every two weeks and likely progressing to monthly as a function of enrollment rate, targeting updates at least every100

patients being enrolled). The details of the trial design rules are presented in the Adaptive Design Section.

Primary Endpoint

The primary endpoint in the trial is an ordered categorical endpoint with three possible outcomes based on the *worst* status of each patient through day 30: 1 = no mechanical ventilation, 2= mechanical ventilation, 3 = death. We label a patient's status for D-dimeras d=1 for low, d=2 for medium, and d=3 for high. These thresholds to define each of these (top 75%, to 50%) will be based on the observed 75th percentile and median for baseline d-dimer at the first interim analysis. These thresholds will then be used for theremainder of the trial for randomization and d-dimer classification.

Primary Analysis

The primary analysis of the ordered categorical endpoint is a cumulative proportionalodds model. Let the probability of an outcome of less than or equal to y be $=$ $PPPP(YY \leq yy)$. Let t be the indicator of treatment arm (*t*=1 is control, *t*=2 is therapeutic anticoagulation). We model the ordinal outcomes using a proportional odds model. The model adjusts for the baseline D-dimer status of each patient and the effect for atreatment, as a function of the baseline status:

$$\log\left(\frac{\pi_{yy}}{\quad}\right) = \alpha_{yy} + \beta_{dd}\delta_{[dd]} + \theta_{dd}\delta_{[tt=2]}\,;\; yy = 1,2$$

$1 - \pi\pi_{yy}$

The additive effects constant across both treatment groups as a function of the baseline subgroup for each patient are modeled through the $\beta\beta$ parameters. The parameter $\delta\delta_{[tt=2]}$ is an indicator function for the patient in the therapeutic anticoagulation treatment groupand $\delta\delta_{[tt=2]}$ is an indicator function for the baseline D-dimer subgroup. The baseline risks for each group are modeled with independent weak prior distributions with the low D- dimer group the referent population:

$\beta\beta_1 \equiv 0,$

$\beta\beta_{dd} \sim NN(0,10^2), dd = 2,3.$

The treatment effect of therapeutic anticoagulation within subgroup *d*, $\theta\theta_{dd}$, represents the cumulative log-odds-ratio effect, where the odds-ratio, $\mathrm{OR_d} = \exp(\theta\theta_{dd})$. If the odds-ratio is greater than 1 then the treatment of therapeutic anticoagulation improves outcomes inthe subgroup by increasing the probability of smaller outcomes (better).

The prior distributions for the control rates of each of the three ordinal classifications are modeled with weak prior distributions as

$\alpha\alpha_{jj} \sim NN(0,10), jj = 1,2,; \alpha\alpha_1 < \alpha\alpha_2.$

A Bayesian hierarchical model is used for the three treatment effects within the subgroups:$\theta\theta_{dd} \sim NN(\mu\mu, \tau\tau^2)$,

$$\mu\mu \sim NN(0,10)$$

$$\tau\tau^2 \sim llll(0.125,0.00281)$$

The prior distribution on the variance of the therapeutic anticoagulation effects is an inverse-gamma distribution with a relative weight of 0.25 observations of an estimated $\tau\tau = 0.15.$

The posterior distributions of the therapeutic anticoagulation effect in each of the subgroups, $\theta\theta_1$, $\theta\theta_2, \theta\theta_3$ are used for response adaptive randomization and decision making in the trial.

At the completion of the trial the posterior mean, median, and 95% credible intervals foreach odds-ratio will be summarized.

Adaptive Design

The trial design is adaptive. A sequence of frequent interim analyses will be conductedas a

function of enrollment rate. The anticipation is to conduct interim analyses every 2weeks which may then be relaxed as the enrollment grows. The target would be to enroll 100 patients between interims.

At each interim analysis the trial could reach a trial conclusion within any of the subgroups which would stop randomization in that subgroup in favor of the control (standard of care) or therapeutic anticoagulation. If no conclusion within a subgroup is reached and randomization continues the randomization probabilities will be set basedon a response adaptive randomization algorithm distinctly within the subgroup.

Subgroup Conclusions

A subgroup may stop for **superiority of therapeutic anticoagulation** . This conclusionwould be reached at any interim analysis in which the probability that therapeutic anticoagulation is more effective than control in the subgroups is 99% or greater. That isa subgroup will stop for superiority of Heparin if:

$\Pr(OORR_{dd} > 1) \geq 0.99, dd = 1,2,3.$

Likewise, a claim of superiority will be made at the conclusion of the trial within a subgroup if the posterior probability of superiority is at least 99%.

The trial may stop for **futility of therapeutic anticoagulation.** If the probability of at least a 20% improvement in the odds-ratio (OR > 1.2) is less than 10% then the trial willstop for futility. That is a subgroup will stop for futility of therapeutic anticoagulation if

$\Pr(OORR > 1.2) < 0.10.$

If randomization continues in a subgroup then **response adaptive randomization** is utilized. The probability for each of the two arms within a subgroup will be set based onthe probability that each arm is the best arm in that subgroup. The randomization for each arm is the probability that arm is the superior arm, truncated at a maximum of 90%for any one arm (minimum of 10% for an arm). That is the randomization probability for therapeutic anticoagulation within each subgroup is $\Pr(OORR_{dd} > 1)$ but truncated at 0.10 below and 0.90 above.

The trial will continue as long as there are subgroups that have not reached a conclusion.

Clinical Trial Simulations

This section describes the clinical trial simulations to understand the power for the primary analysis within each subgroup. Two different assumptions are made for the potential distribution of outcomes in the three ordinal categories. We label these as mildand severe rates. The assumptions for control are:

Outcome	Control Scenario	
	Mild	Severe
No Ventilation	0.75	0.50
Mechanical Ventilation	0.125	0.30
Death	0.125	0.20

Table 1: The assumed scenarios (Mild, Severe) for the control rates

For each of the scenarios an effect size is assumed for the treatment arm, therapeutic anticoagulation. The scenarios for the odds ratio are

Treatment Effects	Odds-Ratio For therapeutic anticoagulation
Harm	0.90
Null Effect	1
25% improvement	1.25
50% Improvement	1.50
75% Improvement	1.75
100% Improvement	2.0

Table 2: The range of effect sizes for therapeutic anticoagulation simulated.

Figure 1 shows the distribution of outcomes for each of the assumed effects for the Mild Scenario and Figure 2 shows the distribution for the Severe Scenario.

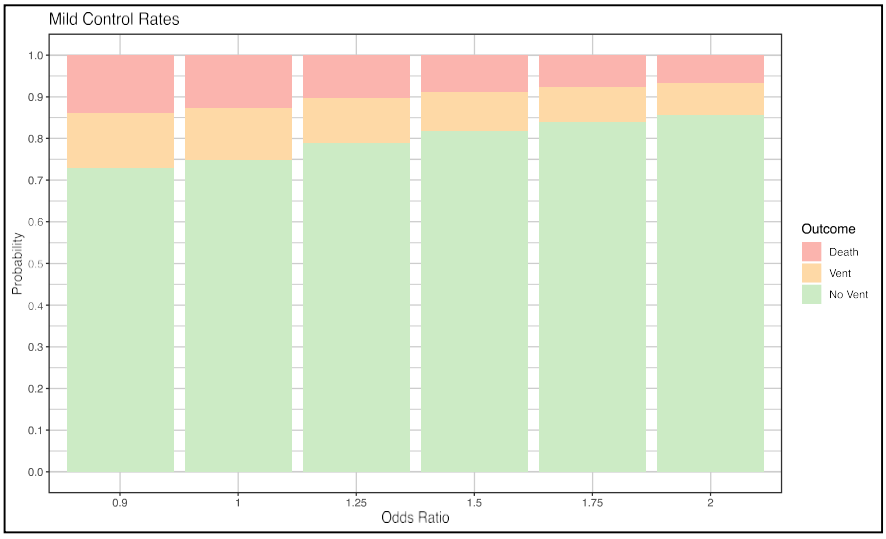

Figure 1: The distribution of outcomes for each treatment effect (OR) for the MildScenario

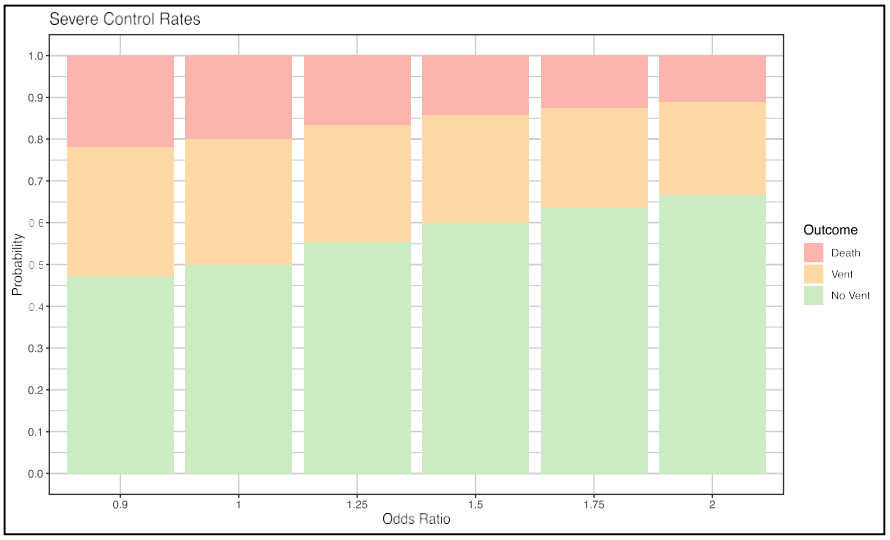

Figure 2: The distribution of outcomes for each treatment effect (OR) for the MildScenario

Simulation Results

For each scenario and effect size 1000 simulated trials are conducted. For the simulations interim analyses are conducted at 100, 200, …, 1000, 1250, 1500, …, 3000.The results are robust to the number and timing of the interims. Figure 3 shows the probability of concluding superiority for therapeutic anticoagulation within a subgroup asa function of the total number of subjects enrolled for each scenario and effect size.
The simulations are done individually within the subgroups and not jointly across the subgroups using the Bayesian Modeling.

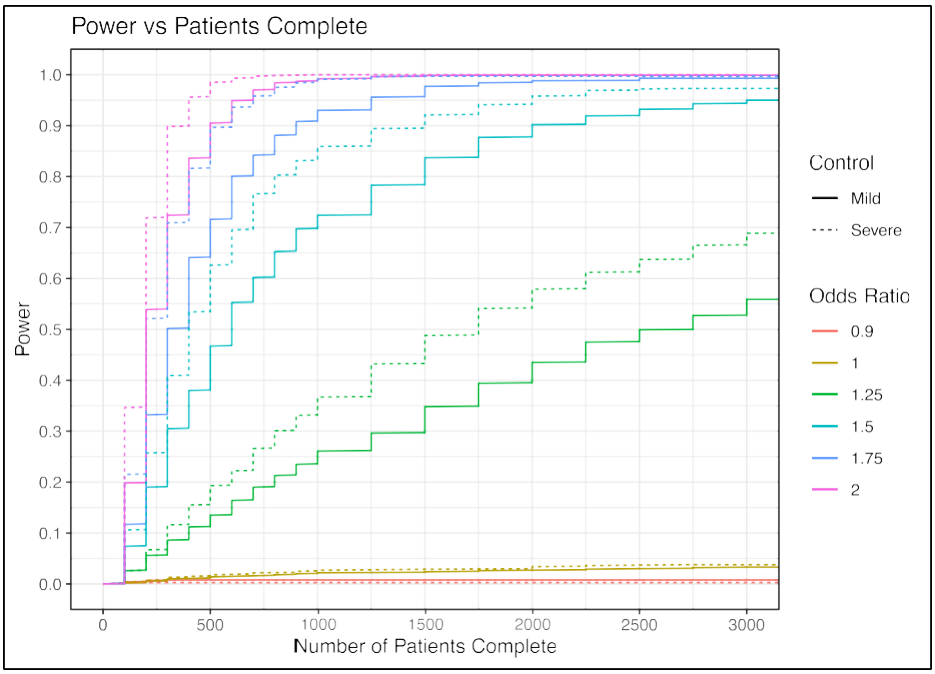

Figure 3: The cumulative probability of concluding superiority for the heparin arm asfunction of the scenario, treatment effect, and sample size.

If therapeutic anticoagulation has a strong effect of an OR=2, then 80% of trials reach superiority by the 300 (severe) and 400 (mild) analysis and has 90% power for 400 (severe) and 500 (mild). The trial has less than 5% cumulative type I error if therapeutic anticoagulation and the control arm equal (no effect). If therapeutic anticoagulation is slightly harmful there is virtually no chance of success. The effect size of 1.25 would be underpowered for the trial with approximately 50% of trials reaching superiority by 3000 patients. This is deemed appropriate as this is a small effect size.

Figure 4 presents the probability of reaching the conclusion of futility for the therapeutic anticoagulation arm as a function of the total number of subjects enrolled for each scenario and effect size.

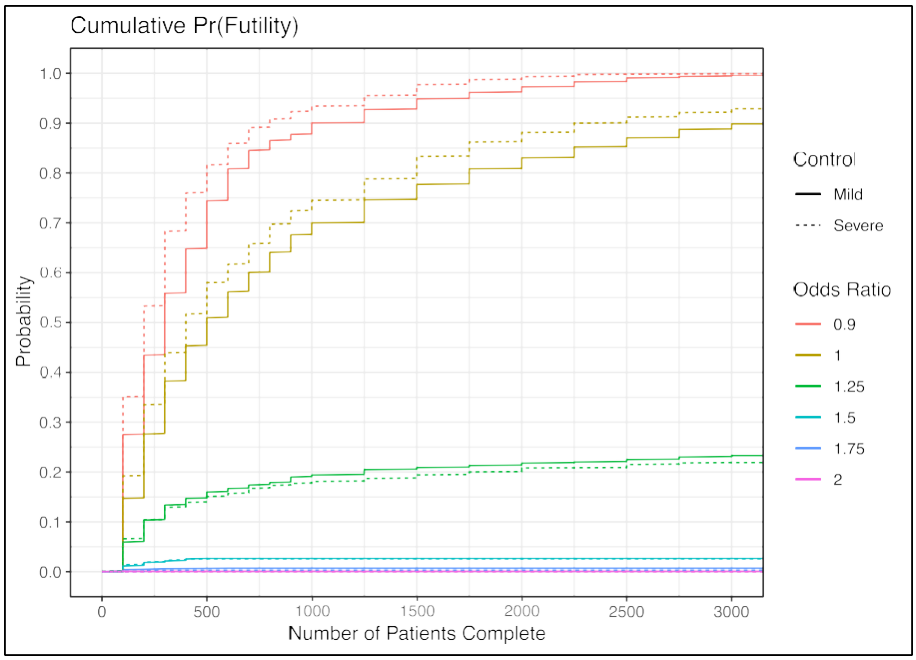

Figure 4: The cumulative probability of concluding superiority for the therapeutic anticoagulation arm as function of the scenario, treatment effect, and sample size.

If therapeutic anticoagulation is slightly harmful (OR=0.90) there is an 80% chance of triggering futility by 500 patients in the trial. For a null effect (no difference for control ortherapeutic anticoagulation) the probability of futility is 80% by 1500 (Severe) and 1750 (Mild). If the effect of therapeutic anticoagulation is small (OR=1.25) then approximately20% of trial will reach a futile conclusion. It's very rare for any trials to reach futility for effect sizes of 1.5 or greater.

12 PUBLICATION POLICES AND DISCLOSURE OF DATA

Intellectual Property

For publications, the first or senior authors will include the Principal Investigators of thestudy. Additional authors will be those who have made the most significant contributionto the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of subjects enrolled and will be reviewed at the end of the trial by the Principal Investigator.

Data Sharing

Data sharing with external parties for collaborative research and analysis will be permitted. Data will be entered in the electronic data capture SOCAR. This informationis accessible to investigators.

13 ETHICS

Ethics Board Approval

Each participating centre will have on file with Ozmosis Research, a list indicating the composition of its IRB/REB consistent with Canadian regulatory guidelines. This list will be updated as appropriate.

A Health Canada REB Attestation Form must be completed and signed by the REB representative. Alternatively, an attestation may be included in the signed local ethics approval document. This documentation must be received by Ozmosis Research beforethe centre can be locally activated.

Each sub study will be reviewed by IRB/REB for determination if full board reviewis needed or not.

Initial approval: All study sites are required to obtain local ethics approval of the protocoland consent form by the appropriate REB/IRB prior to commencement of the clinical trialat each site.

Continuing approval: Annual (or as required by the REB/IRB) re-approval may be requiredfor as long as subjects are being followed on protocol. It will be investigator's responsibilityto apply for and obtain the re-approval.

Amendment: All protocol amendments will be confirmed in writing and submitted, as appropriate, for review by the REB/IRB and health authorities. Amendments will be reviewed and approved by applicable regulatory authorities prior to central implementation of the amendment, and by REB/IRBs prior to local implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial subjects or when the change(s) involves only logistical or administrative aspects of the trial.

REB/IRB Refusals: If an REB/IRB refuses to approve this protocol (or an amendment/revision to this protocol), Ozmosis Research must be notified immediately ofthe date of refusal and the reason(s) for the refusal. Notification will then be made to Health Canada.

14 RECORD ACCESS AND MAINTENANCE OF STUDY RECORDS

Documentation of Subject's Participation

A statement acknowledging the participation of a subject in this clinical trial must be

documented in the subject's medical records along with the signed ICF.

Regulatory Requirements

Health Canada approval is required for this protocol.

The following documents are required:

For participating Canadian centres:

- All Investigators must complete and sign the Health Canada Qualified Investigator Undertaking form.
- All applicable regulatory documents as listed in the Protocol Activation Checklist provided by Ozmosis Research to the sites.
- Ozmosis Research will submit via email to Health Canada a completed Health Canada Clinical Trial Site Information Form after local activation of each participating Canadian centre.

For participating U.S.A centres:

- All Investigators must complete and sign FDA Form 1572. The completed forms must be returned to Ozmosis Research Inc. prior to site activation. (If FDA exemption is not granted)
- All Investigators must complete and submit a Financial Disclosure Statement (If FDA exemption is not granted)
- All Investigators must also submit to Ozmosis Research Inc. an up-to-date (current to within 2 years of the study start) curriculum vitae.
- Laboratory certification / accreditation and normal ranges for local lab(s).
- Consent forms, reviewed by Ozmosis Research Inc. before submission to the local IRB.
- A completed site delegation list.
- A copy of the initial full board approval letter from the local IRB. Continuing approval (full board) will be obtained at least yearly until follow-up on patients is completed and no further data is being obtained for research purpose.

Subject Confidentiality and Access to Source Data/Documents

Any research information obtained about the subject in this study will be kept confidential.A subject will not be identified by name, only by his/her initials. The subject's name or anyidentifying information will not appear in any reports published as a result of this study.

However, information obtained from individual subject's participation in the study may be disclosed with his/her consent to the health care providers for the purpose of obtaining appropriate medical care. The subject's medical records/charts, tests will be made available to Ozmosis Research, University of Manitoba, its potential partners, Health Canada, the REB/IRB and any other regulatory authorities. This is for the purpose of verifying information obtained for this study. Confidentiality will be maintained throughoutthe study within the limits of the law.

A subject's name will not be given to anyone except the researchers conducting the study,who have pledged an oath of confidentiality. All identifying information will be kept behindlocked doors, under the supervision of the study Principal Investigator and will not be transferred outside of the hospital.

A subject may take away his/her permission to collect, use and share information about him/her at any time. If this situation occurs, the subject will not be able to remain in the study. No new information that identifies the subject will be gathered after that date. However, the information

about the subject that has already been gathered and transferred may still be used and given to others as described above in order to preservethe scientific integrity and quality of the study.

Confidentiality of the Study

Data generated as a result of this study are to be available for inspection on request by local health authority auditors, the Sponsor's Study Monitors and other personnel (as appropriate) and by the REB/IRB. The Investigator shall permit sponsor, authorized agents of the sponsor, CRO and regulatory agency employees to enter and inspect any site where the study intervention or records pertaining to the study intervention are held,and to inspect all source documents, unless there are entry restrictions into the hospital sites due to the pandemic. The protocol and other study documents contain confidential information and should not be shared or distributed without the prior written permission of sponsor.

Registration of Clinical Trial

Prior to the first subject being registered/enrolled into this study, the Sponsor will be responsible for ensuring that the clinical trial is registered appropriately to remain eligiblefor publication in any major peer-reviewed journal, adhering to the guidelines put forth bythe International Committee of Medical Journal Editors (ICMJE).

Data Reporting

The data will be entered into the SOCAR database.

Maintenance of Study Records

To enable evaluations and/or audits from Regulatory Authorities, Ozmosis Research orthe Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, CRFs and hospital records),all original signed informed consent forms, source documents, and detailed records of treatment disposition. The Investigator should retain these records for 25 years after study close-out as required by Canadian regulations.

If the investigator relocates, retires, or for any reason withdraws from the study, then the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records.

15 QUALITY ASSURANCE AND QUALITY CONTROL

As per the ICH Guidelines of Good Clinical Practice, the sponsor will be responsible for implementing and maintaining quality assurance and quality control systems.

Monitoring / Auditing

Ozmosis Research will organize monitoring of this study to be conducted as per Monitoring Plan. This may involve remote monitoring if it is not feasible to monitor on-sitedue to hospital restrictions

during this pandemic.

As this trial is conducted under a CTA with Health Canada, your site may be subject toan inspection by Health Canada. Other audits may be conducted by the study sponsoror Ozmosis Research.

16 ADMINISTRATIVE PROCEDURES

Amendments to this Protocols

Modifications of this protocol is only possible by approved protocol amendments authorized by the Sponsor. Where required, all protocol amendments will be approved bythe REB and Health Canada (for Canadian sites) and by the IRB and FDA (For U.S.A sites if FDA exemption is not granted) prior to implementation. The Investigator must notimplement any deviation from, or change to the protocol, except where it is necessary toeliminate an immediate hazard to trial subject or when the change(s) involves only logistical or administrative aspects of the trial.

Protocol Deviations and Violations

All violations or deviations are to be reported to the site's REB/IRB (as per REB/IRB guidelines) for each sub-study, as applicable. All REB/IRB correspondence is to be forwarded to Ozmosis Research. The site must notify Ozmosis Research and/or sponsorimmediately of any protocol violations.

Premature Discontinuation of the Study

The Sponsor reserves the right to discontinue any trial for any reason but intends only toexercise this right for valid scientific or administrative reasons. After such a decision, theInvestigators must contact all participating subjects immediately after notification. Follow-up for subjects will be assured and, where required by the applicable regulatory requirement(s), the relevant regulatory authority(ies) will be informed.

The REB/IRB will be informed promptly and provided with a detailed written explanation for the termination or suspension.

As directed by the Sponsor, all study materials must be collected and all CRFs completedto the greatest extent possible.

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APPENDIX A – FDA GUIDANCE ON CLINICAL TRIAL CONDUCT DURINGCOVID-19 PANDEMIC

FDA Issues Updated Guidance on Clinical Trial Conduct During the COVID-19 Pandemic

On March 18, 2020, FDA issued "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic" to provide general considerations to assist sponsors in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity during the COVID-19 pandemic. On March 27, 2020, FDA amended the guidance to include an appendix to further explain those general considerations by providing answers to questions about conducting clinical trials that the Agency has received during the COVID-19 pandemic. For the updated guidance, please see: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-pandemic.

For additional questions regarding clinical trial conduct during the COVID-19 pandemic, please email Clinicaltrialconduct-COVID19@fda.hhs.gov.

U.S. Food and Drug Administration
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Current Protocol: Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC)

ANTITHROMBOTIC THERAPY TO AMELIORATE COMPLICATIONS OF COVID-19 (ATTACC), IN COLLABORATION WITH ACCELERATING COVID-19 THERAPEUTIC INTERVENTIONS AND VACCINES (ACTIV-4)

Protocol Version #:	3.0
Protocol Date:	29-Sep-2020
Study Number:	OZM-113
Sponsor:	Dr. Ryan Zarychanski, University of Manitoba
Sponsor's Address:	ON 2051 – 675 McDermot Avenue Winnipeg, Manitoba, Canada R3E 0V9 Tel: 204-787-2293 Fax: 204-235-3309 Email: rzarychanski@cancercare.mb.ca
Co-Principal Investigators:	Ryan Zarychanski, MD MSc Patrick R. Lawler, MD MPH Ewan Goligher, MD PhD

Lead Investigator, United States; Robert Rosenson

Lead Investigator, Brazil; Jose Nicolau

Lead Investigator, Mexico: Jorge Escobedo

Steering Committee:	Charlotte Bradbury, MD Marc Carrier, MD, MSc Vlad Dzavik, MD Michael Farkouh, MD Dean Fergusson, PhD MHA Robert Fowler, MD MSc Emily Gibson McDonald, MD MSc Peter Gross, MD MSc Brett L Houston, MD Mansoor Husain, MD Susan Kahn, MD MSc

Anand Kumar, MD
John Marshall, MD
Srinivas Murthy, MD
Arthur Slutsky, MD MSc
Tobias Tritschler MD
Alexis Turgeon, MD

Patient Partners : Suzanne Dubois
Margaret Ostrowski

Protocol History:

Version 1.0; dated 23-APR-2020
Version 2.0; dated 11-MAY-2020

Clinical Trial Management/Clinical Trials Specialist

Lindsay Bond
Ozmosis Research Inc. 65 Queen Street West Suite 2020, Toronto, ON M5H 2M5
Main Line: 416-634-8300
Fax: 416-598-4382
Email: Lindsay.bond@ozmosisresearch.ca

Investigator Initiated Sponsor's Agreement to Protocol Version 3.0, 29-Sep-2020

Name of Authorized Personnel (Print) _____

Title of Authorized Personnel (Print) _____

_____

_____

Signature of Authorized Personnel: _____

Date of Approval: _____
DD-MMM-YYYY

1 SYNOPSIS

Study Title:	**A**nti**T**hrombotic **T**herapy to **A**meliorate **C**omplications of **COVID**-19 (**ATTACC**) in collaboration with Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-4)
Study Design:	A phase III prospective, open-label, adaptive multi-platform randomized controlled trial
Primary Objective/ Endpoint:	The primary endpoint in the trial is days alive and free of organ support at day 21. This endpoint is defined as the number of days that a patient is alive and free of organ support through the first 21 days after trial entry.
Secondary Objectives:	Secondary Safety Endpoints: - Laboratory confirmed heparin induced thrombocytopenia **(HIT)** - **Major bleeding**, defined according to the International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) definitions and bleeding assessment tool in non-surgical patients (Schulman *J Thromb Haemost* 2005): fatal bleeding; and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; and/or bleeding causing a fall in hemoglobin level of ≥20 g/L, or leading to transfusion of 2 or more units of whole blood or red cells. Secondary Efficacy Endpoints: - A composite endpoint of death, deep vein thrombosis, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke collected during hospitalization or at 28 days and 90 days after enrollment (whichever is earlier) - Ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 30 following randomization: no invasive mechanical ventilation, invasive mechanical ventilation, or death.

	- All cause mortality assessed at 28 and 90 days following randomization - All cause mortality during initial hospitalization (includes death after 28 days) - Intubation assessed at 30 days following randomization - Ventilator-free days (days alive not on a ventilator) assessed at 28 days following randomization - Hospital-free days (days alive outside hospital assessed at 28 days following randomization) - Vasopressor-free days (days alive not on a vasopressor) assessed at 28 days following randomization - Renal replacement free days (days alive not on renal replacement) assessed at 28 days following randomization - Hospital re-admission within 28 days - Symptomatic proximal venous thromboembolism (DVT or PE) assessed at 28 and 90 days following randomization - Myocardial infarction assessed at 28 and 90 days following randomization - Ischaemic stroke assessed at 28 and 90 days following randomization - Acute kidney injury as defined by KDIGO criteria - Systemic arterial thrombosis or embolism assessed at 28 and 90 days following randomization - Use of extracorporeal membrane oxygenation (ECMO) support - Mechanical circuit (dialysis or ECMO) thrombosis - WHO ordinal scale (peak scale over 28 days, scale at 14 days, and proportion with improvement by at least 2 categories compared to enrollment, at 28 days)
Duration:	The duration of accrual on this study will be ongoing in nature during the COVID-19 pandemic, following outcomes for each patient up to a maximum of 90 days.

Planned Total Sample Size:	The trial is a Bayesian adaptive design and as such is not predicated on a fixed *a priori* sample size. This design was chosen given uncertainty regarding anticipated event rates and potential treatment effect sizes. Approximately 350 to a maximum of 3000 evaluable patients are anticipated to be enrolled in this adaptive trial in combination with the ACTIV 4 and REMAP-CAP trials, with anticipated reprioritization of key subgroups (including D-dimer defined) as the trial is undertaken.
Drug Administration:	Participants randomized to the investigational arm will receive therapeutic anticoagulation for 14 days (or until hospital discharge or liberation from the need for supplemental oxygen, whichever comes first) with preference for low-molecular weight heparin (LMWH), or alternative unfractionated heparin (UFH). Participants randomized to the control arm will receive usual care, which is anticipated to include thromboprophylactic dose anticoagulation according to local practice.
Inclusion/Exclusion Criteria:	Inclusions: 1. Patients ≥18 years of age providing (possibly through a substitute decision maker) informed consent who require hospitalization anticipated to last ≥72 hours, for microbiologically-confirmed COVID-19, enrolled < 72 hours of hospital admission **or** of COVID-19 confirmation Exclusions: 1. Requirement for chronic mechanical ventilation via tracheostomy prior to hospitalization 2. Patients for whom the intent is to not use pharmacologic thromboprophylaxis 3. Active bleeding 4. Risk factors for bleeding, including: a. intracranial surgery or stroke within 3 months; b. history of intracerebral arteriovenous malformation; c. cerebral aneurysm or mass lesions of the central nervous system;

	d. intracranial malignancy e. history of intracranial bleeding f. history of bleeding diatheses (e.g., hemophilia) g. history of gastrointestinal bleeding within previous 3 months h. thrombolysis within the previous 7 days i. presence of an epidural or spinal catheter j. recent major surgery <14 days k. uncontrolled hypertension (sBP >200 mmHg, dBP >120 mmHg) l. other physician-perceived contraindications to anticoagulation 5. Platelet count <50 x10^9/L, INR >2.0, or baseline aPTT >50 6. Hemoglobin <80 g/L (to minimize the likelihood of requiring red blood cell transfusion if potential bleeding were to occur) 7. Acute or subacute bacterial endocarditis 8. History of heparin induced thrombocytopenia (HIT) or other heparin allergy including hypersensitivity 9. Current use of dual antiplatelet therapy 10. Patients with an independent indication for therapeutic anticoagulation 11. Patients in whom imminent demise is anticipated and there is no commitment to active ongoing intervention 12. Anticipated transfer to another hospital that is not a study site within 72 hours 13. Enrollment in other trials related to anticoagulation or antiplatelet therapy
Study Assessments:	Study assessments are depicted in the study schedule.
Safety Variables & Analysis:	The safety of therapeutic anticoagulation with LWMH or intravenous UFH infusion will be evaluated by AE reports. Treatment-related AEs include bleeding and HIT.
Efficacy Assessments & Analysis	The efficacy of therapeutic-dose parenteral anticoagulation with subcutaneous LMWH or

	intravenous UFH will be evaluated in comparison to usual care.
Reasons for premature discontinuation of therapy:	Treatment will continue until any of the following occurs: • Heparin induced thrombocytopenia or other heparin allergy/hypersensitivity • Thrombocytopenia (platelet count <50 x10^9/L) • Major bleeding, defined based closely on the International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) definitions and bleeding assessment tool in non-surgical patients • Coagulopathy associated with an elevated INR (e.g., >2.0) or hypofibrinogemia • Following invasive procedures where heparin is deemed unsafe to re-institute • Patients requiring systemic fibrinolytic therapy • Treating physician discretion
Statistical Analysis:	Data will be analyzed by an intention to treat analysis for the primary analysis; a per-protocol analysis will also be completed as a secondary analysis. Patients who receive at least one dose of drug will be evaluable for safety and efficacy. Response-adaptive randomization based on D-dimer subgroups is embedded.

Table of Contents

2 LIST OF ABBREVIATIONS

Ensure all abbreviations used within the protocol are listed here

AE	Adverse Event
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
ATTACC	Antithrombotic Therapy to Ameliorate Complications of COVID-19
aPTT	activated partial thromboplastin time
CCC	Clinical Coordinating Centre
CRF	Case Report Form
CRO	Clinical Research Organization
CTA	Clinical Trial Application
dBP	diastolic Blood Pressure
DCC	Data Coordinating Centre
DIC	Disseminated Intravascular Coagulation
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HIT	Heparin-Induced Thrombocytopenia
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IL-6	Interlukin-6
INR	International Normalized Ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis

LAR	Legally Acceptable Representative
LMWH	Low-Molecular Weight Heparin
PE	Pulmonary Embolus
REB	Regulatory Ethics Board
REMAP- CAP	A Randomized, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
sBP	systolic Blood Pressure
SpO_2	Oxygen Saturation
SSC	Scientific and Standardization Committee
UFH	Unfractionated Heparin
VTE	Venous Thromboemboembolism
WHO	World Health Organization

3 BACKGROUND

At the end of 2019, an outbreak of severe respiratory infection had surged in Wuhan, China and, since then, it has rapidly spread across the globe. A novel coronavirus was identified as the cause of this outbreak (Zhu *N Engl J Med* 2020). The World Health Organization declared this new infection a global pandemic on March 11, 2020. This disease has since been known as COVID-19 and the virus that causes COVID-19 was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Zhu *N Engl J Med* 2020; Guan *N Engl J Med* 2020). As of September 2020, more than 30 million people have been diagnosed with COVID-19 and approximately 1 million have died. Currently in Canada, >150,000 patients have been infected and approximately 10,000 have died thus far (Government of Canada 2020).

The clinical spectrum of COVID-19 is extremely variable and not yet completely understood. The incubation period is thought to be within 14 days after exposure, most commonly in the first 5 days (Guan *N Engl J Med* 2020; Wu *JAMA* 2020). Most infections are mild, and a large proportion of infected people likely develop no or very mild symptoms. Approximately 15% of symptomatic patients progress to severe pneumonia, with the need for hospitalization, and 5% develop respiratory failure, shock and multi-organ dysfunction (Wu *JAMA* 2020; Wu *JAMA Inter Med* 2020; Yang *Lancet Respir Med* 2020). The case fatality rate is extremely variable, most likely a function of differences in population demographics and density, diagnostic screening criteria, and death reports among countries (Spychalski *Lancet Infect Dis* 2020). In Wuhan, the case-fatality rate was approximately 5.8%. In Italy, the estimated case-fatality rate in March was 7.2%, while in South Korea it is currently 1.73% (WHO-China 2020; Onder *JAMA* 2020; Korea Centers for Disease Control and Prevention 2020).

There are limited proven treatments for COVID-19, including dexamethasone (Horby NEJM 2020) and possibly hydrocortisone in critically ill patients (Angus *JAMA* 2020) as well as remdesivir (Wiersinga *JAMA* 2020). The current management is supportive (Alhazzani *Crit Care Med* 2020). A number of other therapies are currently under investigation and have been used anecdotally in clinical practice, particularly in those with severe forms of COVID-19. Examples are antiviral drugs, antimalarials (e.g., chloroquine and hydroxychloroquine), alone or in combination with azithromycin, and IL- 6 inhibitors (e.g., tocilizumab) (Alhazzani *Crit Care Med* 2020) – these therapies have been or are now being studied in trials. To date, however, there remains a strong unmet clinical need for effective therapeutic approaches.

4 STUDY RATIONALE

4.1 ATTACC Trial Rationale Overview

Several lines of evidence support the potential efficacy of therapeutic parenteral anticoagulation with heparin for the treatment of COVID-19. First, COVID-19 can be associated with a hypercoagulable state, and many patients may experience significant cardiac and pulmonary macro-and micro-vascular thrombotic complications contributing to clinical deterioration. COVID-19 is associated with an unusually high incidence of venous thromboembolic events (Klok et al. *Thrombosis Research* 2020; Cui *J Thromb Haemost* 2020). Second, heparin directly induces conformation changes in the SARS-CoV-2 receptor spike protein, and may limit cellular invasion into the pulmonary epithelium, myocardium, and vascular endothelium (MyCroft-West bioRxiv pre-print). Third, heparin has direct anti-inflammatory effects that may reduce the severity of organ injury and hemodynamic collapse. Given its ubiquitous availability, heparin may be rapidly translatable to clinical care globally if found to be effective (Thachil *J Thromb Haemost* 2020), at a time when immediately implementable solutions are urgently needed. Nonetheless bleeding concerns are present. D-dimer identifies higher risk COVID-19 patients and may be both a prognostic and predictive enrichment marker, possibly stratifying the benefit of heparin. For example, a recent observational study from Wuhan observed that when D-dimer exceeded 3.0 ug/mL, prophylactic-dose heparin use was associated with an approximately 20% absolute risk reduction in 28- day mortality (32.8% vs 52.4%, p=0.017) (Tang *J Thromb Haemo* 2020), although mortality remained high. More intensive anticoagulation strategies may provide even further event reduction. The present study therefore aims to evaluate the efficacy of therapeutic-dose parenteral heparin versus usual care in hospitalized COVID-19. Given that D-dimer may stratify the benefit of heparin, response adaptive randomization is implemented based on D-dimer cut points, enabling the trial to determine where therapeutic benefit exists across a range of D-dimer levels. The adaptive design is also appropriate for the pandemic, as information to guide sample size estimations is limited.

4.2 Risk Stratification in Patients with COVID-19

Advanced age and underlying comorbidities have been associated with increased likelihood of severe illness (Zhou *Lancet* 2020). Patients with cardiovascular disease or known cardiovascular disease risk factors, such as diabetes and hypertension, are at a particularly high risk of an unfavorable disease course (Wu *JAMA* 2020). Biomarkers are also associated with worse prognosis, including D-dimer and troponin (Zhou *Lancet* 2020). In a retrospective cohort from Wuhan, Shi and collaborators reported that, among 416 consecutive hospitalized patients with COVID-19, 20% had elevated troponin at hospital admission (Shi *JAMA Cardiol* 2020; Figure 1). Compared to patients with normal troponin, these patients had a markedly increased risk of complications, including acute respiratory distress syndrome (ARDS), acute kidney injury and in-

hospital mortality (adjusted HR for mortality: 3.41; 95% CI: 1.62 to 7.16; p=0.001), with 50% of these troponin-positive patients dying (Shi *JAMA Cardiol* 2020). In another observational study, Zhou and collaborators included 191 COVID-19 patients from two hospitals in Wuhan. In unpublished analyses, we have observed that most patients with elevated troponin also have elevated D-dimer, which may mark an upstream coagulopathy producing end-organ injury. Indeed, patients with **D-dimer** greater than 1mcg/mL at admission were at increased risk of in-hospital death (adjusted OR: 18.42; 95% CI: 2.64 to 128.55; p=0.0033). When comparing 113 patients with COVID-19 who died versus 161 who survived, Chen and colleagues found that troponin I and D-dimer levels were markedly higher in deceased patients (median troponin I levels: 40.8 pg/mL (IQR: 14.7-157.8) vs. 3.3 (IQR: 1.9-7.0); median d-dimer levels: 4.6 mcg/mL (IQR: 1.3-21.0) vs. 0.6 (IQR: 0.3-1.3) (Chen *BMJ* 2020). These results are consistent with emerging U.S. reports (Petrilli *bioRxiv* 2020). These biomarkers may be a valuable aid to risk stratification and guidance on resource allocation among hospitalized patients and have been routinely recommended in some institutional protocols (e.g., www.Covidprotocols.org). These observations highlight the potential use of biomarkers to guide treatment decision-making both as **prognostic** and **predictive risk markers**. However, more work is needed to understand the optimal biomarker cut-offs that align treatment with benefit. Furthermore, biomarkers that reflect downstream processes may be later markers, and treatment benefit may be realized with earlier intervention. An adaptive clinical trial with pre-defined biomarker subgroups based on D-dimer level, could address these questions while evaluating therapeutic efficacy.

4.3 Hypercoagulability in Patients with COVID-19

Severe illness from COVID-19 is associated with important derangements in coagulation resulting in a hypercoagulable state. These derangements are strongly associated with poor clinical outcomes and various lines of evidence suggest that the prothrombotic state may be causally related to poor outcomes. Elevated D-dimers may be a biomarker of this pathway (Zhou *Lancet* 2020). In a series of 183 patients, those who died 11% exhibited markedly elevated D-dimers and fibrin degradation products; 15 of the patients who died met the criteria for disseminated intravascular coagulation (DIC), whereas only 1 survivor developed DIC (Tang *J Thromb Haemost* 2020). Similar derangements in hemostasis were documented in a separate case series of 94 patients (Lippi *Clin Chem Lab Med* 2020). Markers of DIC correlate with clinical deterioration including ischemic injury in the fingers and toes (Li *Emerg Microbes Infect* 2020).
Macrovascular embolic events seem frequent. In a case series, pulmonary embolism was identified in 10 of the 25 patients who underwent CT pulmonary angiography (pre-print data, SSRN id: 3548771). The limited autopsy data suggest a constellation of pathological findings including thrombus in pulmonary microvessels (Fox *bioRxiv* 2020; Yao *Chin J Pathol* 2020).

The specific drivers of coagulopathy and DIC in COVID-19 disease are uncertain. SARS-CoV-2 can bind ACE2 and infect and injure endothelium, leading to tissue factor expression, endothelial activation and activation of the coagulation cascade (endotheliopathy). Strikingly, respiratory mechanics in patients requiring mechanical ventilation markedly differs from conventional mechanics seen in ARDS, and in COVID-19 is characterized by high dead space and impaired oxygenation in the absence of significant increase in pulmonary elastance, suggestive of pulmonary vascular occlusion. Similarly, reports of rapid deterioration in left ventricular systolic function also support both coronary and cardiac micro-thrombotic occlusive processed. Coronary events are well known to be increased early in patients with other forms of viral pneumonia, and this may explain the 3 to 4 fold increased in mortality hazard in patients with elevated troponin.

4.4 Managing Hypercoagulability in Patients with COVID-19

Many institutional guidelines, as well as the International Society of Thrombosis and Hemostasis (ISTH), recommend routine venous thromboprophylaxis in patients hospitalized with COVID-19 (e.g., www.Covidprotocols.org; Thachil *J Thromb Haemost* 2020). However, based on the above there is a compelling rationale to administer therapeutic heparin earlier in the disease course, which may also have pleiotropic benefit. In a recently published case-control study from Wuhan, 99 out of 449 consecutive patients received heparin (primarily thromboprophylactic dose heparin) for 7 days or longer (Tang *J Thromb Haemost* 2020). Although no difference in 28-day mortality was observed between patients receiving (or not) heparin (adjusted OR: 1.65; 95% CI: 0.93 to 2.92; p=0.088), among patients with elevated D-dimer, those treated with heparin, compared to those not treated with heparin, experienced lower 28-day mortality (OR for D-dimer> 3mcg/mL: 0.44; 95% CI: 0.27 to 0.87; p=0.017) (Tang *J Thromb Haemost* 2020). Based on clinical experience, an increasing understanding of the pathobiology of COVID-19, and emerging observational evidence, administering therapeutic anticoagulation in patients with COVID-19 has become the practice in some centers who have cared for a large number of these patients, but equipoise remains and currently this is not part of standard of care.

4.5 Other Potential Therapeutic Benefits of Heparin in COVID-19: Anti-viral and Anti-inflammatory Effects

In addition to its antithrombotic benefit, heparin has two additional potential beneficial effects in COVID-19: anti-viral effects that may limit viral invasion and anti-inflammatory effects. Very recently, the SARS-CoV-2 spike protein has been shown to interact with heparin. Upon binding heparin, the spike protein undergoes significant conformational changes that may prevent it from binding ACE2 (Mycroft-West *bioRxiv* 2020). We have discussed these data with the investigators in the U.K., and these anti-viral effects are present for both unfractionated heparin and some low molecular weight heparins.

Heparin had previously also been shown to prevent cellular invasion by SARS-CoV-1 (Vicenzi *Emerg Infect Dis* 2004; De Haan *J Virology 2005*), and is known to inhibit attachment and entry of other enveloped viruses such as HIV and HSV (Moulard *J Virol* 2000). Thus, heparin may exert a direct antiviral effect to prevent viral invasion of pulmonary epithelium, myocardium, and vascular endothelium.

Unfractionated heparin (UFH) also has potentially beneficial anti-inflammatory effects. UFH is a known inhibitor of complement and adhesion molecule expression in the microvasculature (Lever *Br J Pharmacol* 2000). UFH administration prevents acute lung injury and increases survival in various models of septic shock (Gans *Surgery* 1975). In a propensity-matched retrospective cohort study of patients with septic shock, heparin was associated with reduced 28-day mortality (Zarychanski *Crit Care Med* 2008). In a systematic review and meta-analysis of 6 randomized trials of heparin enrolling 2,477 patients with sepsis, the pooled odds ratio for mortality was 0.88 (95% CI: 0.77 to 1.00; I2 = 0%) (Zarychanski *Crit Care Med* 2015).

4.6 Safety of Heparin

The most frequent complication of anticoagulation use is bleeding. However, anticoagulation with parenteral anticoagulation (low molecular weight heparin or unfractionated) has been studied extensively across diverse patient populations and favourable safety data is available. Therapeutic parenteral anticoagulation is commonly used in hospitalized patients for the prevention and treatment of venous thromboembolic disease, acute coronary syndromes, and stroke prevention in patients with atrial fibrillation (Tiryaki AmJ Heal Pharm 2011). Its dosing and management of heparin is thus very familiar to clinicians. Overall, patients receiving therapeutic heparin have a 1-5% risk of major bleeding, depending on underlying risk and duration of exposure (Mismetti Chest 2005; Petersen JAMA 2004; Crowther Blood 2008).

When explored as an intervention for reducing mortality in patients with septic shock requiring intensive care unit admission, unfractionated compared to placebo or usual care demonstrated no significant differences in bleeding (gastrointestinal, central nervous system, epistaxis, hematuria) or need for blood product transfusion (Jaimes Crit Care Med 2009; Zarychanski Crit Care Med 2008). Subsequent meta-analysis of studies comparing UFH or LMWH with placebo or usual care in patients with sepsis admitted to the ICU suggests no increase the risk of major hemorrhage (RR 0.79, 95% CI 0.53–1.17), although its use is associated with a modest increase in minor hemorrhage (RR 1.49, 95% CI 1.07–2.07) (Zarychanski Crit Care Med 2015). In critically-ill patients, increased doses of UFH are not associated with increased clinically significant bleeding (0.2% with higher UFH dosing compared to 0.3% with standard unfractionated dosing, p=0.059) (Reynolds J Hum Pharmacol Drug Ther 2019). When compared to unfractionated, low molecular weight heparin — the preferred anticoagulant of choice in this study in the absence of any clinical contraindications — may exhibit a reduced risk of bleeding (OR 0.43; 95% CI 0.22 to 0.83; p=0.01) (Alikhan

Cochrane Database Syst Rev 2014). In a randomized-controlled trial, no difference in bleeding has been observed with enoxaparin 1.5 mg/kg subcutaneous once daily versus 1 mg/kg twice daily (Merli Annals Internal Med 2001). In this trial of 900 patients with venous thromboembolic disease, the incidence of major haemorrhage did not differ among those receiving unfractionated heparin (2.1%) once-daily enoxaparin (1.7%) or twice-daily enoxaparin group (1.3%).

Patients with an underlying systemic hypercoagulable state, in whom heparin is being given to offset this, may intuitively have a lower risk of bleeding. For example, in cancer-associated venous thromboembolisms (VTEs) – an underlying hypercoagulable state – with an estimated rate of major bleeding of 3.2% over 6 months' follow-up (Lee JAMA 2015; Li Thromb Res 2019).

Major bleeding will be a secondary safety endpoint and will be monitored by the DSMB in frequent interim analyses. Premature discontinuation of therapy related to bleeding, need for procedures requiring >48 hours of interruption, or physician discretion will also be monitored. A minimum hemoglobin cut-off of 80 g/L will be applied to reduce the risk of requiring blood transfusion in patients who experience bleeding.

Heparin-induced thrombocytopenia is another adverse event which can accompany heparin therapy, occurring significantly less often in patients receiving low molecular weight heparin compared with UFH (RR 0.22, 95% CI 0.06 to 0.84) (Junqueira Cochrane Database Syst Rev 2017). The overall incidence of HIT is 0.2–0.5%, and is higher in patients receiving therapeutic doses of UFH (0.79%) compared to those receiving prophylactic doses (<0.1%). (Creekmore J Hum Pharmacol Drug Ther 2006; Smythe Chest 2007).

Injection site adverse effects may include pain, mild local irritation, hard inflammatory nodules and injection site hematomas may follow the subcutaneous injection of a low molecular weight heparin.

Other rare adverse reactions reported with the use of unfractionated heparin and LMWH are hypersensitivity and allergic reactions, hepatic enzymes increase, hypercalcemia, urticaria, pruritus, erythema.

4.7 Background Summary

Taken together, these observations provide a compelling rationale for the use of therapeutic dose heparin in patients with COVID-19. These beneficial effects reflect antithrombotic properties, direct SARS-CoV2 antiviral properties, and anti-inflammatory properties (**Figure 1**). Risks of bleeding from prior studies are small. Risk/benefit may be best aligned using D-dimers. The clinical trial proposed herein looks to prevent clinical deterioration and improve survival in patients hospitalized with COVID-19 with therapeutic-dose heparin treatment, using an adaptive design that allows various D-dimer cut-offs to be studied objectively.

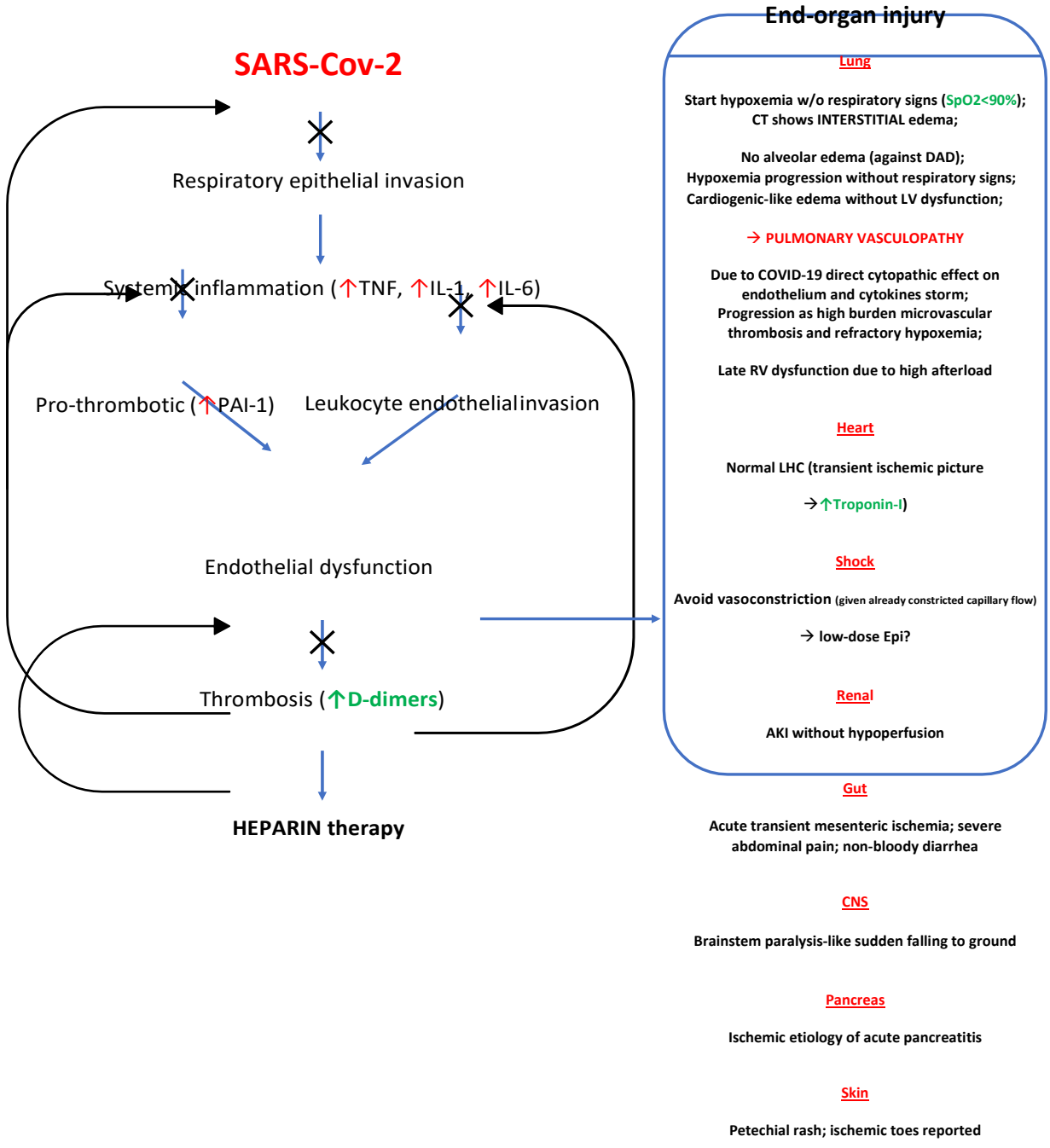

Figure 1: Proposed pathophysiologic pathways in COVID-19 upon which heparin may act.

5 THE TRIAL

5.1 Study Design

A phase III prospective, open-label, adaptive multi-platform randomized controlled trial.

5.2 Patient Population

Participants with laboratory confirmed COVID-19 requiring hospitalization anticipated to last ≥72 hours will be enrolled into this study.

5.3 Primary Endpoint

The primary endpoint in the trial is days alive and free of organ support at day 21. This endpoint is defined as the number of days that a patient is alive and free of organ support through the first 21 days after trial entry. Organ support is defined as receipt of invasive or non-invasive mechanical ventilation, high flow nasal oxygen (>30 L/min), vasopressor therapy, or ECMO support. Death at any time (including beyond 21 days) during the index hospital stay is assigned the worst possible score of –1.

5.4 Secondary Endpoints

Secondary safety endpoints: (determined to occur after enrollment)

- Laboratory-confirmed heparin induced thrombocytopenia **(HIT)**
- Major bleeding, defined according to the International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) definitions and bleeding assessment tool in non-surgical patients (Schulman *J Thromb Haemost* 2005): fatal bleeding; and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; and/or bleeding causing a fall in hemoglobin level of ≥20 g/L, or leading to transfusion of 2 or more units of whole blood or red cells

Secondary efficacy endpoints:

- A composite endpoint of death, deep vein thrombosis, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke collected during hospitalization or at 28 days and 90 days after enrollment (whichever is earlier)
- All cause mortality assessed at 28 and 90 days following randomization
- All cause mortality during initial hospitalization (includes death after 28 days)
- Intubation assessed at 30 days following randomization
- Ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 30 following randomization: no invasive mechanical ventilation, invasive mechanical ventilation, or death

- Ventilator-free days (days alive not on a ventilator) assessed at 28 days following randomization
- Hospital-free days (days alive outside hospital) assessed at 28 days following randomization
- Vasopressor-free days (days alive not on a vasopressor) assessed at 28 days following randomization
- Renal replacement free days (days alive not on renal replacement) assessed at 28 days following randomization
- Hospital re-admission within 28 days
- Symptomatic proximal venous thromboembolism (DVT or PE) assessed at 28 and 90 days following randomization
- Myocardial infarction assessed at 28 days and 90 days following randomization
- Ischaemic stroke assessed at 28 and 90 days following randomization
- Acute kidney injury as defined by KDIGO criteria
- Systemic arterial thrombosis or embolism assessed at 28 and 90 days following randomization
- Use of extracorporeal membrane oxygenation (ECMO) support
- Mechanical circuit (dialysis or ECMO) thrombosis
- Organ support-free days at 28 days following randomization
- WHO ordinal scale (peak scale over 28 days, scale at 14 days, and proportion with improvement by at least 2 categories compared to enrollment, at 28 days)

6 PATIENT ELIGIBILITY

This trial will be conducted in compliance with the protocol and GCP. Any questions about eligibility criteria must be addressed prior to patient registration.

6.1 Inclusion Criteria

1. Patients ≥18 years of age providing (possibly through a substitute decision maker) informed consent who require hospitalization anticipated to last ≥72 hours for microbiologically-confirmed COVID-19, enrolled < 72 hours of hospital admission **or** of COVID-19 confirmation

6.2 Exclusion Criteria

1. Requirement for chronic mechanical ventilation via tracheostomy prior to hospitalization
2. Patients for whom the intent is to not use pharmacologic thromboprophylaxis
3. Active bleeding
4. Risk factors for bleeding, including:
    a. intracranial surgery or stroke within 3 months;
    b. history of intracerebral arteriovenous malformation;
    c. cerebral aneurysm or mass lesions of the central nervous system;

d. intracranial malignancy
e. history of intracranial bleeding
f. history of bleeding diatheses (e.g., hemophilia)
g. history of gastrointestinal bleeding within previous 3 months
h. thrombolysis within the previous 7 days
i. presence of an epidural or spinal catheter
j. recent major surgery <14 days
k. uncontrolled hypertension (sBP >200 mmHg, dBP >120 mmHg)
l. other physician-perceived contraindications to anticoagulation

5. Platelet count <50 x10^9/L, INR >2.0, or baseline aPTT >50
6. Hemoglobin <80 g/L (to minimize the likelihood of requiring red blood cell transfusion if potential bleeding were to occur)
7. Acute or subacute bacterial endocarditis
8. History of heparin induced thrombocytopenia (HIT) or other heparin allergy including hypersensitivity
9. Current use of dual antiplatelet therapy
10. Patients with an independent indication for therapeutic anticoagulation
11. Patients in whom imminent demise is anticipated and there is no commitment to active ongoing intervention
12. Anticipated transfer to another hospital that is not a study site within 72 hours
13. Enrollment in other trials related to anticoagulation or antiplatelet therapy

6.3 Patient Consent

Sample English consent forms for the trial will be provided. A copy of the initial full board REB/IRB approval and approved consent form must be sent to Ozmosis Research. The subject/LAR must sign consent prior to registration or may provide consent as per FDA guidance document Coronavirus (COVID-19) Update: FDA Issues Guidance for Conducting Clinical Trials (Appendix A) or REB/IRB recommendations.

Patients admitted to hospital that have microbiologically-confirmed SARS-CoV-2 will be assessed for eligibility. Screening will include a review of inclusion and exclusion criteria. Study staff will discuss with the treating clinical team a potential subject's suitability to be approached for the trial. Information about the study will be presented to potential subjects (or legally authorized representative, which can include a substitute decision-maker in cases of incapacity). Given the potential for viral transmission and the nature of the studied intervention, consent will be obtained as per the REB/IRB recommendations or FDA Guidance (Appendix A). This is anticipated to include verbal consent and consent by telephone.

6.4 Patient Enrollment

Patient enrollment and randomization will occur through the eCRF system (eSOCDAT).

7 STUDY PLAN

7.1 Anticoagulation Administration

Participants randomized to the therapeutic arm will be given therapeutic-dose parenteral anticoagulation daily, up to 14 days or until *recovery*, defined as hospital discharge or liberation from supplemental oxygen >24 hours (provided supplemental oxygen was originally required), whichever comes first. If patient was on oxygen pre-hospitalization, recovery is defined as return to their baseline oxygen requirement, or hospital discharge (whichever comes first).

Participants randomized to the control arm will receive usual care, which is expected to include thromboprophylactic dose anticoagulation according to local practice. To ensure adequate separation between the study groups the dose of heparin/LMWH used in the usual care arm should not equal more than half of the approved therapeutic dose for that agent for the treatment of venous thromboembolism.

See Section 9 (Medicinal Product) for further details.

7.2 Study Schedule

Subjects will be followed until hospital discharge, after which time telephone contact will be undertaken to ascertain vital status following hospital discharged. (Schedule days refer to post-randomization days.) All post-discharge follow-up is telephone-/remote.

Investigations	Pre-Treatment (Baseline)[6]	Day 1	Day 3	Day 5	Day 7	Day 10	Day 14	Day 21	Day 30	Day 90
Windows	-72 hours	- 3 days							+ 7 days	
Consent & Randomization	X									
Demographics	X									
Medical History	X									
Weight	X									
SOC Vitals documented (SpO2 and FiO2, heart rate, blood pressure, respiratory rate, temperature)[1]	X	X	X		X		X			
Hematology bloodwork (SOC)[1]	X	X	X	X	X	X	X			

Biochemistry bloodwork (SOC)[1]	X	X	X	X	X	X	X			

Troponin (SOC)[1]	X	X	X	X	X	X	X			
D-dimer[2]	X									
D-dimer (SOC)[1]		X	X		X		X			
Optional Biorepository (blood samples)	X	X	X		X		X			
Anticoagulant Administration		X								
Organ-free support outcome								X		
Primary and secondary outcomes[3,]		X								
Survival, DVT, PE, MI (by phone)[3]									X	
WHO ordinal assessment										X
Adverse events[5]		X								
Concomitant medications[5]		X								

Footnotes:

[1]As per routine standard of care, collected while on therapy (until discharge or up to day 14 or recovery). Record the values closest to the day of the assessment. **Values from - 3 days may be used provided the values are temporally after the previous assessment.** If more than 1 value exists, the value closest to the day of study assessment will be used. Exceptions to this rule; troponin (collect highest troponin since last assessment), hemoglobin (collect lowest hemoglobin since last study assessment) and creatinine (collect highest creatinine since last study visit).

[2]**D-dimer is to be collected at baseline for all patients**. This is part of the current standard of care at most institutions, but where it is not, it will be collected as part of the trial protocol at baseline. If possible, it should be reported (i.e., a result available) prior to randomization, so that participants may benefit from response-adaptive randomization; however, patients are still able to be randomized if the D-dimer result is not available prior to randomization, in which case randomization will proceed 1:1.
Nonetheless, a level is required to be drawn at baseline in all cases if one is not already available within 72 hours of randomization. If there is a site that is not able to collect D-dimer for all patients at baseline, this will be discussed with the sponsor on a case-by-case basis.

[3]All post-discharge follow-up is telephone-/remote.

[4]Refer to 'THE TRIAL' section for a list of study outcomes

[5]Treatment-related adverse events are assessed only while on therapy. Concomitant medications are assessed from the time of consent and for the duration of therapy.

[6]The laboratory values closest to randomization should be recorded. Values up to 72 hours prior to randomization can be used for baseline values if the test is not available at the time of randomization and can not be repeated.

8 CONCOMITANT MEDICATIONS

Concomitant medications representing experimental COVID-19 treatments (as long as not related to anticoagulation) and anti-platelet agents, will be collected for the study from time of consent to 14 days or time of pre-defined treatment discontinuation (whichever comes first).

Potential Drug Interactions: refer to the next section and to the current product monographs for up to date interactions.

8.1 Drug Interactions

Heparin should be used with caution in patients receiving non-steroidal anti- inflammatory drugs, thrombolytic agents, glycoprotein IIb/IIIa antagonists, acetylsalicylic acid, platelet inhibitors, vitamin K antagonists, activated protein C, direct factor Xa and IIa inhibitors because of increased risk of bleeding.

9 MEDICINAL PRODUCT

9.1 Characterization of Investigation Medicinal Product

There is a preference for subcutaneous low molecular weight heparin, given ease of administration and resultant reductions in the need for clinical staff-patient interactions, if no contraindication is present. Enoxaparin is the preferred low molecular weight heparin given emerging data supporting potential viral inhibitory properties (Mycroft- West bioRvix preprint and Mark Skidmore, Keele University, personal communication), although tinzaparin or dalteparin are also acceptable, if available. Alternatively, intravenous unfractionated heparin infusion may be also used. The therapy may be switched within a subject during the course of the trial at the discretion of the treating physician. Anticoagulants used in the trial, whether as part of the intervention arm or as part of usual care/control arm, will be sourced, stored and dispensed by participating hospitals according to current practice and local policy.

This is a pragmatic trial of therapeutic anticoagulation, and hence the treating physician should determine what is the most appropriate parenteral anticoagulant for the patients to receive.

For pregnant women, use of non-tinzaparin (Innohep) product is preferred. If tinzaparin is the only product available, then only pre-filled syringes (without benzyl alcohol) will be administered as per the product monograph.

Low molecular weight heparin (LMWH)

LMWH is commenced, administered, and monitored according to local hospital policy, practice and guidelines that pertain to treatment of venous thromboembolism (i.e. not thromboprophylactic doses). The dose selected should be based on measured or estimated weight of the patient.

Adjustment for impairment of renal function should be according to local practice and policy.

Generally accepted dosing regimens for enoxaparin include: 1.5 mg/kg subcutaneous once daily or 1 mg/kg subcutaneous twice daily, assuming no dose adjustment is required. Alternatively, other subcutaneous low molecular weight heparins may be used, including tinzaparin, if available, (generally given at a dose of 175 anti-Xa IU/kg subcutaneous once daily if no dose adjustment is required) or dalteparin (200 IU/kg subcutaneous once daily or 100 IU/kg subcutaneous twice a day if no dose adjustment is required), as available.

Unfractionated heparin (UFH)

If UFH is used, this is commenced, administered, and monitored according to local hospital policy, and guidelines that are used for the treatment of venous thromboembolism (i.e. not for acute coronary syndrome). An intravenous infusion ofunfractionated heparin, is typically dosed according to total body weight and pragmatically adjusted according to local institutional policy to achieve an activated partial thromboplastin time (aPTT) of 1.5-2.5x the reference value. If UFH is used, the availability of a local hospital policy that specifies an aPTT target in this range or an anti-Xa value is a requirement.

9.2 Accountability and Destruction

This standard-of-care study drug for thromboprophylaxis will be provided from standard hospital supply and dosed according to local policy and practice. Sites will be responsible for assuring adequate local supply in coordination with local pharmacy.

9.3 Dose Adjustments

Dosing and dose adjustment of anticoagulants used for therapeutic anticoagulation should conform to local practices and policies. Examples are provided below.

Renal Impairment: In patients with acute or chronic severe renal impairment (creatinine clearance <30 mL/min), dose-adjustments or changes in therapy in patients receiving therapeutic dose LMWH) is typically required. Dose adjustments and continued use of

LMWH in this setting (vs. switching to UFH) is at the discretion of the treating medical team.

Liver Impairment: Low molecular weight heparin should be used with caution in patients with hepatic insufficiency.

9.4 Subject Compliance

Daily drug administration including name of drug, dose, and route of administration will be recorded in the source documents and captured into an eCRF.

9.5 Premature Withdrawal/ Discontinuation Criteria

Treating physicians may choose to discontinue therapy at their discretion. A premature discontinuation of treatment will be defined as an interruption in study drug for >26 hours. Temporary, shorter interruptions, for example to safely facilitate invasive procedures, are not considered interruptions or discontinuations in therapy provided the interruption does not exceed 48 hours. Reasons for treatment discontinuation may include but are not limited to:

- Heparin induced thrombocytopenia or other heparin allergy/hypersensitivity
- Thrombocytopenia if platelet count <50x10^9/L
- Major Bleeding, defined based closely on the ISTH/SSC definitions and bleeding assessment tool in non-surgical patients (below)
- Coagulopathy associated with an elevated INR (e.g. >2.0) or hypofibrinogemia (fibrinogen < 1 g/L)
- Following invasive procedures where heparin is deemed unsafe to re-institute
- Patients requiring systemic anticoagulation or fibrinolytic therapy
- Treating physician discretion

Temporary interruptions in therapy for ≤26hours (e.g., to facilitate invasive procedures) will not be considered a premature treatment discontinuation or a protocol violation.

Change in choice of anticoagulant or dose will not be considered discontinuation of therapy or a protocol violation. Time on unfractionated heparin will be determined as the time during which the infusion was administered, not determined by aPTT level.

Occurrence of HIT must result in cessation UFH or LMWH without recommencement regardless of treatment assignment. Use of an acceptable alternative agent is required in this instance as clinically indicated. Occurrence of HIT is an AE.

10 OPTIONAL BIOREPOSITORY

Blood sample collection will occur at the time points indicated in the Study Plan for patients that have provided informed consent on the optional consent for blood sample collection. It is not mandatory for all institutions to participate in the collection of correlative samples and each institutions willingness and ability to participate will be discussed on a case-by-case basis with the sponsor.

Refer to the Laboratory Manual for details on correlative sample collection.

11 SAFETY AND REPORTING REQUIREMENTS

11.1 Adverse Event (ONLY study drug related AEs will be reported)

As an open label trial of UFH or LMWH, adverse events captured in this trial are events that are **plausibly related** to the investigational agent. Adverse events **plausibly related** to heparin or low molecular weight heparin include major bleeding and HIT.

11.2 Adverse Event Documentation

Treatment-related AEs must be recorded in the eCRFs. Documentation must be supported by an entry in the subject's file.

11.3 Serious Adverse Event (SAE) due to the study drug

SAEs must be serious events that are believed to be **plausibly related** to the study drug and will include:

- Major bleeding (outlined the definition here of the ISTH)
- Laboratory confirmed heparin-induced thrombocytopenia

As per ICH guidelines, a **Serious Adverse Event** is any AE occurring at any dose that

(we will only report study drug related SAEs):

- Results in death
- Is life-threatening
- Requires prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly / birth defect

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event that hypothetically might have caused death if it were more severe.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Important medical event: Any adverse event may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition.

Any death (regardless of cause) that occurs from the time of administration of the first dose of study therapy until 28 days after the final administration of the study drug, and any death occurring after this time that is judged at least possibly related to prior treatment with the study drug, will be promptly reported.

11.4 Reporting Serious Adverse Events (Only Study Drug Related SAEs will be reported)

All serious adverse events (SAE) defined as per ICH guidelines (see above) and other adverse events that are **plausibly related** to the study drug (see section 11: HIT and major bleeding) must be recorded on the eCRF. Any collected event that is deemed serious must be reported through eSOCDAT within 24 hours of the site becoming aware of the event.

11.5 Procedure for Expedited Reporting

Responsibility for Reporting Serious Adverse Events to Health Canada

Ozmosis Research will provide expedited reports of SAEs to Health Canada according to applicable guidelines and regulations (including the 7-day notification for death and life-threatening events), i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

Responsibility for Reporting Serious Adverse Events to Sponsor

Ozmosis Research will be responsible for submitting SAE reports (Initial and/or Follow-up reports) received from the sites, to the Sponsor within 24hrs after receipt of the SAE form at Ozmosis Research.

Reporting Serious Adverse Events to Local Research Ethics Boards

Ozmosis Research will notify all Investigators on this study of all Serious Adverse Events that are reportable to regulatory authorities in Canada. This includes all serious events that are unexpected and related to protocol treatment. Investigators must notify their Research Ethics Boards (REB/IRBs) and file the report with their Investigator Site File. Documentation that serious adverse events (SAEs) have been reported to REB/IRBs must be kept on file at Ozmosis Research.
Documentation can be any of the following:

- letter from the REB/IRB acknowledging receipt
- stamp from the REB/IRB, signed and dated by REB/IRB chair,

acknowledging receipt
- letter demonstrating the SAE was sent to the board

All expedited serious adverse events occurring within a centre should also be reported to local REB/IRBs.

11.6 Study Management and Governance

Clinical Coordination Centre

The Clinical Coordinating Centre (CCC) will be Ozmosis Research who will be responsible for overall study management.

Data Coordinating Centre

The Data Coordinating Centre (DCC) is SOCAR Research in Switzerland. SOCAR will receive statistical support from Berry Consultants, who will perform interim analyses based on shared limited datasets from SOCAR to Berry. Data may also be shared with external research consortia (including other trials) to facilitate pooled analyses and more rapid/timely dissemination of results.

Executive Committee and Steering Committee

The Executive Committee will consist of the Principal Investigators, as well as representatives from the CCC and SOCAR. The Executive Committee is responsible for the execution of the trial according to the study protocol. A Steering Committee will be responsible for providing clinical and methodological guidance, including overall study design, execution, analysis, and publication of the main study results. The Steering Committee will oversee the management of the clinical trial sites and will also act as the Publication Committee. While the study is ongoing, the Committee will approve any protocol amendment that may become necessary and is responsible for maintaining the scientific integrity of the study.

Collaboration with ACTIV

The ACTIV trial platform is a U.S. science initiative that has collaborated with ATTACC and REMAP. The trials are operationally distinct but are working as harmonized trials that will perform primary analysis together.

12 STATISTICAL ANALYSIS

12.1 Study Population

Data from ATTACC, ACTIV and REMAP will be analyzed together as a single multiplatform randomized controlled trial. Each of the three platforms operate individually but in coordination, and with harmonized protocols and DSMB oversight. The adaptive design does not require specification of a sample size a priori. This design was chosen

given uncertainty about effect sizes and event rates given the lack of historical data amidst the emerging pandemic.. The trial will be discontinued when pre- specified criteria for superiority or futility are met according to regular interim analyses, including in subgroups of the overall trial (defined based on biomarkers and clinical parameters). We anticipate enrolling between 350 and 2,000 patients, which gives 90% power to detect an odds ratio ≥ 1.5 for avoiding organ-support or death. Data will be analyzed primarily with intention-to-treat.

12.2 Evaluation of Safety

The safety of therapeutic anticoagulation will be evaluated by means of AE reports.

12.3 Trial Design Introduction

The trial design is an adaptive trial comparing therapeutic anticoagulation with UFH or LMWH vs. usual care. The effect of therapeutic anticoagulation is modeled as potentially different within prespecified patient subgroups based on the baseline D- dimer levels (moderate patients only) or severe status (receiving organ support at baseline). Each patient is classified by their baseline D-dimer levels as high (defined as ≥2-fold increase above the local site's upper limit of normal range of values), and low (below this threshold).

The effect of therapeutic anticoagulation is modeled as a potential function of the patient D-dimer subgroup. Each conclusion for therapeutic anticoagulation is by subgroup with a statistical model that borrows the effect across subgroups.

The adaptive aspects of the trial include response adaptive randomization within each of the 2 D-dimer subgroups as well as any potential conclusions (superiority, futility) for the effect of therapeutic anticoagulation within each of these 2 subgroups.

Interim analyses will be conducted monthly. The details of the trial design rules are presented in the Adaptive Design Section.

12.4 Primary Endpoint

The primary endpoint is an ordinal scale that is a composite end-point that comprises mortality during the acute hospital admission and the number of whole and part study days for which the patient is alive and not requiring organ failure support while admitted

to an ICU up until the end of study day 21. All patients who die before discharge from an acute hospital, irrespective of whether this occurs before or after day 21, will be coded as –1 day. All patients who never receive organ failure support will be coded as 22. Organ support is defined as mechanical ventilation, high flow nasal oxygen >30 L/min, or the use of vasopressors.

12.5 Primary Analysis

Let $Y_i = \{-1, 0, 1, \ldots, 21, 22\}$ denote the ordinal outcome (OSFD) for patient i. The probability of patient i observing y OSFD or less is denoted as $\pi_{iy} = \Pr(Y_i \leq y)$. The model is a proportional odds model, where the log odds-ratio parameters in the model are structured so that a value > 0 implies treatment benefit, and an odds-ratio > 1 implies treatment benefit. The primary analysis model is formulated as follows:

$$\log\left(\frac{\pi_{iy}}{1-\pi_{iy}}\right) = \alpha_{y,s} - [\gamma_P + \nu_{Site,s} + \lambda_{Time,s} + \theta_{a,s:d} + \beta_{Age,s} + \beta_{Sex,s} + \beta_d]$$

1. Each "platform," *P*, has a covariate adjustment in the model, *P*=1 is REMAP- CAP, *P*=2 is ATTACC, and *P*=3 is ACTIV.
2. The "site" variable is the clinical site within the trial. These will be set as distinct sites across all three trials. The site effects are estimated separately within the severe and moderate disease states, but do not vary by d-dimer level.
3. The "time" variable is an indicator of the time epoch in which a patient was enrolled in the trial, numbered increasing from the first most recent epoch to the earliest time for the analysis. Time epochs are two-week time periods, Time=1, and then every 2-week epoch, moving back in time throughout the enrollment in the trial, Time=2,3,4,…. The time effects are modeled separately within the severe and moderate disease states, but do not vary by d-dimer level.
4. The "arm" to which a patient is randomized is labeled as *a* where *a*=1 is the control and *a*=2 is the treatment arm. The effects of arm vary by the disease state and the d-dimer level. The treatment effects for arm *a* within subtype *s*:*d* are modeled with the $\theta_{a,s:d}$ parameters.
5. The "age" variable is a categorical classification of age as ≤ 39, 40-49, 50-59, 60- 69, 70-79, and 80+. The age effects will be estimated separately within the moderate and severe disease states, but do not vary by d-dimer level.
6. The "sex" variable is sex at birth. The sex effects will be estimated separately within the moderate and severe disease states, but do not vary by d-dimer level.
7. The additive effects of d-dimer levels are modeled with the β_d for d = 0, 1, 2, 3.
8. The $\alpha_{y,s}$ parameters determine the baseline rates of the ordinal outcome, which are modeled separately by disease state but not d-dimer level.

13 ADAPTIVE DESIGN

The trial design is adaptive. A sequence of frequent interim analyses will be conducted as a function of enrollment rate. The anticipation is to conduct interim analyses on the 1st day of each month.

In the multiplatform analysis that includes data from ATTACC, each rule is separately evaluated within the three subtypes: moderate state: low d-dimer, moderate state: high d-dimer, and severe state. At each interim analysis the trial could reach a trial conclusion within any of the subgroups which would stop randomization in that subgroup in favor of the control (standard of care) or therapeutic anticoagulation. If no conclusion within a subgroup is reached and randomization continues the randomization probabilities will be set based on a response adaptive randomization algorithm distinctly within the subgroup. At this time, only ATTACC is utilizing responsive adaptive randomization based on probability of treatment successes within a subgroup of d-dimer (moderate state) or within the severe state.

13.1 Subgroup Conclusions

A subgroup may stop for **superiority of therapeutic anticoagulation** . This conclusion would be reached at any interim analysis in which the probability that therapeutic anticoagulation is more effective (OR > 1.5) than control in the subgroups is 99% or greater. That is a subgroup will stop for superiority of therapeutic anticoagulation if:

The trial may stop for **futility of therapeutic anticoagulation.** If the probability of at least a 20% improvement in the odds-ratio (OR > 1.2) is less than 10% then the trial will stop for futility.

The trial will continue as long as there are subgroups that have not reached a conclusion.

14 PUBLICATION POLICES AND DISCLOSURE OF DATA

14.1 Intellectual Property

For publications, the first or senior authors will include the Principal Investigators of the study. Additional authors will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of subjects enrolled and will be reviewed at the end of the trial by the Principal Investigator.

14.2 Data Sharing

Data sharing with external parties for collaborative research and analysis will be permitted. Data will be entered in the electronic data capture SOCAR. This information is

accessible to investigators.

15 ETHICS

Ethics Board Approval

Each participating centre will have on file with Ozmosis Research, a list indicating the composition of its IRB/REB consistent with Canadian regulatory guidelines. This list will be updated as appropriate.

A Health Canada REB Attestation Form must be completed and signed by the REB representative. Alternatively, an attestation may be included in the signed local ethics approval document. This documentation must be received by Ozmosis Research before the centre can be locally activated.

Each sub study will be reviewed by IRB/REB for determination if full board review is needed or not.

Initial approval: All study sites are required to obtain local ethics approval of the protocol and consent form by the appropriate REB/IRB prior to commencement of the clinical trial at each site.

Continuing approval: Annual (or as required by the REB/IRB) re-approval may be required for as long as subjects are being followed on protocol. It will be investigator's responsibility to apply for and obtain the re-approval.

Amendment: All protocol amendments will be confirmed in writing and submitted, as appropriate, for review by the REB/IRB and health authorities. Amendments will be reviewed and approved by applicable regulatory authorities prior to central implementation of the amendment, and by REB/IRBs prior to local implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial subjects or when the change(s) involves only logistical or administrative aspects of the trial.

REB/IRB Refusals: If an REB/IRB refuses to approve this protocol (or an amendment/revision to this protocol), Ozmosis Research must be notified immediately of the date of refusal and the reason(s) for the refusal. Notification will then be made to Health Canada.

16 RECORD ACCESS AND MAINTENANCE OF STUDY RECORDS

16.1 Documentation of Subject's Participation

A statement acknowledging the participation of a subject in this clinical trial must be documented in the subject's medical records along with the signed ICF.

16.2 Regulatory Requirements

Health Canada approval is required for this protocol.

The following documents are required:

For participating Canadian centres:

- All Investigators must complete and sign the Health Canada Qualified Investigator Undertaking form.
- All applicable regulatory documents as listed in the Protocol Activation Checklist provided by Ozmosis Research to the sites.
- Ozmosis Research will submit via email to Health Canada a completed Health Canada Clinical Trial Site Information Form after local activation of each participating Canadian centre.

For participating U.S.A centres:

- This study is IND exempt.
- All Investigators must also submit to Ozmosis Research Inc. an up-to-date (current to within 2 years of the study start) curriculum vitae.
- Laboratory certification / accreditation and normal ranges for local lab(s).
- Consent forms, reviewed by Ozmosis Research Inc. before submission to the local IRB.
- A completed site delegation list.
- A copy of the initial full board approval letter from the local IRB. Continuing approval (full board) will be obtained at least yearly until follow-up on patients is completed and no further data is being obtained for research purpose.

16.3 Subject Confidentiality and Access to Source Data/Documents

Any research information obtained about the subject in this study will be kept confidential. A subject will not be identified by name, only by his/her initials. The subject's name or any identifying information will not appear in any reports published as a result of this study.

However, information obtained from individual subject's participation in the study may be disclosed with his/her consent to the health care providers for the purpose of obtaining appropriate medical care. The subject's medical records/charts, tests will be made available to Ozmosis Research, University of Manitoba, its potential partners, Health

Canada, the REB/IRB and any other regulatory authorities. This is for the purpose of verifying information obtained for this study. Confidentiality will be maintained throughout the study within the limits of the law.

A subject's name will not be given to anyone except the researchers conducting the study, who have pledged an oath of confidentiality. All identifying information will be kept behind

locked doors, under the supervision of the study Principal Investigator and will not be transferred outside of the hospital.

A subject may take away his/her permission to collect, use and share information about him/her at any time. If this situation occurs, the subject will not be able to remain in the study. No new information that identifies the subject will be gathered after that date. However, the information about the subject that has already been gathered and transferred may still be used and given to others as described above in order to preserve the scientific integrity and quality of the study.

16.4 Confidentiality of the Study

Data generated as a result of this study are to be available for inspection on request by local health authority auditors, the Sponsor's Study Monitors and other personnel (as appropriate) and by the REB/IRB. The Investigator shall permit sponsor, authorized agents of the sponsor, CRO and regulatory agency employees to enter and inspect any site where the study intervention or records pertaining to the study intervention are held, and to inspect all source documents, unless there are entry restrictions into the hospital sites due to the pandemic. The protocol and other study documents contain confidential information and should not be shared or distributed without the prior written permission of sponsor.

16.5 Registration of Clinical Trial

Prior to the first subject being registered/enrolled into this study, the Sponsor will be responsible for ensuring that the clinical trial is registered appropriately to remain eligible for publication in any major peer-reviewed journal, adhering to the guidelines put forth by the International Committee of Medical Journal Editors (ICMJE).

16.6 Data Reporting

The data will be entered into the SOCAR database.

16.7 Maintenance of Study Records

To enable evaluations and/or audits from Regulatory Authorities, Ozmosis Research or the Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, source documents, and detailed records of treatment disposition. The Investigator should retain these records for the duration of time required by the applicable regulatory body.

If the investigator relocates, retires, or for any reason withdraws from the study, then the

Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records.

17 QUALITY ASSURANCE AND QUALITY CONTROL

As per the ICH Guidelines of Good Clinical Practice, the sponsor will be responsible for implementing and maintaining quality assurance and quality control systems.

17.1 Monitoring / Auditing

Ozmosis Research will organize monitoring of this study to be conducted as per Monitoring Plan, which may include delegating monitoring responsibilities to other research organizations. This may involve remote monitoring if it is not feasible to monitor on-site due to hospital restrictions during this pandemic.

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by Health Canada. Other audits may be conducted by the study sponsor or Ozmosis Research.

18 ADMINISTRATIVE PROCEDURES

18.1 Amendments to this Protocols

Modification of this protocol is only possible by approved protocol amendments authorized by the Sponsor. Where required, all protocol amendments will be approved by the REB and Health Canada (for Canadian sites) and by the IRB and FDA (For U.S.A sites if FDA exemption is not granted) prior to implementation. The Investigator must not implement any deviation from, or change to the protocol, except where it is necessary to eliminate an immediate hazard to trial subject or when the change(s) involves only logistical or administrative aspects of the trial.

18.2 Protocol Deviations and Violations

All violations or deviations are to be reported to the site's REB/IRB (as per REB/IRB guidelines) for each sub-study, as applicable. All REB/IRB correspondence is to be forwarded to Ozmosis Research. The site must notify Ozmosis Research and/or sponsor immediately of any protocol violations.

18.3 Premature Discontinuation of the Study

The Sponsor reserves the right to discontinue any trial for any reason but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigators must contact all participating subjects immediately after notification. Follow- up

for subjects will be assured and, where required by the applicable regulatory requirement(s), the relevant regulatory authority(ies) will be informed.

The REB/IRB will be informed promptly and provided with a detailed written explanation for the termination or suspension.

As directed by the Sponsor, all study materials must be collected and all CRFs completed to the greatest extent possible.

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20 APPENDIX A – FDA GUIDANCE ON CLINICAL TRIAL CONDUCT DURING COVID-19 PANDEMIC

FDA Issues Updated Guidance on Clinical Trial Conduct During the COVID-19 Pandemic

On March 18, 2020, FDA issued "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic" to provide general considerations to assist sponsors in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity during the COVID-19 pandemic. On March 27, 2020, FDA amended the guidance to include an appendix to further explain those general considerations by providing answers to questions about conducting clinical trials that the Agency has received during the COVID-19 pandemic. For the updated guidance, please see: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-pandemic.

For additional questions regarding clinical trial conduct during the COVID-19 pandemic, please email Clinicaltrialconduct-COVID19@fda.hhs.gov.

U.S. Food and Drug Administration
10903 New Hampshire Avenue, Silver Spring, MD 20993
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21 APPENDIX B – KDIGO CRITERIA FOR ACUTE KIDNEY INJURY

Acute kidney injury after enrollment is defined by KDIGO criteria for Acute Kidney Injury in the setting of not meeting these criteria upon enrollment:

Three Stages:

Stage 1: Serum Cr 1.5-1.9 times baseline, OR ≥ mg/dl increase in serum Cr

Stage 2: Serum Cr 2.0-2.9 times baseline

Stage 3: Serum Cr ≥ 3.0 times baseline, OR increase in serum creatinine to ≥ 4.0mg/dl, OR initiation of renal replacement therapy

22 APPENDIX C – WHO ORDINAL SCALE FOR CLINICAL IMPROVEMENT

(https://www.who.int/blueprint/priority-diseases/keyaction/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf)

Patient State	Score	Descriptor
Uninfected	0	No clinical or virological evidence of infection
Ambulatory	1	No limitation of activities
	2	Symptomatic: Limitation of activities
Hospitalized: Mild disease	3	Hospitalized; no oxygen therapy
	4	Hospitalized; oxygen by mask or nasal prongs
Hospitalized: Severe disease	5	Non-invasive ventilation or high-flow oxygen
	6	Intubation & Mechanical ventilation
	7	Ventilation and additional organ support – pressors, RRT, ECMO
Death	8	Death

SUMMARY OF PROTOCOL CHANGES & RATIONALE

ANTITHROMBOTIC THERAPY TO AMELIORATE COMPLICATIONS OF COVID-19 (ATTACC), IN COLLABORATION WITH ACCELERATING COVID-19 THERAPEUTIC INTERVENTIONS AND VACCINES (ACTIV-4)

Clinical Trial Protocol No:	*Ozmosis Study No. OZM-113*
Sponsor:	Dr. Ryan Zarychanski, Univeristy of Manitoba
Protocol History	
Original:	Version 1.0; dated 27-Apr-2020
Amendment #1:	Version 3.0; dated 29-Sep-2020

***From**: Version 1.0 dated 27-Sep-2020*
***To**: Version 3.1 dated 29-Sep-2020*

Summary of Changes

A description of the key changes that have been made to protocol Version 3.0 from the previous Version 1.0, including rationale for the changes, are listed below. Any minor changes or typographical/grammatical errors will be corrected and will not be listed.

New text is indicated with **bolded-underlined** font and deleted text is indicated with ~~strikethrough~~ font. A rationale for each change is also provided.

Table 1: Summary of Protocol Revisions

Section (Page number of Previous Approved Protocol v2.0)	Change
Global	***Administrative:*** Updated the version number and date of protocol from Version 1.0 dated 27-Apr-2020 to Version 3.0 dated 29-Sep-2020. Updated study title from ANTITHROMBOTIC THERAPY TO AMELIORATE COMPLICATIONS OF COVID-19 (ATTACC) **t**o ANTITHROMBOTIC THERAPY TO AMELIORATE COMPLICATIONS OF COVID-19 (ATTACC), **IN COLLABORATION WITH ACCELERATING COVID-19 THERAPEUTIC INTERVENTIONS AND VACCINES (ACTIV-4)** Added in: **Lead Investigator, United States: Robert RosensonLead** **Investigator, Brazil: Jose Nicolau** **Lead Investigator, Mexico: Jorge Escobedo** Changed ~~Co-investigators~~ to **Steering Committee** and added in **Tobias Tritschler, MD** as he is now a member of the steering committee. Added in: **Patient Partners : Suzanne Dubois** **Margaret Ostrowski** Updated Lindsay Bond's phone number from 416-634-~~8318~~ to 416-634-**8300**

Synopsis Page 4 of 52	***From:*** A prospective, open-label, adaptive multi-platform randomized controlled trial. ***To:*** A **phase III** prospective, open-label, adaptive multi-platform randomized controlled trial ***Rationale:*** *Synopsis was updated to reflect wording in body of protocol.*
Synopsis Page 4 of 52	***From:*** To establish whether therapeutic-dose parenteral anticoagulation improves outcomes (reduces intubation or mortality) by 30 days after randomization. The primary endpoint in the trial is an ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 30 following randomization: no invasive mechanical ventilation, invasive mechanical ventilation, or death. ***To:*** **The primary endpoint in the trial is days alive and free of organ support at day 21. This endpoint is defined as the number of days that a patient is alive and free of organ support through the first 21 days after trial entry.** ~~To establish whether therapeutic-dose parenteral anticoagulation improves outcomes (reduces intubation or mortality) by 30 days after randomization.~~ ~~The primary endpoint in the trial is an ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 30 following randomization: no invasive mechanical ventilation, invasive mechanical ventilation, or death.~~ ***Rationale:*** *The rational for this small but important re-ordering of the primary outcome is to allow for 1) a global collaboration and planned future data merger between 2 other trials REMAP-CAP (UK, Ireland), Australia, New Zealand, and Saudi Arabia) and ACTIV-IV in the United States, 2) expanded enrollment of intubated patients in ATTACC. The new revised primary outcome of 21 day mortality and organ-free support days is a re-expression of our current primary outcome which is an ordinal categorical outcome of intubation status and mortality at 30 days. The original primary outcome doesn't perform for patients who are already intubated.* *The revised primary outcome is a small but important change and will allow ATTACC, REMAP and ACTIV-IV to collectively answer this question and report the results as quickly as possible and for both moderately ill (ward-like) and severely ill (ICU-like) patients around the world.*

Synopsis, Secondary Objectives Page 4, 5, and 21 of 52	***From:*** Secondary Efficacy Endpoints: - Mortality assessed at 30 and 90 days following randomization - Intubation assessed at 30 days following randomization - Organ support-free days at day 21 - ICU-free days assessed at 30 days following randomization - Use of non-invasive mechanical ventilation or high flow nasal cannula - Ventilator free days (days alive not on a ventilator) assessed at 30 days following randomization - Hospital-free days (days alive outside hospital assessed at 30 days following randomization) - Symptomatic proximal venous thromboembolism (DVT or PE) assessed at 30 and 90 days following randomization - Myocardial infarction assessed at 30 and 90 days following randomization - Ischaemic stroke assessed at 30 and 90 days following randomization A prospective, open-label, randomized, multicenter, adapative clinical trial. ***To:*** Secondary Efficacy Endpoints: - **A composite endpoint of death, deep vein thrombosis, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke collected during hospitalization or at 28 days and 90 days after enrollment (whichever is earlier)** - **Ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 30 following randomization: no invasive mechanical ventilation, invasive mechanical ventilation, or death.** - **All cause ~~M~~m**ortality assessed at **28**~~30~~ and 90 days following randomization - **All cause mortality during initial hospitalization (includes death after 28 days)** - Intubation assessed at 30 days following randomization - ~~Organ support-free days at day 21~~ - ICU-free days assessed at 30 days following randomization - ~~Use of non-invasive mechanical ventilation or high flow nasal cannula~~ - Ventilator- free days (days alive not on a ventilator) assessed at **28**~~30~~ days following randomization - Hospital-free days (days alive outside hospital assessed at **28**~~30~~ days following randomization) - **Vasopressor-free days (days alive not on a vasopressor) assessed at 28 days following randomization** - **Renal replacement free days (days alive not on renal replacement) assessed at 28 days following randomization** - **Hospital re-admission within 28 days** - Symptomatic proximal venous thromboembolism (DVT or PE) assessed at **28**~~30~~ and 90 days following randomization - Myocardial infarction assessed at **28**~~30~~ and 90 days following randomization - Ischaemic stroke assessed at **28**~~30~~ and 90 days following randomization - **Acute kidney injury as defined by KDIGO criteria** - **Systemic arterial thrombosis or embolism assessed at 28 and 90 days following randomization**

	- **Use of extracorporeal membrane oxygenation (ECMO) support** - **Mechanical circuit (dialysis or ECMO) thrombosis** - **WHO ordinal scale (peak scale over 28 days, scale at 14 days, and proportion with improvement by at least 2 categories compared to enrollment, at 28 days)** ~~A prospective, open-label, randomized, multicentre, adaptive clinical trial.~~ ***Rationale:*** *The ATTACC trial (OZM-113) has collaborated with ACTIV-IV and REMAP-CAP. As such, the enpoints have been adjusted to align within the studies.This will allow ATTACC, REMAP and ACTIV-IV to collectively answer this question and report the results as quickly as possible.*
Synopsis Page 5 of 52	***From:*** The duration of this study will be ongoing in nature during the COVID-19 pandemic following outcomes up to a maximum of 90 days. ***To:*** The duration **of accrual** on this study will be ongoing in nature during the COVID-19 pandemic, following outcomes **for each patient** up to a maximum of 90 days. ***Rationale:*** *Updated for clarification of the meaning of this sentence.*
Synopsis Page 5 of 52	***From:*** The trial is a Bayesian adaptive design and as such is not predicated on a fixed a priori sample size. This design was chosen given uncertainty regarding anticipated event rates and potential treatment effect sizes. Approximately 350 to a maximum of 3000 evaluable patients are anticipated to be enrolled in this adaptive trial, with anticipated reprioritization of key subgroups (including D-dimer defined) as the trial is undertaken. ***To:*** The trial is a Bayesian adaptive design and as such is not predicated on a fixed *a priori* sample size. This design was chosen given uncertainty regarding anticipated event rates and potential treatment effect sizes. Approximately 350 to a maximum of 3000 evaluable patients are anticipated to be enrolled in this adaptive **trial in combination with the ACTIV 4 and REMAP-CAP trials**, with anticipated reprioritization of key subgroups (including D-dimer defined) as the trial is undertaken. ***Rationale:*** *Updated to reflect partnership with the ACTIV-4 and REMAP-CAP trials.*

Synposis, Inclusion/ Exclusion Criteria Page 5, 6, 7, and 22 of 52	***From:*** Inclusions: 1. Patients ≥18 years of age providing (possibly through a substitute decision maker) informed consent who require hospitalization anticipated to last ≥72 hours, with microbiologically-confirmed COVID-19, enrolled < 72 hours of hospital admission or of COVID-19 confirmation Exclusions: 1. Receiving invasive mechanical ventilation 12. Pregnancy ***To:*** Inclusions: 1. Patients ≥18 years of age providing (possibly through a substitute decision maker) informed consent who require hospitalization anticipated to last ≥72 hours, ~~with~~ **for** microbiologically-confirmed COVID-19, enrolled < 72 hours ofhospital admission **or** of COVID-19 confirmation Exclusions: 1. ~~Receiving invasive~~ **Requirement for chronic** mechanical ventilation **via tracheostomy prior to hospitalization** 12. ~~Pregnancy~~ ***Rationale:*** *Exclusion #1 was adjusted to align the trial protocols of ATTACC, REMAP-CAP and ACTIV-IV. With this modification, ATTACC can enroll and report on severely ill patients receiving invasive mechanical ventilation. REMAP-CAP made analogous amendment so that they could include moderately-ill patients that ATTACC was previously only including. This will facilitate global enrollment and future merging of trial data. Chronic mechanical ventilation via tracheostomy prior to hospitalization was added to clarify the type of ventilated patients eligible for ATTACC.* *Exclusion#12: Neither unfractionated heparin nor low molecular weight heparin cross the placenta and pose no added risk in pregnancy. Excluding pregnancy is not consistent with two similar trials;* • *Heparin anticoagulation to improve outcomes in septic shock* • *Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) for COVID-19 Infections* *Both of these protocols evaluate the same dose of heparin in the same populations (septic shock; some of whom will have COVID-19) and COVID-19 patients; some of whom will have septic shock).*

Synopsis Page 7 and 8 of 52	***From:*** Temporary interruptions in therapy ≤24 hours (e.g., to facilitate invasive procedures) will not be considered a premature treatment discontinuation or a protocol violation. Change in choice of anticoagulant or dose will not be considered discontinuation of therapy or a protocol violation. Time on unfractionated heparin will be determined as the time during which the infusion was administered, not determined by aPTT level. • Occurrence of HIT must result in cessation UFH or LMWH without recommencement regardless of treatment assignment. Use of an acceptable alternative agent is required in this instance as clinically indicated. Occurrence of HIT is an SAE. ***To:*** ~~Temporary interruptions in therapy ≤24 hours (e.g., to facilitate invasive procedures) will not be considered a premature treatment discontinuation or a protocol violation.~~ ~~Change in choice of anticoagulant or dose will not be considered discontinuation of therapy or a protocol violation. Time on unfractionated heparin will be determined as the time during which the infusion was administered, not determined by aPTT level.~~ • ~~Occurrence of HIT must result in cessation UFH or LMWH without recommencement regardless of treatment assignment. Use of an acceptable alternative agent is required in this instance as clinically indicated. Occurrence of HIT is an SAE~~ ***Rationale:*** *Removed to avoid repetition and inclusion of unnecessary information in the synopsis. The removed language is still present in the body of the protocol.*
Synopsis Page 8 of 52	***Deleted:*** ~~Sample Size Determination~~ ~~This is an adaptive randomized trial. The trial will be discontinued when pre-specified criteria for superiority or futility are met according to regular interim analyses. The trial will be capable of enrolling a maximum of 3,000 patients, although most scenarios will achieve 90% power to detect an odds ratio ≥ 1.5 for avoiding intubation or death at appreciably lower sample sizes.~~ ***Rationale:*** *Removed to avoid inclusion of unnecessary information in the study synopsis. The sample size is already mentioned in the synopsis in the 'Planned Total Sample Size' section. Sample size determination details are included in the body of the protocol.*

Background Page 14 of 52	***From:*** At the end of 2019, an outbreak of severe respiratory infection has surged in Wuhan, China and, since then, it has rapidly spread across the globe. A novel coronavirus was identified as the cause of this outbreak (Zhu N Engl J Med 2020). The World Health Organization declared this new infection a global pandemic on March 11, 2020. This disease has since been known as COVID-19 and the virus that causes COVID-19 was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Zhu N Engl J Med 2020; Guan N Engl J Med 2020). As of the beginning of April 2020, more than 2 million people have been diagnosed with COVID-19 and more than 140,000 have died. Currently in Canada, >30,000 patients have been infected and >1,100 have died thus far (Government of Canada 2020). The clinical spectrum of COVID-19 is extremely variable and not yet completely understood. The incubation period is thought to be within 14 days after exposure, most commonly in the first 5 days (Guan N Engl J Med 2020; Wu JAMA 2020). Most infections are mild, and a large proportion of infected people likely develop no or very mild symptoms. Approximately 15% of symptomatic patients progress to severe pneumonia, with the need for hospitalization, and 5% develop respiratory failure, shock and multi-organ dysfunction (Wu JAMA 2020; Wu JAMA Inter Med 2020; Yang Lancet Respir Med 2020). The case fatality rate is extremely variable, most likely a function of differences in population demographics and density, diagnostic screening criteria, and death reports among countries (Spychalski Lancet Infect Dis 2020). In Wuhan, the case-fatality rate was approximately 5.8%. In Italy, the estimated case-fatality rate in March was 7.2%, while in South Korea it is currently 1.73% (WHO-China 2020; Onder JAMA 2020; Korea Centers for Disease Control and Prevention 2020). There are no proven effective treatments for COVID-19 and current management is supportive (Alhazzani Crit Care Med 2020). A number of therapies are currently under investigation and have been used anecdotally in clinical practice, particularly in those with severe forms of COVID-19. Examples are antiviral drugs (e.g., remdesivir), antimalarials (e.g., chloroquine and hydroxychloroquine), alone or in combination with azithromycin, and IL-6 inhibitors (e.g., tocilizumab) (Alhazzani Crit Care Med 2020) – these therapies are now being studied in trials. To date, however, there remains a strong unmet clinical need for effective therapeutic approaches. ***To:*** At the end of 2019, an outbreak of severe respiratory infection ha**d**~~s~~ surged in Wuhan, China and, since then, it has rapidly spread across the globe. A novel coronavirus was identified as the cause of this outbreak (Zhu *N Engl J Med* 2020). The World Health Organization declared this new infection a global pandemic on March 11, 2020. This disease has since been known as COVID-19 and the virus that causes COVID-19 was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Zhu *N Engl J Med* 2020; Guan *N Engl J Med* 2020). As of~~ the beginning of April~~**September** 2020, more than ~~2~~**30** million people have been diagnosed with COVID-19 and ~~more than 140,000~~ **approximately 1 million** have died. Currently in Canada, >~~30~~**150**,000 patients have been infected and ~~>1,100~~ **approximately 10,000** have died thus far (Government of Canada 2020). The clinical spectrum of COVID-19 is extremely variable and not yet completely understood. The incubation period is thought to be within 14 days after exposure, most commonly in the first 5 days (Guan *N Engl J Med* 2020; Wu *JAMA* 2020). Most infectionsare mild, and a large proportion of infected people likely develop no or very mild symptoms. Approximately 15% of symptomatic patients progress to severe pneumonia, with the need for hospitalization, and 5% develop respiratory failure, shock and multi-organ dysfunction (Wu *JAMA* 2020; Wu *JAMA Inter Med* 2020; Yang *Lancet Respir Med* 2020). The case fatality rate is extremely

	variable, most likely a function of differences in population demographics and density, diagnostic screening criteria, and death reports among countries (Spychalski *Lancet Infect Dis* 2020). In Wuhan, the case-fatality rate was approximately 5.8%. In Italy, the estimated case-fatality rate in March was 7.2%, while in South Korea it is currently 1.73% (WHO-China 2020; Onder *JAMA* 2020; Korea Centers for Disease Control and Prevention 2020). There are ~~no~~**limited** proven ~~effective~~ treatments for COVID-19~~ and~~**, including dexamethasone (Horby NEJM 2020) and possibly hydrocortisone in critically ill patients (Angus *JAMA* 2020) as well as remdesivir (Wiersinga *JAMA* 2020). The** current management is supportive (Alhazzani *Crit Care Med* 2020). A number of **other** therapies are currently under investigation and have been used anecdotally in clinical practice, particularly in those with severe forms of COVID-19. Examples are antiviral drugs ~~(e.g., remdesivir),~~, antimalarials (e.g., chloroquine and hydroxychloroquine), alone or in combination with azithromycin, and IL-6 inhibitors (e.g., tocilizumab) (Alhazzani *Crit Care Med* 2020) – these therapies **have been or** are now being studied in trials. To date, however, there remains a strong unmet clinical need for effective therapeutic approaches. ***Rationale:*** *Updated to reflect current COVID-19 statistics and current knowledge of effective treatments.*
Study Rationale Page 16 of 52	***From:*** Many institutional guidelines, as well as the International Society of Thrombosis and Hemostasis (ISTH), recommend routine venous thromboprophylaxis in patients hospitalized with COVID-19 (e.g., www.covidprotocols.org; Thachil J Thromb Haemost 2020). However, based on the above there is a compelling rationale to administer therapeutic heparin earlier in the disease course, which may also have pleiotropic benefit. In a recently published case-control study from Wuhan, 99 out of 449 consecutive patients received heparin (primarily thromboprophylactic dose heparin) for 7 days or longer (Tang J Thromb Haemost2020). Although no difference in 28-day mortality was observed between patients receiving (or not) heparin (adjusted OR: 1.65; 95% CI: 0.93 to 2.92; p=0.088), among patients with elevated D-dimer, those treated with heparin, compared to those not treated with heparin, experienced lower 28-day mortality (OR for D-dimer> 3mcg/mL: 0.44; 95% CI: 0.27 to 0.87; p=0.017) (Tang J Thromb Haemost 2020). Based on clinical experience, an increasing understanding of the pathobiology of COVID-19, and emerging observational evidence, administering therapeutic anticoagulation in patients with COVID-19 has become the practice in some centers who have cared for a large number of these patients, but equipoise remains and currently this is not part of standard of care. At the time of writing, only one trial of 491 registered trials on www.covid19-trials.org is testing therapeutic enoxaparin, with a planned sample size of 60 patients and a primary endpoint of time to virus eradication (http://www.chictr.org.cn/showproj.aspx?proj=50795). ***To:*** Many institutional guidelines, as well as the International Society of Thrombosis and Hemostasis (ISTH), recommend routine venous thromboprophylaxis in patients hospitalized with COVID-19 (e.g., www.covidprotocols.org; Thachil *J Thromb Haemost* 2020). However, based on the above there is a compelling rationale to administer therapeutic heparin earlier in the disease course, which may also have pleiotropic benefit. In a recently published case-control study from Wuhan, 99 out of 449 consecutive patients received heparin (primarily thromboprophylactic dose heparin) for 7 days or longer (Tang *J Thromb Haemost* 2020). Although no difference in 28-day mortality was observed between patients receiving (or not) heparin (adjusted OR: 1.65; 95% CI: 0.93 to 2.92; p=0.088), among patients with elevated D-dimer, those treated with heparin, compared to those not treated

	with heparin, experienced lower 28-day mortality (OR for D-dimer> 3mcg/mL: 0.44; 95% CI: 0.27 to 0.87; p=0.017) (Tang *J Thromb Haemost* 2020). Based on clinical experience, an increasing understanding of the pathobiology of COVID-19, and emerging observational evidence, administering therapeutic anticoagulation in patients with COVID-19 has become the practice in some centers who have cared for a large number of these patients, but equipoise remains and currently this is not part of standard of care. ~~At the time of writing, only one trial of 491 registered trials on www.covid19-trials.org is testing therapeutic enoxaparin, with a planned sample size of 60 patients and a primary endpoint of time to virus eradication (http://www.chictr.org.cn/showproj.aspx?proj=50795).~~ ***Rationale:*** *Removed because information is outdated.*
Study Design Page 20 of 52	***From:*** The duration of this study will be ongoing in nature during the COVID-19 pandemic following outcomes up to a maximum of 90 days. ***To:*** ~~The duration of this study will be ongoing in nature during the COVID-19 pandemic following outcomes up to a maximum of 90 days.~~ **A phase III prospective, open-label, adaptive multi-platform randomized controlled trial.** ***Rationale:*** *Updated to more accurately describe the study design.*
Patient Population Page 20 of 52	***From:*** Participants with laboratory confirmed COVID-19 requiring hospitalization anticipated to last ≥72 hours, but prior to intubation, will be enrolled into this study. ***To:*** Participants with laboratory confirmed COVID-19 requiring hospitalization anticipated to last ≥72 hours~~, but prior to intubation,~~ will be enrolled into this study. ***Rationale:*** *Updated to reflect change to exclusion criterion #1.*

Primary Objective Page 20 of 52	***Deleted:*** **~~Primary Objective~~** ~~To establish whether therapeutic-dose parenteral anticoagulation improves outcomes (reduces intubation or mortality) by 30 days following randomization.~~ ***Rationale:*** *Removed as no longer relevant due to the collaboration with the ACTIV-4 trial. The primary endpoint is listed in the later section in the protocol.*
Primary Endpoint Page 21 of 52	***From:*** The primary endpoint in the trial is an ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 30 following randomization: no invasive mechanical ventilation, invasive mechanical ventilation, or death. ***To:*** The primary endpoint in the trial is ~~an ordered categorical~~ **days alive and free of organ support at day 21. This** endpoint ~~with three possible outcomes based on~~is defined as the ~~worst status~~ **number** of ~~each~~ **days that a** patient **is alive and free of organ support** through ~~day 30 following randomization: no~~ **the first 21 days after trial entry. Organ support is defined as receipt of** invasive **or non-invasive** mechanical ventilation, ~~invasive mechanical ventilation, or death.~~ **high flow nasal oxygen (>30 L/min), vasopressor therapy, or ECMO support. Death at any time (including beyond 21 days) during the index hospital stay is assigned the worst possible score of –1.** ***Rationale:*** *The ATTACC trial (OZM-113) has collaborated with ACTIV-IV and REMAP-CAP. As such, the enpoints have been adjusted to align within the studies.This will allow ATTACC, REMAP and ACTIV-IV to collectively answer this question and report the results as quickly as possible.*
Secondary Objectives Page 21 of 52	***Deleted:*** **~~Secondary Objectives~~** • ~~To determine safety of therapeutic-dose parenteral anticoagulation~~ • ~~To evaluate efficacy of therapeutic dose parenteral anticoagulation~~ ***Rationale:*** *Removed to avoid repetition. The secondary safety and efficacy enpoints are listed in the later section in the protocol.*

Patient Eligibility Page 22 of 52	***From:*** This trial will be conducted in compliance with the protocol and GCP. Any questions about eligibility criteria must be addressed prior to patient registration. Patients will be enrolled within 72 hours of admission. ***To:*** This trial will be conducted in compliance with the protocol and GCP. Any questions about eligibility criteria must be addressed prior to patient registration. ~~Patients will be enrolled within 72 hours of admission.~~ ***Rationale:*** *Updated to avoid repetition and confusion as this statement is not completely accurate. Per inclusion criterion #1, patients many enroll within 72 hours of admission or COVID-19 confirmation.*
Patient Registration Page 23 of 52	***From:*** Patient Registration The randomization and registration process will be provided to the sites at site start-up phase. ***To:*** Patient **Enrollment** ~~Registration~~ ~~The~~ **Patient enrollment and** randomization ~~and registration process~~ will ~~be provided to~~**occur through** the ~~sites at site start-up phase.~~**eCRF system (eSOCDAT).** ***Rationale:*** *Updates to reflect the current randomization procedures.*
Study Plan Page 24 of 52	***From:*** Study Schedule Participants will be given therapeutic-dose parenteral anticoagulation daily, up to 14 days or until recovery, defined as hospital discharge or liberation from supplemental oxygen >24 hours (provided supplemental oxygen was originally required), whichever comes first. Subjects will be followed until hospital discharge, after which time telephone contact will be undertaken to ascertain vital status following hospital discharged. (Schedule days refer to post-randomization days.) All post-discharge follow-up is telephone-/remote. ***To:*** **Anticoagulation Administration** ~~Study Schedule~~ Participants **randomized to the therapeutic arm** will be given therapeutic-dose parenteral anticoagulation daily, up to 14 days or until *recovery*, defined as hospital discharge or liberation from supplemental oxygen >24 hours (provided supplemental oxygen was originally required), whichever comes first. **If patient was on oxygen pre-hospitalization, recovery is defined as return to their baseline oxygen requirement, or hospital discharge (whichever comes first).**

	Participants randomized to the control arm will receive usual care, which is expected to include thromboprophylactic dose anticoagulation according to local practice. To ensure adequate separation between the study groups the dose of heparin/LMWH used in the usual care arm should not equal more than half of the approved therapeutic dose for that agent for the treatment of venous thromboembolism. ***See Section 9 (Medicinal Product) for further details.*** **Study Schedule** Subjects will be followed until hospital discharge, after which time telephone contact will be undertaken to ascertain vital status following hospital discharged. (Schedule days refer to post-randomization days.) All post-discharge follow-up is telephone-/remote. ***Rationale:*** *Additional information provided in this section to provide further instructions to the site staff on anticoagulation administration. Although there is no data to support the use of higher than standard doses of heparin/LWWH for venous thromboprophylaxis in COVID-19 patients, the dose of these agents in the usual care arm has varied more than anticipated or recommended by international bodies (American College of Chest Physicians, International Society of Thrombosis and Hemostasis, etc). To ensure the trial has therapeutic separation between study arms, the dose of heparin/UFH has been limited to be a dose that is half of the therapeutic dose.*
Medicinal Product Page 28 and 32 of 52	***From:*** Characterization of Investigation Medicinal Product For patients randomized to the intervention arm, patients will recieve therapeutic-dose parenteral anticoagulation, with preference for subcutaneous low molecular weight heparin, given ease of administration and resultant reductions in the need for clinical staff-patient interactions, if no contraindication is present. Enoxaparin is the preferred low molecular weight heparin given emerging data supporting potential viral inhibitory properties (Mycroft-West bioRvix preprint and Mark Skidmore, Keele University, personal communication), although tinzaparin or dalteparin are also acceptable, if available. Alternatively, intravenous unfractionated heparin infusion may be also used. The therapy may be switched within a subject during the course of the trial at the discretion of the treating physician. Study Drug Administration Anticoagulants used in the trial, whether as part of the intervention arm or as part of usual care/control arm, will be sourced, stored and dispensed by participating hospitals according to current practice and local policy. This is a pragmatic trial of therapeutic anticoagulation, and hence the treating physician should determine what is the most appropriate parenteral anticoagulant for the patients to receive. For pregnant women, use of non-tinzaparin (Innohep) product is preferred. If tinzaparin is the only product available, then only pre-filled syringes (without benzyl alcohol) will be administered as per the product monograph.

Low molecular weight heparin (LMWH)
LMWH is commenced, administered, and monitored according to local hospital policy, practice and guidelines that pertain to treatment of venous thromboembolism (i.e. not thromboprophylactic doses). The dose selected should be based on measure or estimated weight of the patient.

Adjustment for impairment of renal function should be according to local practice and policy

The *preferred therapeutic anticoagulant* is enoxaparin. Generally accepted dosing regimens for enoxaparin include: 1.5 mg/kg subcutaneous once daily or 1 mg/kg subcutaneous twice daily, assuming no dose adjustment is required. Alternatively, other subcutaneous low molecular weight heparins may be used, including tinzaparin, if available, (generally given at a dose of 175 anti-Xa IU/kg subcutaneous once daily if no dose adjustment is required) or dalteparin (200 IU/kg subcutaneous once daily or 100 IU/kg subcutaneous twice a day if no dose adjustment is required), as available.

Unfractionated heparin (UFH)
If UFH is used, this is commenced, administered, and monitored according to local hospital policy, and guidelines that are usedfor the treatment of venous thromboembolism (i.e. not for acute coronary syndrome). Intravenous infusion of unfractionated heparin, is typically dosed according to total body weight and pragmatically adjusted according to local institutional policy to achieve an activated partial thromboplastin time (aPTT) of 1.5-2.5x the reference value. If UFH is used, the availability of a local hospital policy that has specifies an aPTT target in this range or an anti-Xa value is a requirement.

To:
~~For patients randomized to the intervention arm, patients will recieve therapeutic-dose parenteral anticoagulation, with~~ **There is a** preference for subcutaneous low molecular weight heparin, given ease of administration and resultant reductions in the need for clinical staff-patient interactions, if no contraindication is present. Enoxaparin is the preferred low molecular weight heparin given emerging data supporting potential viral inhibitory properties (Mycroft-West bioRvix preprint and Mark Skidmore, Keele University, personal communication), although tinzaparin or dalteparin are also acceptable, if available. Alternatively, intravenous unfractionated heparin infusion may be also used. The therapy may be switched within a subject during the course of the trial at the discretion of the treating physician.

~~Study Drug Administration~~
Anticoagulants used in the trial, whether as part of the intervention arm or as part of usual care/control arm, will be sourced, stored and dispensed by participating hospitals according to current practice and local policy.
This is a pragmatic trial of therapeutic anticoagulation, and hence the treating physician should determine what is the most appropriate parenteral anticoagulant for the patients to receive.

For pregnant women, use of non-tinzaparin (Innohep) product is preferred. If tinzaparin is the only product available, then only pre-filled syringes (without benzyl alcohol) will be administered as per the product monograph.

Low molecular weight heparin (LMWH)
LMWH is commenced, administered, and monitored according to local hospital policy, practice and guidelines that pertain to

	treatment of venous thromboembolism (i.e. not thromboprophylactic doses). The dose selected should be based on measured or estimated weight of the patient. Adjustment for impairment of renal function should be according to local practice and policy. ~~The *preferred therapeutic anticoagulant* is enoxaparin.~~ Generally accepted dosing regimens for enoxaparin include: 1.5 mg/kg subcutaneous once daily or 1 mg/kg subcutaneous twice daily, assuming no dose adjustment is required. Alternatively, other subcutaneous low molecular weight heparins may be used, including tinzaparin, if available, (generally given at a dose of 175 anti-Xa IU/kg subcutaneous once daily if no dose adjustment is required) or dalteparin (200 IU/kg subcutaneous once daily or 100 IU/kg subcutaneous twice a day if no dose adjustment is required), as available. Unfractionated heparin (UFH) If UFH is used, this is commenced, administered, and monitored according to local hospital policy, and guidelines that are used for the treatment of venous thromboembolism (i.e. not for acute coronary syndrome). ~~Intravenous~~ **An intravenous** infusion of unfractionated heparin, is typically dosed according to total body weight and pragmatically adjusted according to local institutional policy to achieve an activated partial thromboplastin time (aPTT) of 1.5-2.5x the reference value. If UFH is used, the availability ofa local hospital policy that ~~has~~ specifies an aPTT target in this range or an anti-Xa value is a requirement. ***Rationale:*** *Minor adjustments made to enhance clarity and avoid unnecessary repetition.*
Premature Withdrawal/ Discontinuation Criteria Page 29 and 30 of 52	***From:*** Treating physicians may choose to discontinue therapy at their discretion. A premature discontinuation of treatment will be defined as an interruption in study drug for >24 hours. Temporary, shorter interruptions, for example to safely facilitate invasive procedures, are not considered interruptions or discontinuations in therapy provided the interruption does not exceed 48 hours. • Reasons for treatment discontinuation may include but is not limited to: • Heparin induced thrombocytopenia or other heparin allergy/hypersensitivity • Thrombocytopenia if platelet count <50x109/L • Major Bleeding, defined based closely on the ISTH/SSC definitions and bleeding assessment tool in non-surgical patients (below) • Coagulopathy associated with an elevated INR (e.g. >2.0) or hypofibrinogemia • Following invasive procedures where heparin is deemed unsafe to re-institute • Patients requiring systemic fibrinolytic therapy • Treating physician discretion Temporary interruptions in therapy for ≤24 hours (e.g., to facilitate invasive procedures) will not be considered a premature treatment discontinuation or a protocol violation Change in choice of anticoagulant or dose will not be considered discontinuation of therapy or a protocol violation. Time on unfractionated heparin will be determined as the time during which the infusion was administered, not determined by aPTT level. Occurrence of HIT must result in cessation UFH or LMWH without recommencement regardless of treatment assignment. Use ofan ~~acceptable alternative agent is required in this instance as clinically indicated. Occu~~rrence of HIT is an SAE.

	To: Treating physicians may choose to discontinue therapy at their discretion. A premature discontinuation of treatment will be defined as an interruption in study drug for >~~24~~**26** hours. Temporary, shorter interruptions, for example to safely facilitate invasive procedures, are not considered interruptions or discontinuations in therapy provided the interruption does not exceed 48 hours. Reasons for treatment discontinuation may include but **are**~~is~~ not limited to: • Heparin induced thrombocytopenia or other heparin allergy/hypersensitivity • Thrombocytopenia if platelet count <50x10^9/L • Major Bleeding, defined based closely on the ISTH/SSC definitions and bleeding assessment tool in non-surgical patients (below) • Coagulopathy associated with an elevated INR (e.g. >2.0) or hypofibrinogemia **(fibrinogen < 1 g/L)** • Following invasive procedures where heparin is deemed unsafe to re-institute • Patients requiring systemic **anticoagulation or** fibrinolytic therapy • Treating physician discretion Temporary interruptions in therapy for ~~≤24 hours~~**26hours** (e.g., to facilitate invasive procedures) will not be considered a premature treatment discontinuation or a protocol violation. Change in choice of anticoagulant or dose will not be considered discontinuation of therapy or a protocol violation. Time on unfractionated heparin will be determined as the time during which the infusion was administered, not determined by aPTT level. Occurrence of HIT must result in cessation UFH or LMWH without recommencement regardless of treatment assignment. Use ofan acceptable alternative agent is required in this instance as clinically indicated. Occurrence of HIT is an ~~SAE~~**AE.** ***Rationale:*** *Per sponsor, treatment interuptions of greater than 26 hours are acceptable, should not affect data integrity, and allows more flexibility for sites compaired to 24 hours. Other minor updates made to this section to provide sites with clarification and more detailed information.*
Optional Biorespository	***Added:*** **OPTIONAL BIOREPOSITORY** **Blood sample collection will occur at the time points indicated in the Study Plan for patients that have provided informed consent on the optional consent for blood sample collection. It is not mandatory for all institutions to participate in the collection of correlative samples and each institutions willingness and ability to participate will be discussed on a case-by-case basis with the sponsor.** **Refer to the Laboratory Manual for details on correlative sample collection.** ***Rationale:*** *An optional biorepository sub-study is now available for sites and patients to participate in if they choose to do so.*

Reporting Serious Adverse Events Page 32 of 52	***From:*** All serious adverse events (SAE) defined as per ICH guidelines (see above) and other adverse events that are related to the study drug must be recorded on case report forms. In addition, all serious adverse events that are related to the study drug must be reported by using the SAE form and must be submitted to Ozmosis. Related SAEs should be reported within 24 hours of becoming aware of the event. Serious Adverse Event Reporting Instructions All serious adverse events that are related to study drug must be reported as follows: Within 24 hours: Report initial information (on trial specific SAE report form) by fax or e-mail to: Ozmosis Research Inc Phone: 416-634-8300 Fax: 416-598-4382 E-mail: ozmsafety@ozmosisresearch.caThe initial information should always contain: - Name of Reporter/Investigator, - Subject Identification, - Adverse Event Term, - Study Drug Dose and Start/Stop Dates On the next working day: Fax completed trial-specific Serious Adverse Event form ***To:*** All serious adverse events (SAE) defined as per ICH guidelines (see above) and other adverse events that are **plausibly** relatedto the study drug **(see section 11: HIT and major bleeding)** must be recorded on ~~case report forms. In addition, all~~ **the eCRF. Any collected event that is deemed** serious ~~adverse events that are~~ **related** ~~to the study drug~~ must be reported ~~by using the~~ ~~SAE form and must be submitted to Ozmosis.~~ **Related** ~~SAEs should be reported~~ **through eSOCDAT** within 24 hours *of the site* becoming aware of the event. ~~Serious Adverse Event Reporting Instructions~~ **All** ~~serious adverse events that are related to study drug must be reported as follows:~~ ~~Within 24 hours: Report initial information (on trial specific SAE report form) by fax or e-mail to:~~ ~~Ozmosis Research Inc~~ ~~Phone: 416-634-8300~~ ~~Fax: 416-598-4382~~ ~~E-mail: ozmsafety@ozmosisresearch.ca~~ ~~The initial information should always contain:~~ ~~Name of Reporter/Investigator,~~ ~~Subject Identification,~~ ~~Adverse Event Term,~~ ~~Study Drug Dose and Start/Stop Dates~~ ~~On the next working day: Fax completed trial-specific Serious Adverse Event form~~

	Rationale: *Section updated to reflect the current process for reporting of SAE's.*
Study Management and Governance Page 33 of 52	***Added:*** **Collaboration with ACTIV** **The ACTIV trial platform is a U.S. science initiative that has collaborated with ATTACC and REMAP. The trials are operationally distinct but are working as harmonized trials that will perform primary analysis together.** ***Rationale:*** *Included to explain the multi-trial collaboration.*
Statistical Analysis Page 34 of 52	***From:*** Study Population The adaptive design does not require specification of a sample size a priori. This design was chosen given uncertainty about effect sizes and event rates given the lack of historical data amidst the emerging pandemic. The study population is anticipated tobe 350-3000 patients. Simulations below outline the anticipated sample sizes in detail. The trial will be discontinued when pre- specified criteria for superiority or futility are met according to regular interim analyses, including in subgroups of the overall trial (defined based on biomarkers and clinical parameters). We anticipate enrolling between 350 and 2,000 patients, which gives 90% power to detect an odds ratio ≥ 1.5 for avoiding intubation or death. Data will be analyzed primarily with intention-to-treat. ***To:*** Study Population **Data from ATTACC, ACTIV and REMAP will be analyzed together as a single multiplatform randomized controlled trial. Each of the three platforms operate individually but in coordination, and with harmonized protocols and DSMB oversight.** The adaptive design does not require specification of a sample size a priori. This design was chosen given uncertaintyabout effect sizes and event rates given the lack of historical data amidst the emerging pandemic. ~~The study population is anticipated to be 350-3000 patients. Simulations below outline the anticipated sample sizes in detail.~~ The trial will be discontinuedwhen pre-specified criteria for superiority or futility are met according to regular interim analyses, including in subgroups of the overall trial (defined based on biomarkers and clinical parameters). We anticipate enrolling between 350 and 2,000 patients, which gives 90% power to detect an odds ratio ≥ 1.5 for avoiding ~~intubation~~ **organ-support** or death. Data will be analyzed primarily with intention-to-treat. ***Rationale:*** *The ATTACC trial (OZM-113) has collaborated with ACTIV-IV and REMAP-CAP and their data will be analyzied together to collectively answer this question and report the results as quickly as possible.*

Statistical Analysis Page 34 of 52	***From:*** Trial Design Introduction The trial design is an adaptive trial comparing therapeutic anticoagulation with UFH or LMWH vs. usual care. The effect of therapeutic anticoagulation is modeled as potentially different within prespecified patient subgroups based on the baseline d-dimer levels. Each patient is classified by their baseline D-dimer levels as high (top quartile), medium (3rd quartile), and low (less than median). The effect of therapeutic anticoagulation is modeled as potentially a function of the patient D-dimer subgroup. Each conclusion for therapeutic anticoagulation is by subgroup with a statistical model that borrows the effect across subgroups. The adaptive aspects of the trial include response adaptive randomization within each of the 3 subgroups as well as any potential conclusions (superiority, futility) for the effect of therapeutic anticoagulation within each of these 3 subgroups. Interim analyses will be conducted periodically (starting every two weeks and likely progressing to monthly as a function of enrollment rate, targeting updates at least every 100 patients being enrolled). The details of the trial design rules are presented in the Adaptive Design Section. ***To:*** Trial Design Introduction The trial design is an adaptive trial comparing therapeutic anticoagulation with UFH or LMWH vs. usual care. The effect of therapeutic anticoagulation is modeled as potentially different within prespecified patient subgroups based on the baseline ~~d-dimer levels.~~**D-dimer levels (moderate patients only) or severe status (receiving organ support at baseline),** Each patient is classified by their baseline D-dimer levels as high (~~top quartile), medium (~~3rd ~~quartile~~ **defined as ≥2-fold increase above the local site's upper limit of normal range of values**), and low (~~less than median~~below this threshold). The effect of therapeutic anticoagulation is modeled as ~~potentially a~~ **potential** function of the patient D-dimer subgroup. Each conclusion for therapeutic anticoagulation is by subgroup with a statistical model that borrows the effect across subgroups. The adaptive aspects of the trial include response adaptive randomization within each of the ~~3~~ **2 D-dimer** subgroups as well as any potential conclusions (superiority, futility) for the effect of therapeutic anticoagulation within each of these ~~3~~2 subgroups. Interim analyses will be conducted ~~periodically (starting every two weeks and likely progressing to~~ monthly ~~as a function of enrollment rate, targeting updates at least every 100 patients being enrolled).~~. The details of the trial design rules are presented in the Adaptive Design Section. ***Rationale:*** *Updated to reflect the changes in the statistical analysis that are a result of the change in exclusion criterion #1 (patients that are mechanically ventilated can now be included).*
Statistical Analysis Page 34 and 35 of 52	***From:*** Primary Endpoint The primary endpoint in the trial is an ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 30: 1 = no mechanical ventilation, 2= mechanical ventilation, 3 = death. We label a patient's status for D- dimer as d=1 for low, d=2 for medium, and d=3 for high. These thresholds to define each of these (top 75%, to 50%) will be based on the observed 75th percentile and median for baseline d-dimer at the first interim analysis. These thresholds will then beused for the remainder of the trial for randomization and d-dimer classification. ***To:***

	Primary Endpoint ~~The primary endpoint in the trial is an ordered categorical endpoint with three possible outcomes based on the *worst* status of each patient through day 30: 1 = no mechanical ventilation, 2= mechanical ventilation, 3 = death. We label a patient's status for D- dimer as d=1 for low, d=2 for medium, and d=3 for high. These thresholds to define each of these (top 75%, to 50%) will be based on the observed 75th percentile and median for baseline d-dimer at the first interim analysis. These thresholds will then be used for the remainder of the trial for randomization and d-dimer classification.~~ **The primary endpoint is an ordinal scale that is a composite end-point that comprises mortality during the acute hospital admission and the number of whole and part study days for which the patient is alive and not requiring organ failure support while admitted to an ICU up until the end of study day 21. All patients who die before discharge from an acute hospital, irrespective of whether this occurs before or after day 21, will be coded as –1 day. All patients who never receive organ failure support will be coded as 22. Organ support is defined as mechanical ventilation, high flow nasal oxygen >30 L/min, or the use of vasopressors.** ***Rationale:*** *The ATTACC trial (OZM-113) has collaborated with ACTIV-IV and REMAP-CAP. As such, the enpoints have been adjusted to align within the studies.This will allow ATTACC, REMAP and ACTIV-IV to collectively answer this question and report the results as quickly as possible. As such, the statistical analysis section pertaining to the endpoint analysis required updating.*
Statistical Analysis Page 35 and 36 of 52	***From:*** Primary Analysis The primary analysis of the ordered categorical endpoint is a cumulative proportional odds model. Let the probability of an outcome of less than or equal to y be $= Pr(Y \leq y)$. Let t be the indicator of treatment arm (*t*=1 is control, *t*=2 is therapeutic anticoagulation). We model the ordinal outcomes using a proportional odds model. The model adjusts for the baseline D-dimer status of each patient and the effect for a treatment, as a function of the baseline status: $$\log\left(\frac{\pi_y}{1-\pi_y}\right) = \alpha_y + \beta_d\delta_{[d]} + \theta_d\delta_{[t=2]}\,;\; y = 1,2$$ The additive effects constant across both treatment groups as a function of the baseline subgroup for each patient are modeled through the β parameters. The parameter $\delta_{[t=2]}$ is an indicator function for the patient in the therapeutic anticoagulation treatment group and $\delta_{[t=2]}$ is an indicator function for the baseline D-dimer subgroup. The baseline risks for each group are modeled with independent weak prior distributions with the low D-dimer group the referent population: , $\beta_1 \equiv 0$. $\beta_d \sim N(0,10^2), d = 2,3$ The treatment effect of therapeutic anticoagulation within subgroup *d*, θ_d, represents the cumulative log-odds-ratio effect, where

the odds-ratio, $\mathrm{OR_d} = \exp(\theta_d)$. If the odds-ratio is greater than 1 then the treatment of therapeutic anticoagulation improves outcomes in the subgroup by increasing the probability of smaller outcomes (better).

The prior distributions for the control rates of each of the three ordinal classifications are modeled with weak prior distributions as . $\alpha_j \sim N(0,10), j = 1,2,; \alpha_1 < \alpha_2$

A Bayesian hierarchical model is used for the three treatment effects within the subgroups:

, $\theta_d \sim N(\mu, \tau^2)$

$\mu \sim N(0,10)$

$\tau^2 \sim IG(0.125,0.00281)$

The prior distribution on the variance of the therapeutic anticoagulation effects is an inverse-gamma distribution with a relative weight of 0.25 observations of an estimated $\tau = 0.15$.

The posterior distributions of the therapeutic anticoagulation effect in each of the subgroups, $\theta_1, \theta_2, \theta_3$ are used for response adaptive randomization and decision making in the trial.

At the completion of the trial the posterior mean, median, and 95% credible intervals for each odds-ratio will be summarized.

To:
Primary Analysis

~~The primary analysis of the ordered categorical endpoint is a cumulative proportional odds model. Let the probability of an outcome of less than or equal to y be $= Pr(Y \leq y)$. Let t be the indicator of treatment arm (t=1 is control, t=2 is therapeutic anticoagulation). We model the ordinal outcomes using a proportional odds model. The model adjusts for the baseline D-dimer status of each patient and the effect for a treatment, as a function of the baseline status:~~

~~$\log\left(\frac{\pi_y}{1-\pi_y}\right) = \alpha_y + \beta_d \delta_{[d]} + \theta_d \delta_{[t=2]}; y = 1,2$~~

~~The additive effects constant across both treatment groups as a function of the baseline subgroup for each patient are modeled through the =paramters The parameter ——— is an indicator function for the patient in the therapeutic anticoagulation treatment~~

group and $\delta_{[t=2]}$ is an indicator function for the baseline D-dimer subgroup. The baseline risks for each group are modeled with independent weak prior distributions with the low D-dimer group the referent population:

$\beta_1 = 0$,

$\beta_d \sim N(0, 10^2), d = 2,3$

The treatment effect of therapeutic anticoagulation within subgroup d, θ_d, represents the cumulative log-odds-ratio effect, where the odds-ratio, $\mathrm{OR}_d = \exp(\theta_d)$. If the odds-ratio is greater than 1 then the treatment of therapeutic anticoagulation improves outcomes in the subgroup by increasing the probability of smaller outcomes (better).

The prior distributions for the control rates of each of the three ordinal classifications are modeled with weak prior distributions as

$\alpha_j \sim N(0, 10), j = 1,2,; \alpha_1 < \alpha_2$

A Bayesian hierarchical model is used for the three treatment effects within the subgroups:

$\theta_d \sim N(\mu, \tau^2)$

$\mu \sim N(0, 10)$

$\tau^2 \sim IG(0.125, 0.00281)$

The prior distribution on the variance of the therapeutic anticoagulation effects is an inverse-gamma distribution with a relative weight of 0.25 observations of an estimated $\tau = 0.15$.

The posterior distributions of the therapeutic anticoagulation effect in each of the subgroups, $\theta_1, \theta_2, \theta_3$ are used for response adaptive randomization and decision making in the trial.

At the completion of the trial the posterior mean, median, and 95% credible intervals for each odds-ratio will be summarized

Let $Y_i = \{-1, 0, 1, \ldots, 21, 22\}$ denote the ordinal outcome (OSFD) for patient i. The probability of patient i observing y OSFD or less is denoted as $\pi_{iy} = \Pr(Y_i \leq y)$. The model is a proportional odds model, where the log odds-ratio parameters in the model are structured so that a value > 0 implies treatment benefit, and an odds-ratio > 1 implies treatment benefit. The primary analysis model is formulated as follows:

	$$\log\left(\frac{\pi_{iy}}{1-\pi_{iy}}\right) = \alpha_{y,s} - [\gamma_P + \nu_{Site,s} + \lambda_{Time,s} + \theta_{a,s:d} + \beta_{Age,s} + \beta_{Sex,s} + \beta_d]$$ **1. Each "platform." *P*, has a covariate adjustment in the model. *P*=1 is REMAP-CAP, *P*=2 is ATTACC, and *P*=3 is ACTIV.** **2. The "site" variable is the clinical site within the trial. These will be set as distinct sites across all three trials. The site effects are estimated separately within the severe and moderate disease states, but do not vary by d-dimer level.** **3. The "time" variable is an indicator of the time epoch in which a patient was enrolled in the trial, numbered increasing from the first most recent epoch to the earliest time for the analysis. Time epochs are two-week time periods. Time=1, and then every 2-week epoch, moving back in time throughout the enrollment in the trial. Time=2,3,4,…. The time effects are modeled separately within the severe and moderate disease states, but do not vary by d-dimer level.** **4. The "arm" to which a patient is randomized is labeled as *a* where *a*=1 is the control and *a*=2 is the treatment arm. The effects of arm vary by the disease state and the d-dimer level. The treatment effects for arm *a* within subtype *s*:*d* are modeled with the $\theta_{a,s:d}$ parameters.** **5. The "age" variable is a categorical classification of age as ≤ 39, 40-49, 50-59, 60-69, 70-79, and 80+. The age effects will be estimated separately within the moderate and severe disease states, but do not vary by d-dimer level.** **6. The "sex" variable is sex at birth. The sex effects will be estimated separately within the moderate and severe disease states, but do not vary by d-dimer level.** **7. The additive effects of d-dimer levels are modeled with the β_d for d = 0, 1, 2, 3.** **8. The $\alpha_{y,s}$ parameters determine the baseline rates of the ordinal outcome, which are modeled separately by disease state but not d-dimer level.** ***Rationale:*** *The ATTACC trial (OZM-113) has collaborated with ACTIV-IV and REMAP-CAP. As such, the enpoints have been adjusted to align within the studies.This will allow ATTACC, REMAP and ACTIV-IV to collectively answer this question and report the results as quickly as possible.As such, the statistical analysis section pertaining to the endpoint analysis required updating.*
Statistical Analysis Page 36 of 52	***From:*** Adaptive Design The trial design is adaptive. A sequence of frequent interim analyses will be conducted as a function of enrollment rate. The anticipation is to conduct interim analyses every 2 weeks which may then be relaxed as the enrollment grows. The target wouldbe to enroll 100 patients between interims. At each interim analysis the trial could reach a trial conclusion within any of the subgroups which would stop randomization in that subgroup in favor of the control (standard of care) or therapeutic anticoagulation. If no conclusion within a subgroup is reached and randomization continues the randomization probabilities will be set based on a response adaptive randomization algorithm

	distinctly within the subgroup. ***To:*** Adaptive Design The trial design is adaptive. A sequence of frequent interim analyses will be conducted as a function of enrollment rate. The anticipation is to conduct interim analyses ~~every 2 weeks which may then be relaxed as the enrollment grows. The target wouldbe to enroll 100 patients between interims.~~ **on the 1st day of each month.** **In the multiplatform analysis that includes data from ATTACC, e~~E~~ach rule is separately evaluated within the three subtypes: moderate state; low d-dimer, moderate state; high d-dimer, and severe state.** At each interim analysis the trial could reach a trial conclusion within any of the subgroups which would stop randomization in that subgroup in favor of the control (standard of care) or therapeutic anticoagulation. If no conclusion within a subgroup is reached and randomization continues the randomization probabilities will be set based on a response adaptive randomization algorithm distinctly within the subgroup. **At this time, only ATTACC is utilizing responsive adaptive randomization based on probability of treatment successes within a subgroup of d-dimer (moderate state) or within the severe state.** ***Rationale:*** *The ATTACC trial (OZM-113) has collaborated with ACTIV-IV and REMAP-CAP. As such, the enpoints have been adjusted to align within the studies.This will allow ATTACC, REMAP and ACTIV-IV to collectively answer this question and report the results as quickly as possible.As such, the statistical analysis section pertaining to the endpoint analysis required updating.*
Statistical Analysis Page 36 and 37 of 52	***From:*** Subgroup Conclusions A subgroup may stop for superiority of therapeutic anticoagulation . This conclusion would be reached at any interim analysis in which the probability that therapeutic anticoagulation is more effective than control in the subgroups is 99% or greater. That is a subgroup will stop for superiority of Heparin if: $\Pr(OR_d > 1) \geq 0.99, d = 1,2,3$ Likewise, a claim of superiority will be made at the conclusion of the trial within a subgroup if the posterior probability of superiority is at least 99%. The trial may stop for futility of therapeutic anticoagulation. If the probability of at least a 20% improvement in the odds-ratio (OR > 1.2) is less than 10% then the trial will stop for futility. That is a subgroup will stop for futility of therapeutic anticoagulation if $\Pr(OR > 1.2) < 0.10$ If randomization continues in a subgroup then response adaptive randomization is utilized. The probability for each of the two arms within a subgroup will be set based on the probability that each arm is the best arm in that subgroup. The randomization for each arm is the probability that arm is the superior arm, truncated at a maximum of 90% for any one arm (minimum of 10% for an arm). That is the randomization probability for therapeutic anticoagulation within each subgroup is $\Pr(OR_d > 1)$ but truncated at 0.10 below and 0.90 above. The trial will continue as long as there are subgroups that have not reached a conclusion.

	To: Subgroup Conclusions A subgroup may stop for superiority of therapeutic anticoagulation . This conclusion would be reached at any interim analysis in which the probability that therapeutic anticoagulation is more effective (OR > 1.5) than control in the subgroups is 99% or greater. That is a subgroup will stop for superiority of ~~Heparin~~ **therapeutic anticoagulation** if: ~~$\Pr(OR_d > 1) \geq 0.99, d = 1,2,3$~~ ~~Likewise, a claim of superiority will be made at the conclusion of the trial within a subgroup if the posterior probability of superiority is at least 99%.~~ The trial may stop for futility of therapeutic anticoagulation. If the probability of at least a 20% improvement in the odds-ratio (OR > 1.2) is less than 10% then the trial will stop for futility. ~~That is a subgroup will stop for futility of therapeutic anticoagulation if~~ ~~$\Pr(OR > 1.2) < 0.10$~~ ~~If randomization continues in a subgroup then response adaptive randomization is utilized. The probability for each of the two arms within a subgroup will be set based on the probability that each arm is the best arm in that subgroup. The randomization for each arm is the probability that arm is the superior arm, truncated at a maximum of 90% for any one arm (minimum of 10% for an arm).~~ ~~That is the randomization probability for therapeutic anticoagulation within each subgroup is $\Pr(OR_d > 1)$ but truncated at0.10 below and 0.90 above.~~ The trial will continue as long as there are subgroups that have not reached a conclusion. ***Rationale:*** *The ATTACC trial (OZM-113) has collaborated with ACTIV-IV and REMAP-CAP. As such, the enpoints have been adjusted to align within the studies.This will allow ATTACC, REMAP and ACTIV-IV to collectively answer this question and report the results as quickly as possible. As such, the statistical analysis section pertaining to the endpoint analysis required updating.*
Statistical Analysis Page 37 and 38 of 52	***Deleted:*** ~~**Clinical Trial Simulations**~~ ~~This section describes the clinical trial simulations to understand the power for the primary analysis within each subgroup. Two different assumptions are made for the potential distribution of outcomes in the three ordinal categories. We label these as mild and severe rates. The assumptions for control are:~~ ~~Table 1: The assumed scenarios (Mild, Severe) for the control rates~~ ~~For each of the scenarios an effect size is assumed for the treatment arm, therapeutic anticoagulation. The scenarios for the odds ratio are~~

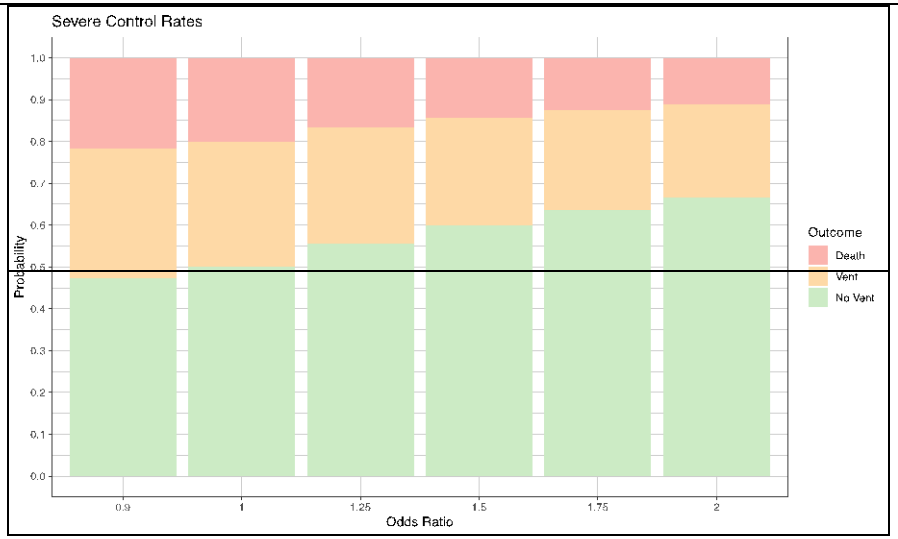
~~Outcome~~	~~Control Scenario~~	
	~~Mild~~	~~Severe~~
~~No Ventilation~~	~~0.75~~	~~0.50~~
~~Mechanical Ventilation~~	~~0.125~~	~~0.30~~
~~Death~~	~~0.125~~	~~0.20~~

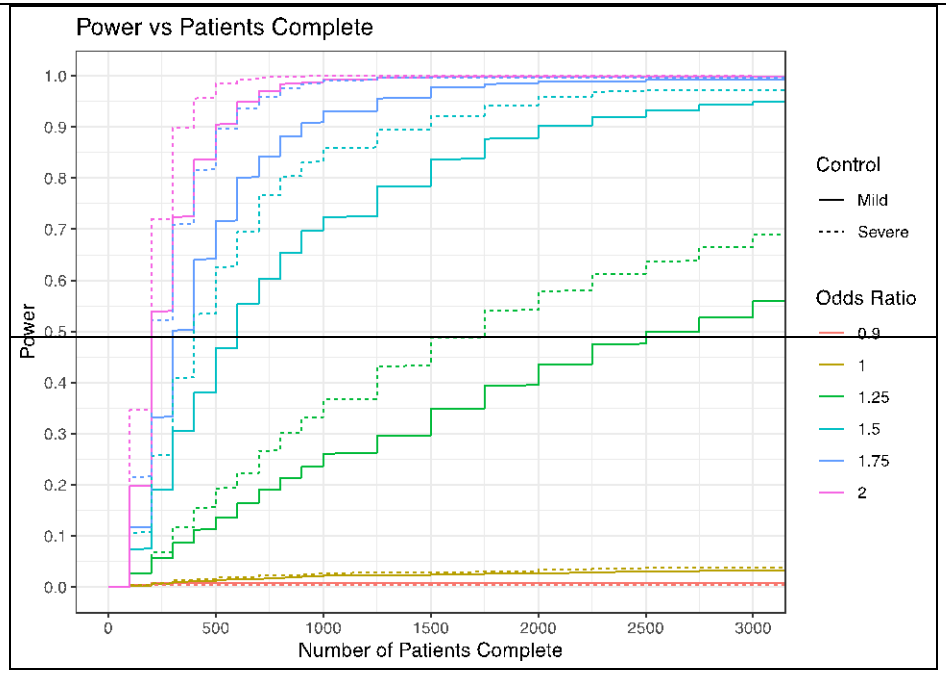
Treatment Effects	Odds-Ratio For therapeutic anticoagulation
Harm	0.90
Null Effect	1
25% improvement	1.25
50% Improvement	1.50
75% Improvement	1.75
100% Improvement	2.0

Table 2: The range of effect sizes for therapeutic anticoagulation simulated.

Figure 1 shows the distribution of outcomes for each of the assumed effects for the Mild Scenario and Figure 2 shows thedistribution for the Severe Scenario.

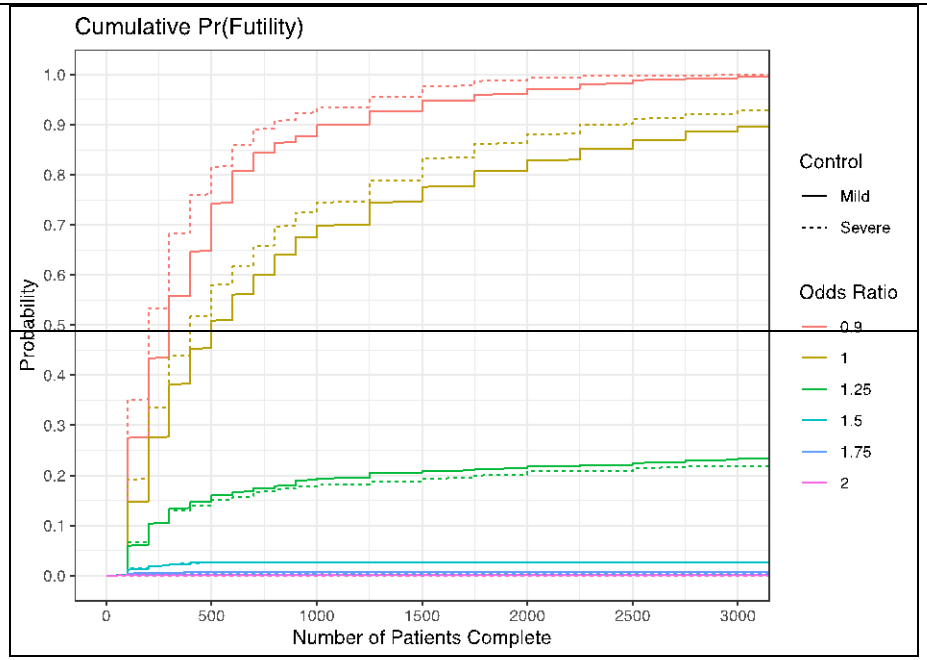
Figure 1: The distribution of outcomes for each treatment effect (OR) for the Mild Scenario

	 ~~Figure 2: The distribution of outcomes for each treatment effect (OR) for the Mild Scenario~~ ***Rationale:*** *Removed to avoid inclusion of unnecessary information in the protocol.*
Statistical Analysis Page 39 and 40 of 52	***Deleted:*** ~~Simulation Results~~ ~~For each scenario and effect size 1000 simulated trials are conducted. For the simulations interim analyses are conducted at 100, 200, …, 1000, 1250, 1500, …, 3000. The results are robust to the number and timing of the interims. Figure 3 shows the probability of concluding superiority for therapeutic anticoagulation within a subgroup as a function of the total number of subjects enrolled for each scenario and effect size. The simulations are done individually within the subgroups and not jointly across the subgroups using the Bayesian Modeling.~~



~~Figure 3: The cumulative probability of concluding superiority for the heparin arm as function of the scenario, treatment effect, and sample size.~~

~~If therapeutic anticoagulation has a strong effect of an OR=2, then 80% of trials reach superiority by the 300 (severe) and 400 (mild) analysis and has 90% power for 400 (severe) and 500 (mild). The trial has less than 5% cumulative type I error if therapeutic anticoagulation and the control arm equal (no effect). If therapeutic anticoagulation is slightly harmful there is virtually no chance of success. The effect size of 1.25 would be underpowered for the trial with approximately 50% of trials reaching superiority by 3000 patients. This is deemed appropriate as this is a small effect size.~~
~~Figure 4 presents the probability of reaching the conclusion of futility for the therapeutic anticoagulation arm as a function of the total number of subjects enrolled for each scenario and effect size.~~



~~Figure 4: The cumulative probability of concluding superiority for the therapeutic anticoagulation arm as function of the scenario, treatment effect, and sample size.~~

~~If therapeutic anticoagulation is slightly harmful (OR=0.90) there is an 80% chance of triggering futility by 500 patients in the trial. For a null effect (no difference for control or therapeutic anticoagulation) the probability of futility is 80% by 1500 (Severe) and 1750 (Mild). If the effect of therapeutic anticoagulation is small (OR=1.25) then approximately 20% of trial will reach a futile conclusion. It's very rare for any trials to reach futility for effect sizes of 1.5 or greater.~~

Rationale: *Removed to avoid inclusion of unncessary information in the protocol.*

Record Access and Maintenance of Study Records Page 43 of 52	***From:*** For participating U.S.A centres: • All Investigators must complete and sign FDA Form 1572. The completed forms must be returned to Ozmosis Research Inc. prior to site activation. (If FDA exemption is not granted) • All Investigators must complete and submit a Financial Disclosure Statement (If FDA exemption is not granted) • All Investigators must also submit to Ozmosis Research Inc. an up-to-date (current to within 2 years of the study start) curriculum vitae. • Laboratory certification / accreditation and normal ranges for local lab(s). • Consent forms, reviewed by Ozmosis Research Inc. before submission to the local IRB. • A completed site delegation list. • A copy of the initial full board approval letter from the local IRB. Continuing approval (full board) will be obtained at least yearly until follow-up on patients is completed and no further data is being obtained for research purpose. ***To:*** For participating U.S.A centres: • ~~All Investigators must complete and sign FDA Form 1572. The completed forms must be returned to Ozmosis Research Inc. prior to site activation. (If FDA exemption is not granted)~~ • ~~All Investigators must complete and submit a Financial Disclosure Statement (If FDA exemption is not granted)~~ • **This study is IND exempt.** • All Investigators must also submit to Ozmosis Research Inc. an up-to-date (current to within 2 years of the study start) curriculum vitae. • Laboratory certification / accreditation and normal ranges for local lab(s). • Consent forms, reviewed by Ozmosis Research Inc. before submission to the local IRB. • A completed site delegation list. • A copy of the initial full board approval letter from the local IRB. Continuing approval (full board) will be obtained at least yearly until follow-up on patients is completed and no further data is being obtained for research purpose. ***Rationale:*** *This study is IND exempt, therefore the FDA Form 1573 and Financial Discolure Statements are not required for U.S. sites.*

Record Access and Maintenance of Study Records Page 45 of 52	***From:*** Maintenance of Study Records To enable evaluations and/or audits from Regulatory Authorities, Ozmosis Research or the Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, source documents, and detailed records of treatment disposition. The Investigator should retain these records for 25 years after study close-out as required by Canadian regulations. ***To:*** Maintenance of Study Records To enable evaluations and/or audits from Regulatory Authorities, Ozmosis Research or the Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, source documents, and detailed records of treatment disposition. The Investigator should retain these records for ~~25 years after study close-out as~~ **the duration of time** required by ~~Canadian regulations~~the **applicable regulatory body.** ***Rationale:*** *As this protocol is used across a number of different countries, this wording has been updated to state the site level study records should be maintained per the local regulatory body requirements.*
Quality Assurance and Quality Control Page 46 of 52	***From:*** Monitoring/Auditing Ozmosis Research will organize monitoring of this study to be conducted as per Monitoring Plan. This may involve remote monitoring if it is not feasible to monitor on-site due to hospital restrictions during this pandemic. ***To:*** Monitoring/Auditing Ozmosis Research will organize monitoring of this study to be conducted as per Monitoring Plan~~.~~ **, which may include delegating monitoring responsibilities to other research organizations.** This may involve remote monitoring if it is not feasible to monitor on-site due to hospital restrictions during this pandemic. ***Rationale:*** *Wording updated because other CRO's/ARO's will be conducting monitoring for study sites in other countries.*

<table>
<tr><td>Appendix B – KDIGO Criteria for Acute Kidney Injury</td><td>Added:

<u>Acute kidney injury after enrollment is defined by KDIGO criteria for Acute Kidney Injury in the setting of not meeting these criteria upon enrollment:</u>

<u>Three Stages:</u>

<u>Stage 1: Serum Cr 1.5-1.9 times baseline, OR ≥ mg/dl increase in serum Cr</u>
<u>Stage 2: Serum Cr 2.0-2.9 times baseline</u>
<u>Stage 3: Serum Cr ≥ 3.0 times baseline, OR increase in serum creatinine to ≥ 4.0mg/dl, OR initiation of renal replacement therapy</u>

Rationale: KDIGO criteria is being used for one of the updated secondary enpoints, therefore the criteria has been added as an appendix.</td></tr>
<tr><td>Appendix C – WHO Ordinal Scale for Clinical Improvement</td><td>Added:

<u>(https://www.who.int/blueprint/priority-diseases/keyaction/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf)</u>

<table>
<tr><th>Patient State</th><th>Score</th><th>Descriptor</th></tr>
<tr><td>Uninfected</td><td>0</td><td>No clinical or virological evidence of infection</td></tr>
<tr><td rowspan="2">Ambulatory</td><td>1</td><td>No limitation of activities</td></tr>
<tr><td>2</td><td>Symptomatic: Limitation of activities</td></tr>
<tr><td rowspan="2">Hospitalized: Mild disease</td><td>3</td><td>Hospitalized; no oxygen therapy</td></tr>
<tr><td>4</td><td>Hospitalized; oxygen by mask or nasal prongs</td></tr>
<tr><td rowspan="3">Hospitalized: Severe disease</td><td>5</td><td>Non-invasive ventilation or high-flow oxygen</td></tr>
<tr><td>6</td><td>Intubation & Mechanical ventilation</td></tr>
<tr><td>7</td><td>Ventilation and additional organ support – pressors, RRT, ECMO</td></tr>
<tr><td>Death</td><td>8</td><td>Death</td></tr>
</table>

Rationale: WHO Ordinal Scale was added as a secondary objective, therefore the ordinal scale has been included as an appendix.</td></tr>
</table>

Study Schedule

Investigations	Pre-Treatment (Baseline)	Day1	Day3	Day7	Day 14	Day 21	Day 30	Day 90
Windows		+/- 3 days					+/- 3 days	+/- 7 days
Consent & Registration	X							
Demographics	X							
Medical History	X							
Weight	X							
SOC Vitals documented (SpO2 and FiO2, heart rate, blood pressure, respiratory rate, temperature)[1]	X	X	X	X	X			
Hematology bloodwork (SOC)[1]	X	X	X	X	X			
Biochemistry bloodwork (SOC)[1]	X	X	X	X	X			
Troponin (SOC)[1]	X	X	X	X	X			
D-dimer (SOC)[1]	X	X	X	X	X			
Anticoagulant Administration[2]		X[2]	X[2]	X[2]	X[2]			
Organ-free support outcome						X		
Primary and secondary outcomes[3, 4]		X						
Survival, DVT, PE, MI (by phone)[3]								X
Adverse events[5]		X						
Concomitant medications[5]		X						

Footnotes:

[1]as per routine standard of care, collected while on therapy (until discharge or up to 14d or recovery);record the “worst” value observed during internal since last assessment;

[2] Participants randomized to the investigational arm will receive therapeutic anticoagulation for 14 days (or until hospital discharge or liberation from supplemental oxygen >24 hours if previously required, whichever comes first) with heparin, with preference for subcutaneous low molecular weight heparin (enoxaparin preferred, although dalteparin or tinzaparin are also acceptable, as available) if no contraindication is present; alternatively, intravenous unfractionated heparin infusion may be used.
Participants randomized to the control arm will receive usual care, which is anticipated to include thromboprophylactic dose anticoagulation according to local practice.
For pregnant women, use of non-tinzaparin (Innohep) product is preferred. If tinzaparin is the only product available, then only pre-filled syringes (without benzyl alcohol) will be administered as per theproduct monograph.

[3]all post-discharge follow-up is telephone-/remote.

[4]Primary and secondary outcomes to be collected include:Primary outcome:

an ordered categorical endpoint with three possible outcomes based on the worst status of eachpatient through day 30 following randomization: no invasive mechanical ventilation, invasive mechanical ventilation, or death.

Secondary outcomes:
Laboratory confirmed Heparin induced thrombocytopenia (HIT)
Major bleeding, defined according to the International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) definitions and bleeding assessment tool in non-surgical patients (Schulman *J Thromb Haemost* 2005):
fatal bleeding; and/or
symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal,intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; and/or
bleeding causing a fall in hemoglobin level of ≥20 g/L, or leading to transfusion of 2 or more units of whole blood or red cells.
-Organ support-free days at day 21
-Intubation assessed at 30 days following randomization
-ICU-free days assessed at 30 days following randomization
-Use of non-invasive mechanical ventilation or high flow nasal cannula
-Ventilator free days (days alive not on a ventilator) assessed at 30 days following randomization
-Hospital-free days (days alive outside hospital assessed at 30 days following randomization)
-Symptomatic proximal venous thromboembolism (DVT or PE) assessed at 30 and 90 days following randomization
-Myocardial infarction assessed at 30 days and 90 days following randomization
-Ischaemic stroke assessed at day 30 and 90 days following randomization
-Mortality assessed at 30 and 90 days following randomization

[5]Treatment-related adverse events and concomitant medications assessed only while on therapy.

Version 3.1

Study Schedule

Investigations	Pre-Treatment (Baseline)[6]	Day 1	Day3	**Day5**	Day7	**Day 10**	Day 14	Day 21	Day0	Da 90
Windows	**-72 hours**	~~+/-~~ **-** 3 days							~~+/-~~ **+** **7**~~3~~ days	~~+/-~~ **+**7 da
Consent & **Randomization** ~~Registration~~	X									
Demographics	X									
Medical History	X									
Weight	X									
SOC Vitals documented (SpO2 and FiO2, heart rate, blood pressure, respiratory rate, temperature)[1]	X	X	X		X		X			
Hematology bloodwork (SOC)[1]	X	X	X	**X**	X	**X**	X			
Biochemistry bloodwork (SOC)[1]	X	X	X	**X**	X	**X**	X			

Troponin (SOC)[1]	X	X	X	**X**	X	**X**	X			
D-dimer[2]	**X**									
D-dimer (SOC)[1]	~~X~~	X	X		X		X			
Optional Biorepository (blood samples)	**X**	**X**	**X**		**X**		**X**			
Anticoagulant ~~Administration~~[2]**Administration**		~~X~~[2]**X** –								
Organ-free support outcome								X		
Primary and secondary outcomes[3,4]–		X								
Survival, DVT, PE, MI (by phone)[3]									X	X
WHO ordinal assessment										**X**
Adverse events[5]		X								
Concomitant medications[5]		X								

Footnotes:

[1]**A**~~a~~s per routine standard of care, collected while on therapy (until discharge or up to ~~14d or recovery); record the "worst" value observed during internal since last assessment;~~**day 14 or recovery). Record the values closest to the day of the assessment. Values from - 3 days may be used provided the values are temporally after the previous assessment. If more than 1 value exists, the value closestto the day of study assessment will be used. Exceptions to this rule: troponin (collect highest troponin since last assessment), hemoglobin (collect lowest hemoglobin since last study assessment) and creatinine (collect highest creatinine since last study visit).**

~~[2] Participants randomized to the investigational arm will receive therapeutic anticoagulation for 14 days (or until hospital discharge or liberation from supplemental oxygen >24 hours if previously required, whichever comes first) with heparin, with preference for subcutaneous low molecular weight heparin (enoxaparin preferred, although dalteparin or tinzaparin are also acceptable, as available) if no contraindication is present; alternatively, intravenous unfractionated heparin infusion may be used.~~

~~Participants randomized to the control arm will receive usual care, which is anticipated to include thromboprophylactic dose anticoagulation according to local practice.~~

For pregnant women, use of non-tinzaparin (Innohep) product is preferred. If tinzaparin is the only product available, then only pre-filled syringes (without benzyl alcohol) will be administeredas per the product monograph.

[2]D-dimer is to be collected at baseline for all patients. This is part of the current standard of care at most institutions, but where it is not, it will be collected as part of the trial protocol at baseline. If possible, it should be reported (i.e., a result available) prior to randomization, so that participants may benefit from response-adaptive randomization; however, patients are still able tobe randomized if the D-dimer result is not available prior to randomization, in which case randomization will proceed 1:1. Nonetheless, a level is required to be drawn at baseline in all cases if one is not already available within 72 hours of randomization. If there is a site that is not able to collect D-dimer for all patients at baseline, this will be discussed with the sponsor on a case-by-case basis.

[3]**A**~~a~~ll post-discharge follow-up is telephone-/remote.

[4] **Refer to 'THE TRIAL' section for a list of study outcomes** ~~**Primary** and secondary outcomes to be collected include:~~

~~Primary outcome:~~
~~an ordered categorical endpoint with three possible outcomes based on the worst status of eachpatient through day 30 following randomization: no invasive mechanical ventilation, invasive mechanical ventilation, or death.~~

~~Secondary outcomes:~~
~~Laboratory confirmed Heparin induced thrombocytopenia (HIT)~~
~~Major bleeding, defined according to the International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) definitions and bleedingassessment tool in non-surgical patients (Schulman *J Thromb Haemost* 2005):~~
~~fatal bleeding; and/or~~
~~symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal,intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; and/or~~
~~bleeding causing a fall in hemoglobin level of ≥20 g/L, or leading to transfusion of 2 or more units of whole blood or red cells.~~
~~Organ support-free days at day 21~~
~~Intubation assessed at 30 days following randomization ICU-free days assessed at 30 days following randomization~~
~~Use of non-invasive mechanical ventilation or high flow nasal cannula~~
~~Ventilator free days (days alive not on a ventilator) assessed at 30 days following randomizationHospital-free days (days alive outside hospital assessed at 30 days following randomization) Symptomatic proximal venous thromboembolism (DVT or PE) assessed at 30 and 90 days following randomization~~
~~Myocardial infarction assessed at 30 days and 90 days following randomizationIschaemic stroke assessed at day 30 and 90 days following randomization Mortality assessed at 30 and 90 days following randomization~~

[5]Treatment-related adverse events ~~and concomitant medications~~ are assessed only while ontherapy.
Concomitant medications are assessed from the time of consent and for the duration of therapy.

[6]The laboratory values closest to randomization should be recorded. Values up to 72 hours prior to randomization can be used for baseline values if the test is not available atthe time of randomization and can not be repeated.

Rationale:
- *Window added at baseline to provide further guidance for sites, as this was not previously indicated*
- *Windows for Day 1 to Day 90 were updated to enhance consistency of data collection*
- *D-dimer is now a required assessment for this study at baseline (line added to study calendar and explained in Footnote #2). The D-dimer results are used to inform the response adaptive randomization and since the study has progressed, the sponsor observed a number of sites for which collection of D-dimer at hospital admission is not SOC, therefore the sponsor has decided to mandate the collection of D-dimer at baseline.*
- *The original Footnote #2 was removed to avoid repetition. This information is provided in the Anticoagulation Administration section which is right above the study calendar in the protocol.*
- *Optional biorepository was added as a line to the calendar to inform sites of the timing of sample collection.*

- WHO ordinal assessment was added because it was added as a secondary endpoint.
- Footnote #4 was adjusted to avoid unnecessary repetition.
- Footnote #5 was adjusted to better align with the instructions in the body of the protocol.
- Footnote #6 was added to provide instructions to sites regarding the values to record for baseline.

Protocol 3: A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19 (ACTIV-4 Acute)

A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19

Short Title: ACTIV-4 ACUTE (AC-INPT)

ClinicalTrials.gov Number: NCT04505774

Supported by:

National Heart Lung and Blood Institutes (NHLBI), National Institute of Neurological Disorders (NINDS), ACTIV (ACTIV IV), National Institutes of Health (NIH), Biomedical Advanced Research and Development Authority (BARDA), Operation Warp Speed (OWS),

U.S. Department of Health & Human Services (HHS)

Version Number: 1.0

21AUG2020

Trial Chair	Judith Hochman, MD Harold Snyder Family Professor & Associate Director of Cardiology Senior Associate Dean for Clinical Sciences Co-Director, NYU-HHC Clinical and Translational Science Institute NYU School of Medicine 530 First Avenue, Skirball 9R New York, NY 10016 Tel 212-263-6927 Email: judith.hochman@nyumc.org
Coordinating Center	Stephen Wisniewski, PhD Professor of Epidemiology Vice Provost for Budget and Analytics University of Pittsburgh Email: STEVEWIS@pitt.edu Matthew Neal, MD Roberta G. Simmons Assistant Professor of Surgery Attending Surgeon, Division of Trauma and Acute Care Surgery Assistant Professor of Clinical and Translational Science and Critical Care Medicine Departments of Surgery, Critical Care Medicine, and the Clinical and Translational Science Institute (CTSI), University of Pittsburgh University of Pittsburgh Medical Center F1271.2 PUH 200 Lothrop Street Pittsburgh, PA 15213 Tel: 412-647-1158 Fax: 412-647-1448 Email: nealm2@upmc.edu
Trial Biostatisticians	Scott Berry, PhD President, Senior Statistical Scientist Berry Consultants Tel 979-575-6280 Email scott@berryconsultants.com Eric Leifer, PhD NHLBI leifere@nhlbi.nih.gov << >>
NHLBI Representative	Andrei Kindzelski, MD kindzleskial@nhlbi.nih.gov
HHS Representative	Rachel Harrigan Rachel.Harrigan@hhs.gov
IND	Waiver
ClinicalTrials.gov Identifier	NCT04505774

Statement of Compliance

In the United States this study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") and the General Data Protection Regulations (GDPR) will be applied only to the extent that it is compatible with FDA and DHHS regulations.

Outside of the United States this study will be conducted according to local legal and regulatory requirements and regulations, ICH guidelines, and GDPR guidelines as applicable.

The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations (if applicable), and ICH E6(R2) GCP guidelines.

Version Date: Aug. 2020

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

_____

Name of Facility

_____

Location of Facility (City, Country)

Table of Contents

List of Abbreviations

AE	Adverse Event/Adverse Experience
ARDS	Acute Respiratory Distress Syndrome.
AT	Arterial Thrombosis
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CrCl	Creatinine Clearance
COVID-19	Coronavirus Disease
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DIC	Disseminated Intravascular Coagulation
DSMB	Data and Safety Monitoring Board
DVT	Deep Vein Thrombosis
ECMO	Extracorporeal Membrane Oxygenation
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
FFR	Federal Financial Report
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GI	Gastrointestinal
HFNO	High-flow (≥30L/min) Nasal Oxygen
HIPAA	Health Insurance Portability and Accountability Act
HIT	Heparin Induced Thrombocytopenia
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent to Treat
KDIGO	Kidney Disease Improving Global Outcomes
LAR	Legally Authorized Representative

LOS	Length of Stay
MI	Myocardial Infarction
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
NIV	Non-invasive ventilation
OHRP	Office for Human Research Protections
OHSR	Office of Human Participants Research
OSFD	Organ Support Free Days
PE	Pulmonary Embolism
PI	Principal Investigator
PRBC	Packed Red Blood Cells
PTT	Partial Thromboplastin Time
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
sICH	Symptomatic Intracranial or Intracerebral Hemorrhage
SOC	Standard of Care
SOP	Standard Operating Procedure
US	United States
VTE	Venous thromboembolism
WHO	World Health Organization

Master Protocol Summary

Title	A Multicenter, Adaptive, Randomized, Open Label Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19
Short Title	ACTIV-4 ACUTE
Brief Summary	This is a randomized, open label, adaptive platform trial to compare the effectiveness of antithrombotic strategies for prevention of adverse outcomes in COVID-19 positive inpatients
Objectives	**1.** To determine the most effective antithrombotic strategy for increasing the number of days free of organ support and reducing death. **2.** To determine the most effective antithrombotic strategy on the composite endpoint of death, deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), ischemic stroke, or other systemic arterial thrombosis (AT). **3.** To assess the safety of antithrombotic strategies through the endpoint of major bleeding as defined by ISTH. **4.** To compare the effect of antithrombotic strategies on the endpoint of all-cause mortality in the study population. Assessment of efficacy and safety will yield information of the net clinical benefit of different antithrombotic strategies in the study population. It will also yield information on outcomes specific to under- represented minority populations, specifically African- and Hispanic-descent persons.
Methodology	Adaptive Randomized Platform Trial

Endpoints	Primary Endpoint: 21 Day Organ Support Free Days, which is defined as the number of days that a patient is alive and free of organ support through the first 21 days after trial entry. Organ Support is defined as receipt of invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, or ECMO support, with death at any time (including beyond 21 days) during the index hospitalization assigned -1 days. Key Secondary Endpoint: Composite endpoint of death, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke at hospital discharge or 28 days, whichever occurs first. Other Secondary Endpoints: Composite endpoint of death, deep vein thrombosis, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke at hospital discharge or 28 days, whichever occurs first. Acute kidney injury defined by KDIGO criteria, Individual endpoints comprising the key secondary endpoint, death during hospitalization, 28 Day Ventilator-Free Days, 28 Day Vasopressor Free Days, 28 Day Renal Replacement Free Days, WHO clinical scale, 28 Day Hospital Free Days, 28 day organ support free days, and all-cause mortality at 90 days. Primary Safety Endpoint: Major bleeding (as defined by the ISTH) Secondary Safety Endpoint: Confirmed heparin induced thrombocytopenia (HIT)
Study Duration	Approximately 1 year
Participant Duration	Hospital duration with periodic contact at post-discharge, including at 90 days, with potential contact up to 1 year
Duration of assigned treatment strategy	During hospitalization (unless otherwise specified in description of arm)
Population	Adult patients hospitalized for COVID-19
Study Sites	Approximately 400 sites
Number of participants	The sample size is described in each arm-specific appendix.
Description of Study Agents	Randomized arms- see appendix This platform trial allows for multiple therapies to be investigated in this trial over time. The trial is governed by a Master Protocol that describes the trial design, endpoint collection, primary endpoint, and inclusion/exclusion criteria. Different therapies, referred to as arms, are detailed in arm-specific appendices. These arm-specific appendices work in a modular fashion as arms are removed and added to the platform trial.
Key Procedures	Observation during hospitalization, contact at 90 days post-enrollment, and collection of standard of care laboratory results. Ancillary biobanking will be completed in consenting patients at capable centers.

Statistical Analysis	Inferences in this trial are based on a Bayesian statistical model, which considers the variation in outcomes by site, disease state, time, and arm of the trial. The specific analyses for each arm, including interim analysis schedule, are specified in each arm-specific appendix.

1 Introduction, Background Information and Scientific Rationale

1.1 *Background Information, Significance and Relevant Literature*

The severe acute respiratory syndrome coronavirus 2, which causes the highly contagious coronavirus disease 2019 (COVID-19), has resulted in a global pandemic.

The clinical spectrum of COVID-19 infection is broad, encompassing asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure and death. The risk of thrombotic complications is increased, even as compared to other viral respiratory illnesses, such as influenza (1-4). A pro-inflammatory cytokine response as well as induction of procoagulant factors associated with COVID-19 has been proposed to contribute to thrombosis as well as plaque rupture through local inflammation (5). Patients with COVID-19 are at increased risk for arterial and vein thromboembolism(6), with high rates observed despite thromboprophylaxis (7). Autopsy reports have noted micro and macro vascular thrombosis across multiple organ beds consistent with an early hypercoagulable state (8).

Notably, in COVID-19, data in the U.K. and U.S. document that infection and outcomes of infection are worse in African and Hispanic descent persons than in other groups. The reasons for this are uncertain.

Viral Infection and Thrombosis

A large body of literature links inflammation and coagulation; altered hemostasis is a known complication of respiratory viral infections (9-11). Procoagulant markers are severely elevated in viral infections. Specifically, proinflammatory cytokines in viral infections upregulate expression of tissue factor, markers of thrombin generation, platelet activation, and down-regulate natural anticoagulant proteins C and S (11).

Studies have demonstrated significant risk of deep venous thrombosis (DVT), pulmonary embolism (PE), and myocardial infarction (MI) associated with viral respiratory infections (10,12). In a series of patients with fatal influenza H1N1, 75% had pulmonary thrombi on autopsy (a rate considerably higher than reported on autopsy studies among the general intensive care unit population (13).
Incidence ratio for acute myocardial infarction in the context of Influenza A is over 10 (14). Severe acute respiratory syndrome coronavirus-1 (SARS CoV-1) and influenza have been associated with disseminated intravascular coagulation (DIC), endothelial damage, DVT, PE, and large artery ischemic stroke (11,15). Obi et al. found that patients with Influenza H1N1 and acute respiratory distress syndrome (ARDS) had a 23.3-fold higher risk for pulmonary embolism, and a 17.9-fold increased risk for deep vein thrombosis (16). Compared to those treated with systemic anticoagulation, those without treatment were 33 times more likely to suffer a VTE (16).

Thrombosis, both microvascular and macrovascular, is a prominent feature in multiple organs at autopsy in fatal cases of COVID-19 (8). Thrombosis may thus contribute to respiratory failure, renal failure, and hepatic injury in COVID-19. The number of megakaryocytes in tissues is higher than in other forms of ARDS, and thrombi are platelet-rich based on specific staining. Thrombotic stroke has been reported in young COVID-19 patients with no cardiovascular risk factors (17). Both arterial and venous thrombotic events have been seen in increasing numbers of hospitalized patients infected with COVID-19. The incidence of thrombosis has ranged from 10 to 30% in hospitalized patients; however, this varies by type of thrombosis captured (arterial or vein) and severity of illness (ICU level care, requiring mechanical ventilation, etc.).

D-dimer, a biomarker of fibrin formation and degradation, is elevated in conditions associated with thrombosis, and has been strongly associated with increased mortality among patients with COVID- 19 (1, 2, 3, 6, 7). In a retrospective analysis of 191 patients with COVID-19, Zhou et al. found that non-survivors were more likely to have D-dimer levels > 1 ug/mL than survivors (81% v 24%) (1).
Similarly, in a study of 183 patients, Tang et al. noted that non-survivors had significantly higher D- dimer values on admission than survivors (2.12 v 0.61 ug/mL, P < 0.001) (2). In a retrospective study, patients with COVID-19 and D-dimer values > 6-fold upper limit of normal had lower 28-day mortality when treated with prophylactic anticoagulation compared with no anticoagulation (32.8% v 52.4%, p=0.017) (8). Data suggest a strong association between D-dimer and the outcomes of ICU intubation and all-cause mortality, and the association between D-dimer and (1) mortality, (2) critical illness, (3) acute kidney injury, and (4) thrombotic risk is increased at a D-dimer between 1X to 2X the upper limit of normal. Thrombosis is also increased in those with elevated inflammation indexed by C-reactive protein level (20). Preliminary data suggest that platelet activity is increased in COVID-19(18) and that biomarkers of platelet activity correlate with the incidence of death or thrombosis in hospitalized patients with COVID-19. Platelet-fibrin thrombi have been observed in alveolar capillaries, where they may affect gas exchange (8), and in the renal peri-tubular capillaries, where they may contribute to acute tubular necrosis and renal dysfunction. Consistently, autopsy findings demonstrate an increase in the number of circulating megakaryocytes outside the bone marrow and lung. Finally, thrombotic events have been noted – even among patients treated with full dose anticoagulation.

There may be racial and ethnic differences in response to COVID 19 infection. It is hypothesized that antithrombotic interventions being tested will benefit all patients, including those who are disproportionately affected. (21–25, 26).

The ACTIV-4 ACUTE investigators postulate that an antithrombotic regimen will improve clinical outcomes in COVID-19 patients. This protocol intends to define the optimal regimen in an adaptive randomized trial of patients hospitalized with COVID-19 at risk for adverse clinical outcomes. The primary outcome will be the number of days free of organ support within 21 days after randomization. This primary outcome was selected because thrombosis is thought to contribute to the pathogenesis of multi-organ failure in COVID-19, because it is pragmatic and yet clinically relevant, and to align with ongoing studies that may or may not involve antithrombotic therapy, in a time frame relevant to acute illness. Organ support free days is defined by days in which patient is not on invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, or ECMO support (see Appendix 2), with death assigned the value of –1 days.

1.1.1 Adaptive Design

This platform trial will have multiple arms, which may be dropped or added as the platform trial progresses. Sample size will be flexible: the trial will be stopped for efficacy or futility based on pre- determined statistical thresholds as defined in the arm-specific appendix (Appendix 3 and 4). Each arm will have an adaptive component for determinations of futility or success.

1.2 *Potential Risks & Benefits*

See arm-specific Appendices for details

2 Study Design

2.1 *Overall Study Design*

This trial design is built as a process – with the possibility of multiple interventions being investigated. The trial is designed to be flexible, and these flexible aspects are planned as part of the protocol. This trial may incorporate a flexible number of interventions, and the number of interventions may evolve as the science evolves. Intervention arms will be added or dropped based on criteria defined in arm-specific appendices. Co-enrollment in other trials is permitted as long as the other trial does not test agents with antithrombotic properties and there is no other scientific contraindication.

2.2 *Randomization*

Randomization assignments are at the participant level and are assigned at baseline. Randomization will be stratified by enrolling site and may also be stratified by severity of illness and/or other arm-specific criteria. In general, allocation will be equally distributed across arms for which the participant is eligible, but may be altered with future arm-specific appendices.

3 Objectives and Purpose

The overarching objective of this adaptive platform design is to iteratively learn which antithrombotic strategy is the best for reducing the primary, secondary, and safety outcomes. Additional alternative strategy(-ies) will be compared to the current standard of care arm, which may trigger new standard of care designated arms as appropriate based on interim analysis results and evolving literature.
This process will continue until no new strategies replace the standard of care or potential options for additional antithrombotic interventions are exhausted.

4 Study Design and Endpoints

4.1 *Description of Study Design*

This trial design is built as a process – with the possibility of multiple interventions being investigated. This is an open label randomized trial of patients hospitalized for COVID-19 who are assigned to different antithrombotic regimens.

4.2 *Study Endpoints*

4.2.1 Primary Study Endpoint

21 Day Organ-Support free-days. The primary endpoint is the number of days that a patient is alive and free of organ support through 21 days after trial entry. Organ support is defined by receipt of invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, or ECMO support. If the patient dies at any time (including beyond 21 days) during the index hospital stay, they are assigned the worst possible score of –1.

4.2.2 Secondary Endpoints

- **Key Secondary Endpoint**: A composite endpoint of death, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke during hospitalization or at 28 days after enrollment (whichever is earlier)

Other Secondary Endpoints:

- A composite endpoint of death, deep vein thrombosis, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke during hospitalization or at 28 days after enrollment (whichever is earlier)
- 28 Day Hospital free days (non-ICU level patients)
- 28 Day Ventilator-Free Days (ICU level patients)
- 28 Day Vasopressor-Free Days (ICU level patients)
- 28 Day Renal Replacement Free Days
- Hospital readmission within 28 days
- Acute kidney injury as defined by KDIGO criteria
- Deep vein thrombosis
- Pulmonary embolism
- Systemic arterial thrombosis or embolism
- Myocardial infarction
- Ischemic stroke
- Use of extracorporeal membrane oxygenation (ECMO) support
- Mechanical circuit (dialysis or ECMO) thrombosis
- All-cause mortality at 28 days
- Organ support free days at 28 days
- All-cause mortality during initial hospitalization (includes death after 28 days)
- WHO ordinal scale (peak scale over 28 days, scale at 14 days, and proportion with improvement by at least 2 categories compared to enrollment, at 28 days)
- All-cause mortality at 90 days

4.2.3 All-cause mortality at 90 days Additional Study Endpoints

- Individual endpoints of the thrombotic endpoint
- Length of Hospital stay
- Exploratory endpoints (subset of sites)
  - Cardiac injury (e.g., troponin)
  - Trajectories of biomarkers related to COVID-19
  - DIC

See arm-specific Appendices for additional tertiary endpoints of interest specific to arm.

4.2.4 Safety Endpoints

- Major Bleeding (as defined by the ISTH)
- Symptomatic intracranial or intracerebral hemorrhage (evaluated as a separate endpoint from other major bleeding) (19)
- Confirmed Heparin induced thrombocytopenia (laboratory confirmed by anti-PF4 test or Serotonin Release Assay (SRA))

5 Study Enrollment

5.1 *Inclusion Criteria*

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- ≥ 18 years of age
- Hospitalized for COVID-19*
- Enrolled within 72 hours of hospital admittance or 72 hours of positive COVID test
- Expected to require hospitalization for > 72 hours
- (See arm-specific Appendices for additional criteria and details)

*It is strongly recommended to confirm SARSCoV2 with a positive microbiological test prior to randomization. At centers where there is delay in confirming the diagnosis, a sufficiently high clinical suspicion is sufficient to proceed with randomization as long as confirmation is expected within 24 hours.

5.2 *Exclusion Criteria*

- Imminent death
- Requirement for chronic mechanical ventilation via tracheostomy prior to hospitalization
- Pregnancy
- See arm-specific appendices.

5.3 *Vulnerable Subjects*

Critically ill patients with COVID-19 may not have capacity to provide consent. This trial will include participants who have no capacity to consent only if their legal proxy is able to consent on their behalf. It has become increasingly apparent that individuals with COVID-19 are at risk for thrombotic (and bleeding) events. Patients without the capacity to consent for themselves will have a potential for direct benefit by being part of the trial.

Participation in this trial is expected to facilitate careful monitoring of both thrombotic and bleeding endpoints, which may benefit participants.

Capacity assessment will be conducted by the treating physician or an independent medical provider with appropriate expertise based on the standard clinical assessment of capacity and

communicated to the study team. Surrogate consent will be provided by the subject's Legally Authorized Representative as defined by local policies and state/country regulations.

Consent will be obtained from the LAR before any study related procedures begin. Participants' capacity will be monitored throughout the study by working with the treatment team. Once the participant regains the capacity to consent, they will be informed of their participation in the study and will have an opportunity to withdraw from further participation in the study. The enrollment of patients without capacity is important because critically ill patients, especially those who are not ambulatory, are at higher risk of developing clotting complications.

5.4 *Strategies for Recruitment and Retention*

Listings of patients admitted to the participating sites with COVID-19 may be reviewed for eligibility by the study team, to identify and recruit potential participants, until study enrollment goals have been met. The study team should communicate with the inpatient care team. All treating physicians will be informed of the study and will have the option to advise of any conditions that would preclude any individual patient being approached.

5.5 *Duration of Study Participation*

Duration of study participation is, 90 days from enrollment. Participants may be contacted for follow-up for approximately one year.

Total Number of Participants

The total sample size for the Platform trial is not pre-determined. The sample size for each arm will be set in the arm-specific appendix and will incorporate an adaptive design. There will be interim monitoring to allow early stopping for futility, efficacy, or safety. If one strategy proves to be efficacious, then this strategy may become the reference arm for comparison(s) with new experimental treatment(s). New arms can be introduced according to scientific and public health needs. Some arms may not relate solely to antithrombotic therapy.

5.6 *Participant Withdrawal or Termination*

5.6.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. Discontinuation of a study agent, regardless of the reason, e.g. patient or physician request, or adverse event, does not constitute study withdrawal. Patient data will still be collected as planned and analyzed as intent to treat unless the participant withdraws consent for continued follow-up. An investigator may terminate participation in the study if:

- Any situation occurs such that continued participation in the study would not be in the best interest of the participant

5.7 *Premature Termination or Suspension of Study*

All deaths and DSMB-specified severe adverse events within the study period will be reviewed by the DSMB. The decision to stop or suspend the study, or an arm of the study, will be made by the DSMB after considering the totality of the data and the benefit-risk of continuing the study.

This study, or an arm of the study, may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants in a strategy, such as excess mortality and/or major bleeding (this will be determined by the oversight data safety monitoring plan; See 7.4.7)
- Demonstration of efficacy or lack thereof that would warrant stopping (See 7.4.7)
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent and Procedural Intervention

6.1 *Study Agents*

Each arm in this platform trial will include different treatment strategies. Information about the treatment strategies for a given arm can be found in the arm -specific appendices.

6.2 *Duration of Therapy*

Once participants are randomized to a treatment strategy (arm), they will remain on treatment for the duration specified by the relevant appendix. However, if a participant randomized to one arm develops an indication for a different strategy (e.g., thrombotic event, worsening clinical status), the participant will be treated based on institutional guidelines with any measures required by local clinical judgment.

7 Study Procedures and Schedule

7.1 *Study Schedule*

Activity	**Screening/ Enrollment**	**Hospital Duration**	**28 days and/or hospital discharge*** **	**90-days post randomization**
Eligibility				
Consent	X			
Demographic and Medical History	X			
Assessment of Inclusion/Exclusion criteria	X			
Self-reported race/ethnicity and gender	X			
Study Drug Administration				

Randomization	X			
Study treatment	X	X		
Study Procedures				
Height	X			
Weight	X			
Vital signs	X			
Concomitant medications	X	X		
WHO ordinal assessment	X	X	X	X
Outcomes Assessment		X	X	X
SOC Laboratory Assessments				
Chemistry panel	X	X		
Hematology panel	X	X		
See arm-specific appendix for additional measures				
D-dimer*	X			
Blood Group**	X			

*D-dimer is strongly recommended for measurement in all participants as close to the time of randomization as feasible.
**Blood group will come from hospital record or self report if available. Biospecimens see appendix 4.
***Assessments indicated in the table above will be ascertained at discharge, or at 28 days, whichever comes first. Participants must be followed for vital status until discharged from the hospital or another care facility (if transferred on organ support) up to 90 days. To maximize retention, participants will be contacted intermittently (e.g. at one and two months post-discharge)

Laboratory Procedures/Evaluations

See arm specific appendices.

All analyses will be performed on SOC labs and procedures done for usual care. The standard operating procedures for samples to be collected for research purposes are included as Appendix
5. All research samples will be timed with clinical lab draws to limit provider exposure. Collection of research samples as outlined in Appendix 5 is strongly encouraged where safe and feasible.

7.1.1 Visit 1 and Hospitalization Visits (see arm-specific appendices for details)

Visit 1 (Screening and Randomization)

1. Informed consent obtained
2. Assessment of inclusion/exclusion criteria assessed
3. Screening, consisting of reviewing participant medical history and information in their chart such as height, weight, vital signs, and normal clinically performed laboratory assessments, including pregnancy test for all women of childbearing age.
4. If confirmed eligible, following randomization, initiation of treatment with the assigned strategy

Hospitalization Visits

1. Recording of specifics of study treatment according to assigned arm
2. Laboratory assessments as part of standard of care
3. Daily WHO ordinal assessment
4. Ongoing daily outcomes and safety assessment

7.1.2 28 days and/or Date of Hospital Discharge

1. Recording of outcomes and safety assessments as reported by participant or observed by investigator
2. WHO Ordinal Assessment
3. Recording of vital status and ascertainment of events
4. Recording of participant's adherence to treatment strategy, if patient is in hospital

These assessments will be ascertained at discharge, or at 28 days, whichever comes first. Participants must be followed for vital status until discharged from the hospital or another care facility (if transferred on organ support) up to 90 days.

Participants may be contacted by a research contact and/or by the participating hospital study team periodically for longer term follow-up for approximately a year. To maximize retention, participants will be contacted intermittently (e.g. at one and two months post-discharge). Discharge visits must be completed.

7.2 *Concomitant Medications, Treatments, and Procedures*

Concomitant medications taken during study participation will be recorded on the case report forms (CRFs). Concomitant medications to be recorded are:

- Other antithrombotics (e.g., aspirin and other antiplatelet agents)
- Any medications used for the treatment of COVID-19 infection (e.g., remdesivir, steroids, IL- 6 inhibitor such as tocilizumab)
- Others specified in arm-specific appendices

7.3 *Expedited Critical and Major Event Reporting*

All efficacy and safety outcome events will be assessed and documented in the participants' study records. The ACTIV-4 Platform will have a uniform policy for reporting adverse events to ensure that all events are assessed quickly and are submitted to the DSMB, IRB(s), and other groups as needed (e.g., FDA), following each group's reporting guidelines and timelines. Events meeting the independent DSMB-specified criteria will be reported immediately and within the time frames specified by the DSMB.

Sites are required to follow their local reporting guidelines.

7.4 *Data and Safety Monitoring Plan and Study Halting Rules*

The ACTIV-4 Platform will have a uniform Data and Safety Monitoring Plan, encompassing all research carried out within the Platform.

8 Statistical Considerations

8.1 *Statistical and Analytical Plans (SAP)*

There will be a formal Statistical Analysis Plan (SAP) and each arm added to the trial will have its own arm-specific SAP. This will include the primary analysis, the primary

comparison, futility and success rules, and interim analysis schedule. The SAP will be created prior to the first interim analysis for the study and each arm-specific SAP will be created before the first interim analysis for that arm.

8.2 *Statistical Modeling for the Primary Analysis*

Inferences in this trial are based on a Bayesian statistical model for the ordinal primary outcome, organ-support free-days (OSFD). There is a single Bayesian model for the primary outcome across each arm and subpopulation. The Bayesian model is an ordinal cumulative logistic regression model described below.

Let $Y_i = \{-1, 0, 1, \ldots, 21, 22\}$ denote the ordinal outcome (OSFD) for patient i. The probability of patient i observing y OSFD or less is denoted as $\pi_{iy} = \Pr(Y_i \leq y)$. The parameters in the model are structured so that a value > 0 implies treatment benefit, and hence an odds-ratio > 1 implies treatment benefit. The generic primary analysis model is formulated as follows:

$$\log\left(\frac{\pi_{iy}}{1-\pi_{iy}}\right) = \alpha_{y,s} - [\nu_{Site,s} + \lambda_{Time,s} + \theta_{a,s:d} + \beta_{Age,s} + \beta_{Sex,s} + \beta_d]$$

1. The "subtype" variable, *s*, corresponds to the two patient subgroups defined by disease severity:
    a. subtype = 1 is non-ICU level care
    b. subtype = 2 is ICU-level care
2. The d-dimer level for a patient, d, is classified for a patient as
    a. d=1 is a low or unknown d-dimer level
    b. d=2 is a high d-dimer

The d-dimer level is only used for non-ICU (s=1) patients. We use the notation s:d to imply the parameterization would be s=1, d=1 (non-ICU level care, low d-dimer); s=1, d=2 (non-ICU level care, high d-dimer); and s=2 (ICU care).

3. The "site" variable is the clinical site within the trial. These will be site effects estimated separately within the non-ICU and ICU level of case disease states, but not varying by d- dimer levels.
4. The "time" variable is an indicator of the month of enrollment in the trial, numbered decreasing from the first enrollment to the last enrollment for the analysis. The time effects will be estimated separately within the non-ICU and ICU level of case disease states, but not varying by d-dimer levels.
5. The "arm" the patient is randomized to is labeled as *a*. The effects of arm are modeled by both the disease state and the d-dimer level.
6. The "age" variable is a categorical classification of age as ≤ 39, 40-49, 50-59, 60-69, 70-79, and 80+. The age effects will be estimated separately within the non-ICU and ICU level of case disease states, but not varying by d-dimer levels.
7. The "sex" variable is sex at birth. The sex effects will be estimated separately within the non-ICU and ICU level of case disease states, but not varying by d-dimer levels.

If additional covariates (e.g. race and ethnicity) are added to the model they will by default, unless otherwise specified, vary by disease state, but not d-dimer levels.

The $\alpha_{y,subtype}$ parameters are the baseline rates of the ordinal outcome, which are modeled separately by disease subtype. The additive effects of d-dimer levels are modeled with the β_d.

8.3 *Model Priors*

The treatment effects for arm *a*, within disease subtype *s* and d-dimer level *d* are modeled with the $\theta_{a,s:d}$ parameters. The β parameters model any covariate effects included in the model. The λ parameters model the effect of time within the pandemic.

The ordinal endpoint rates are modeled using an inverse Dirichlet model where the individual probabilities for the 24 outcomes are based on 10 patients weight on real-world evidence-based outcomes (details in the SAP).

$$logit(\alpha_{y,s}) \sim Dirichlet(10 * P), where \ldots$$

The site effects, ν_{Site}, are modeled using a hierarchical model where site is nested within the country of the site:

$$\nu_{Site,s} \sim N(\mu_{country,s}, \tau^2_{country,}), site = 2, \ldots, N_{Site}$$

$$\mu_{country,s} \sim N(0,1);\ \tau^2_{country,} \sim IG(0.25,0.1),\ s = 1,2$$

A referent site, expected to be the largest enrolling site, will be set such that $\nu_{Site} \equiv 0$. The hyper- parameters of the site hierarchical model are separate by disease state *s*.

The effect of time (*T*) is modeled using a second-order normal dynamic linear model separately by disease state, *s*. The most recent two time periods are modeled as the referent time epochs with the time parameters set to 0. The preceding time epochs are modeled as a normal dynamic linear model as:

$$\lambda_1 = \lambda_2 \equiv 0$$

$$\lambda_3 \sim N(0,0.15^2)$$

$$\lambda_T - 2\lambda_{T-1} + \lambda_{T-2} \sim N(0, \tau^2_{Time}),\ T \geq 4$$

The treatment effect parameters are set against a control arm, which will be labeled in the arm- specific appendix. The treatment effect for the control arm, labeled as arm *a* = 1, will be set to 0 for each of the disease subtype and d-dimer level:

$$\theta_{1,subtype,d} \equiv 0$$

The effect of each other arm introduced will be modeled hierarchically across disease subtype and d-dimer level. The treatment effects for each arm, *a*, are modeled as:

$$\theta_{a,s:d} \sim N(\mu_a, \tau^2_a),\ s{:}\ d = 1{:}\ 1, 1{:}\ 2, 2, \qquad a = 1, \ldots, N_{arms}$$

$$\mu_a \sim N(0,1);\ \tau^2_a \sim IG(0.25,0.1)\ \text{(TBD)}$$

Any additional covariates included in the model will have independent N(0,1) priors unless otherwise specified.

8.4 *Assessing Effectiveness*

The treatment effect parameters, θ, represent the log-odds ratio, of the treatment, for the cumulative logistic for the ordinal model. In this parametrization an odds ratio > 1, or a log-odds ratio > 0, signifies improved outcomes relative to the referent control treatment. The odds-ratio parameter $\exp(\theta)$, labeled OR, will be used to summarize the treatment effect relative to control or $\exp(\theta_{a_1} - \theta_{a_2})$ for the odds-ratio between arms a_1 and a_2. The posterior mean, median, standard deviation, and 95% credible intervals for the odds-ratio will be used to summarize relative treatment effects.

The posterior probability that an arm, a_1, is superior to another arm, say, a_2, is:

$$\Pr(\theta_{a_1} > \theta_{a_2}).$$

This probability will be used for triggers of superiority of one arm to another arm.

The posterior probability that an arm, a_1, is superior to another arm, say, a_2, by a specified difference on the odds-ratio scale is:

$$\Pr(\exp(\theta_{a_1}) > \exp(\theta_{a_1}) + \delta).$$

This probability will typically be used for futility. If the probability is small that a treatment has benefit above a control of some specified amount (δ), the arm may be dropped for futility.

8.5 *Analysis Datasets*

The intention-to-treat (ITT) analysis dataset will be the source of data for primary analyses. This will include all randomized participants regardless of actual receipt or compliance with therapy. The safety analysis set will consist of all participants who received at least one dose of study medication. The per protocol analysis will be conducted based on adherence to assigned treatment; this dataset will support sensitivity analyses to complement the primary ITT analyses.

The ITT group for an arm consists of the participants that were randomized in the platform that were eligible to be randomized to that arm. This may vary from the platform ITT population, which consists of all participants randomized.

Participants who are randomized to receive one strategy may in fact be treated with another strategy based on health status and provider discretion. Exploratory analyses will estimate the causal effect of the treatment for these participants 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.

8.5.1 Safety Analyses

Monitoring for safety will be conducted continuously. For each arm-specific appendix potential adverse events of importance will be identified. A Bayesian monitoring rule will be used to summarize the adverse event rates across all arms for the adverse events of importance within each arm-specific appendix. A Bayesian prior distribution of a beta (0.1, 0.9) will be used to model the likelihood of each adverse event of importance. For each adverse event of importance, the posterior mean event rates, the posterior mean of the difference between each arm, and the 95% credible intervals for the risk-difference and odds-ratio will be summarized.

8.5.2 Adherence and Retention Analyses

The primary analysis is by intention to treat. Per protocol analysis will be conducted based on adherence to assigned treatment. For any scheduled follow-up post hospital discharge every effort will be made to recontact participants who are unreachable. Due to the short trial participation timeline, excellent patient retention is anticipated.

8.5.3 Baseline Descriptive Statistics

All variables will be summarized using mean, median, standard deviation, and range (for continuous variables) and frequency (for categorical variables). Treatment groups will be compared with respect to baseline characteristics to verify randomization balance.

8.5.4 Planned Interim Analysis

An independent data safety and monitoring board (DSMB) will review all interim analyses prepared by an unblinded statistical analysis committee.

8.5.5 Safety Review

Monitoring for safety will be conducted continuously. The DSMB will be monitoring safety for each arm-specific appendix. The DSMB monitoring plan includes guidance on stopping specific arms for safety concerns.

8.5.6 Tabulation of Individual Response Data

The composite outcome evaluated will be tabulated and broken down by component (e.g., death, pulmonary embolus, symptomatic DVT, myocardial infarction, etc.). Note that some participants may experience more than one component of the primary endpoint.

8.5.7 Exploratory Analyses

Exploratory analyses will be conducted in a subset of participants on whom additional clinical and basic science assays are performed. These will be descriptive and hypothesis-generating.

8.6 *Sample Size*

Sample size for the platform trial is not pre-determined. The platform trial will run as long as there is a need and there are investigational arms enrolling. The sample size for each arm will be specified in the arm-specific appendix. Interim analyses for each arm will take place in the platform trial and detailed in the arm-specific appendix. Conclusions of futility or superiority may be drawn specific to a patient subtype. Effort will be taken to conduct all interim analyses at the same time in the platform trial since there is a single Bayesian model of the efficacy of all arms conducted. If one strategy proves to be efficacious, then this strategy may become the reference arm for comparison(s) with new experimental treatment(s). New arms can be introduced according to scientific and public health needs.

Generic sample size calculations for an ordinal endpoint of 21-day OSFD with a maximum sample size of 1000 for an investigational arm, compared to a second control arm with 1000 participants (2000 participants total), yields over 80% power for an odds-ratio change of 1.25 on the OSFD endpoint. An odds ratio of 1.5 has approximately 90% power for 400 participants per arm. An odds-ratio of 2 results in more than 90% power for the first interim analysis of 200 participants per arm.

The following figure presents the assumptions for the ordinal outcome of organ-support free days for the control arm and the distribution under each assumed treatment effect for the cumulative odds-ratio used for these power calculations. The second figure presents the power for each assumed effect size for each fixed sample size (the x-axis is the total number on the two arms).

9 Measures to Minimize Bias

9.1 *Enrollment/Randomization*

Enrollment

1. Patients hospitalized for COVID-19 are screened daily within the eligibility time window for inclusion/exclusion criteria. Any patient who meets all inclusion criteria and no exclusion criteria will be approached for enrollment.

2. Patients remain in the intention-to-treat group if they meet the criterion for another treatment strategy after randomization.

10 Randomization

Randomization assignments are performed for participants at baseline. Randomization will be equal across all arms a patient is eligible. Randomization stratification will be done by site, and disease subtype (ICU and non-ICU level care).

11 Source Documents and Access to Source Data/Documents

The ACTIV-4 Platform will have uniform policies describing what source documents are, how to make corrections, and who can access them.

12 Quality Assurance and Quality Control

The ACTIV-4 Platform will have uniform policies for quality assurance at the data entry level and site monitoring.

13 Ethics/Protection of Human Subjects

13.1 *Ethical Standard*

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 *Institutional Review Board*

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 *Informed Consent Process*

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant, and written documentation of informed consent is required prior to starting intervention/administering study product.

A written consent will be sought from every participant via a face to face consenting process or remotely by using an e-consent option as per IRB approved method.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Informed consent will be obtained following institutional COVID policy to protect study staff.

An extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be provided to participants. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Participants who have no capacity to consent for themselves will have a surrogate consenting process via legally authorized representative.

13.4 *Posting of Clinical Trial Consent Form*

The informed consent form will be posted on the Federal website after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

13.5 *Participant and Data Confidentiality*

The ACTIV-4 Platform will have uniform policies for protecting the privacy of participants and maintaining confidentiality. These policies will adhere to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

14 Data Handling and Record Keeping

14.1 *Data Collection and Management Responsibilities*

The ACTIV-4 Platform will have uniform policies for data management.

14.2 *Study Records Retention*

The ACTIV-4 Platform will have uniform policies for records retention.

14.3 *Protocol Deviations*

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective

actions are to be developed by the site and implemented promptly.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.4 *Publication and Data Sharing Policy*

The ACTIV-4 Platform will have uniform policies for publications and data sharing.

15 Study Finances

15.1 *Funding Source*

National Institutes of Health

15.2 *Costs to the Participant*

Participant health insurance may be billed for the costs of medical care during this study since these expenses would have happened even if the participant were not in the study. If the participant's insurance does not cover these costs or the participant does not have insurance, these costs will be participant's responsibility.

16 Conflict of Interest Policy

The ACTIV-4 Platform will have uniform policies for identifying and disclosing potential conflicts of interest.

17 References

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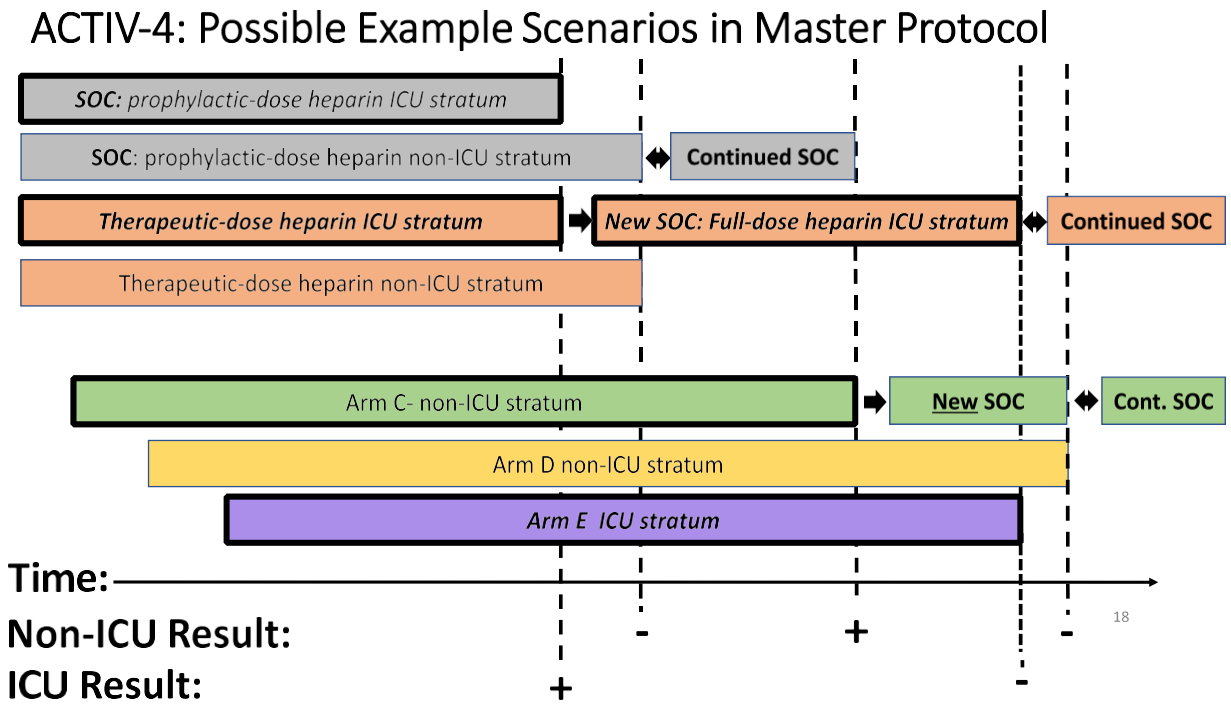
Appendix 1: Criteria for Addition and Replacement of Arms



Appendix 2: Definition and Determination of Outcomes

A2.1 Approach to ascertainment and verification of outcomes

Outcomes are assessed locally and will not be centrally adjudicated in this pragmatic trial platform, except as specified in the arm-specific appendix. Outcomes should be assessed by a local investigator or other qualified study team member who is blinded to treatment assignment, using the definitions below.

A2.2 Outcome definitions

21 Day Organ-Support Free-Days (OSFD)

Defined as the number of days that a patient is alive and free of organ support through 21 days after trial entry. Organ support is defined by receipt of invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, or ECMO support. If the patient dies at any time (including beyond 21 days) during the index hospital stay, they are assigned the worst possible score of –1.

- Non-invasive mechanical ventilation is defined as BIPAP or CPAP when used for acute respiratory support (the use of BIPAP or CPAP at night or when sleeping for sleep apnea is not considered organ support).
- High Flow Nasal Cannula Oxygen is defined as delivery of oxygen through a system that typically delivers oxygen at 30 to 60 liters per minute (but may be as low as 20 liters per minute) with a titratable FiO2.
- Invasive mechanical ventilation is defined as positive pressure ventilation through endotracheal tube or tracheostomy.
- Vasopressor support includes infusion of any vasopressor or inotropic medication.
- A patient must be extubated and not receiving mechanical ventilation for at least 2 days before being considered free of mechanical ventilation. If a patient was extubated and re- intubated and placed back on mechanical ventilation within 1 or 2 days, the patient is considered to be on mechanical ventilation during those 1 or 2 days before re-intubation.
- Any patient dying in the acute hospital stay (even if beyond day 21) are assigned 21 Day Organ-Support Free Days of –1.
- If there is intervening time in which a patient is free of organ support but goes back on organ support the intervening time does not count toward the organ support free days endpoint. Only time before organ support and after the last use of organ support are counted as “free days.”
- If a patient was discharged alive without mechanical ventilation prior to Day 21, the patient is assumed to be free of organ support after hospital discharge for the remainder of the 21 days.
- If a patient was discharged alive on mechanical ventilation prior to Day 21, a call to the discharge facility is needed to confirm ventilation status on Day 21 and the last day on mechanical ventilation.

Primary Endpoint

Days free of organ support within 21 days after randomization. Organ support free days (OSFD) is defined as days in which patient is not on invasive or non-invasive mechanical ventilation, high flow

nasal oxygen, or vasopressor therapy or ECMO support. If the patient dies at any time (including beyond 21 days) during the index hospital stay, they are assigned the worst possible score of –1.

To be specific about which organ support was affected, secondary outcomes include: ventilator free days, renal replacement free days, vasopressor free days.

Justification for use of OSFD:

- Pragmatic
- Can be calculated from WHO ordinal scores
- Incorporates clinically important need for organ support but also duration of organ support
- No additional data collection is necessary to calculate secondary outcomes of vent free days, renal replacement free days, and vasopressor free days to understand which organ support was most impacted
- Incorporates mortality as the worst possible outcome

Deep vein thrombosis

Deep vein thrombosis will be diagnosed by venous ultrasound or point-of-care ultrasound (POCUS) or other imaging modality and documented in a note, and performed for clinical indications. A positive ultrasound test is defined by a noncompressible or partially noncompressible venous segment and should be reported. Thrombosis may involve the cerebral venous sinus or any venous bed, including the upper extremities. Routine screening for deep vein thrombosis is not recommended. If deep vein thrombosis is diagnosed and treated without imaging due to imaging availability concerns or risk of exposure to SARS CoV-2, this will be classified as probable deep vein thrombosis. Later imaging is preferable in these cases when possible.

Pulmonary embolism

Pulmonary embolism will be confirmed by chest CT with PE protocol, pulmonary angiography or ventilation-perfusion scan. Events may also be defined without this imaging by the care team, as evidenced by, for example, “clot in transit” on echocardiogram. If PE is diagnosed and treated without imaging due to imaging availability concerns or risk of exposure to SARS CoV-2, this will be classified as probable PE. Later imaging is preferable in these cases when possible.

Stroke/ Peripheral Arterial Systemic Thromboembolism

Stroke or systemic embolism as diagnosed by imaging (i.e., head CT, lower extremity CT angiogram) or deemed “highly-likely” by the provider based on physical examination (i.e., acute hemiplegia thought to be due to stroke, acute distal lower extremity hypoperfusion). Systemic thromboembolism may involve the retinal artery, spinal cord or other vascular beds. Classification of ischemic vs. other etiologies is based on neuroimaging. Venous sinus thrombosis will be included in the category of vascular occlusion/ischemic stroke on the venous side. Primary CNS hemorrhage: Intracerebral hemorrhage, Subarachnoid hemorrhage, Subdural hematoma, rarely- epidural hematoma, spinal hematoma. Secondary hemorrhagic stroke: Ischemic infarct containing blood - often subclassified by size- PH1, PH2, PH3.

ICU Level of care disease state

Defined as planned admission to ICU or receipt of organ support as defined in the 21-day organ support free days.

Myocardial infarction

Myocardial infarction is defined according to the universal definition of MI, which excludes myocardial injury e.g., isolated elevation of cardiac troponin. MI must include rise and fall of cardiac troponin above the 99th percentile with at least one of the following: symptoms of acute ischemia, ECG changes consistent with ischemia, new/presumed new wall-motion abnormalities or other imaging evidence of MI, abnormal coronary angiography (e.g. identification of a coronary thrombus).

Acute Kidney Injury

Acute kidney injury after enrollment is defined by KDIGO criteria for Acute Kidney Injury in the setting of not meeting these criteria upon enrollment:

THREE STAGES:

- Stage 1: Serum Cr 1.5–1.9 times baseline, OR ≥ 0.3 mg/dl increase in serum Cr
- Stage 2: Serum Cr 2.0–2.9 times baseline
- Stage 3: Serum Cr ≥ 3.0 times baseline, OR Increase in serum creatinine to ≥ 4.0mg/dl, OR Initiation of renal replacement therapy

Disseminated Intravascular Coagulation (DIC) (Overt) – DIC score ≥ 5

1. Platelet count ≥ 100 K (0); 50–100K (1 point); < 50K (2 points)
2. Elevated D-dimer: no increase (0 points); moderate increase (1 point); severe increase (3 points) according to local criteria.
3. Prolonged PT < 3 seconds (0 points); 3–6 seconds (1 point); ≥ 6 seconds (2 points)
4. Fibrinogen level ≥ 100 (0 points); < 100 (1 point) mg/dL

ISTH Defined Major Bleeding

Bleeding that:

1. Resulted in death,
2. Occurred in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, intramuscular with compartment syndrome, or pericardial), or
3. Associated with either a decrease in the hemoglobin level of at least 2 g per deciliter or a transfusion of at least 2 units of packed red cells

Symptomatic Intracranial or Intracerebral Hemorrhage (sICH)

sICH is defined as any acute extravasation of blood into the brain parenchyma, subarachnoid space, subdural space, or epidural space as demonstrated by imaging or autopsy, associated with any clinical deterioration or death

WHO ordinal scale for clinical improvement (https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf)

Patient State	Score	Descriptor
Uninfected	0	No clinical or virological evidence of infection
Ambulatory	1	No limitation of activities
	2	Symptomatic: Limitation of activities
Hospitalized: Mild disease	3	Hospitalized; no oxygen therapy
	4	Hospitalized; oxygen by mask or nasal prongs
Hospitalized: Severe	5	Non-invasive ventilation or high-flow oxygen

disease	6	Intubation & Mechanical ventilation
	7	Ventilation and additional organ support – pressors, RRT, ECMO
Death	8	Death

Appendix 3: Therapeutic-dose Anticoagulation (Arm A)

Any of the following strategies are recommended for therapeutic-dose anticoagulation:

*A3.1 Therapeutic Dose Anticoagulation***

<table>
<tr><th>CrCl</th><th>BMI</th><th>Enoxaparin</th><th>Dalteparin</th><th>Tinzaparin</th><th>Heparin</th></tr>
<tr><td rowspan="2">≥30</td><td><40</td><td>1 mg/kg SC q12h
OR
1.5 mg/kg SC q24h</td><td>200 units/kg SC q24h
OR
100 units/kg SC q12h</td><td rowspan="2">175 units/kg SC q24h</td><td rowspan="2">IV bolus, with continuous infusion to titrate to anti-Xa 0.3-0.7 IU/mL or corresponding aPTT values*</td></tr>
<tr><td>≥40</td><td>1 mg/kg SC q12h</td><td>100 units/kg SC q12h</td></tr>
<tr><td rowspan="2"><30</td><td><40</td><td colspan="4" rowspan="2">Heparin IV bolus, with continuous infusion to titrate to anti-Xa 0.3-0.7 IU/mL or corresponding aPTT values*</td></tr>
<tr><td>≥40</td></tr>
</table>

* Initial bolus dose determined by sites, encouraging use of dosing algorithm designed for treatment of VTE. UFH anti-Xa titration is preferred over aPTT if available because achieving a therapeutic aPTT may be challenging in patients with a pro-inflammatory state such as COVID-19.

Note: Tinzaparin commonly used in Canada

Note: Fondaparinux not advised in this setting due to its long half life

**These drugs are considered standard of care as an anticoagulants (1). Different drugs are used in different regions, countries, and hospital formularies. In this pragmatic trial of antithrombotic therapy in COVID-19, sites will use the anticoagulant that they typically use in the hospital setting.

It is recommended that participants be given therapeutic-dose parenteral anticoagulation daily for at least 14 days or until hospital discharge, whichever comes first. Treatment may continue beyond 14 days at the discretion of the most responsible physician. At the time of treatment discontinuation, standard of care antithrombotic prophylaxis should be administered.

If there is transfer to ICU level care, continue assigned treatment unless there are contraindications.

A3.2 Discontinuation of study intervention:

Patients randomized based on suspicion of COVID 19 whose tests do not confirm SARS CoV2 infection should not continue to receive study assigned therapeutic dose anticoagulation.

Anticoagulation should be discontinued if there is clinical bleeding or other complications sufficient to warrant cessation in the opinion of the treating clinician. Major bleeding, including death due to bleeding, is an SAE. Assigned treatment may be resumed if deemed appropriate by the treating clinician.

Occurrence of HIT must result in the cessation of UFH or LMWH without recommencement regardless of treatment assignment. The use of an acceptable

alternative agent is required in this instance as clinically indicated. Occurrence of HIT is an SAE.

Study interventions can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient. Temporary cessation – for the shortest period of time possible, but not longer than 24 hours – such as to allow surgical or other procedures is not a protocol deviation.

Temporary or permanent cessation of study intervention for bleeding is not a protocol deviation.

A3.3 Study Schedule

Activity	**Screening/ Enrollment**	**Hospital Duration**	**28 days and/or hospital discharge+**	**90 days post randomization**
Eligibility				
Consent	X			
Demographic and Medical History	X			
Assessment of Inclusion/Exclusion criteria	X			
Self-reported race/ethnicity and sex	X			
Pregnancy Test, for women of childbearing potential	X			
Study Drug Administration				
Randomization	X			
Study treatment	X	X		
Study Procedures				
Height	X			
Weight	X			
Vital signs	X	X		
Concomitant medications	X	X		
WHO ordinal assessment	X	X	X	X
Outcomes assessment		X	X	X++
SOC Laboratory Assessments				
Chemistry panel	X	X	X^	
CBC with platelet count	X	X	X^	
Blood Group*	X			
PT, PTT if known	X	X		
Anticoagulation Monitoring (e.g., PTT/ Antifactor Xa level)**	X	X (site-specific)		
D-dimer***	X	X	X^	
Troponin****	X	X	X^	
Coagulation and inflammatory markers*****	X	X	X^	
Optional Biorepository	X	X		

*Blood group taken from hospital record or self report if that is not available.

** Frequency and mode (Anti-factor Xa/aPTT) of testing will be based on site routine. Anti-factor Xa monitoring is preferred over PTT

***Baseline D-dimer is required with SOC labs (sample needs to be obtained prior to randomization, but results do not need to be available at the time of randomization). All values collected should be recorded

****Strongly recommended as part of routine care

***** Optional, listed in case report form

[+]Assessments indicated in the table above will be ascertained at discharge, or at 28 days, whichever comes first. Participants must be followed for vital status until discharged from the hospital or another care facility (if transferred on organ support) up to 90 days. To maximize retention, participants will be contacted intermittently (e.g. at one and two months post-discharge)

[++]Participants will be contacted to ascertain vital status.functional status and quality of life. (Instruments detailed in the manual of operations)

^ May be collected at hospital discharge and at 28 days in participants who remain in hospital at that time

A3.4 Potential Risks & Benefits

A3.4.1 Known Potential Risks

Participants are monitored as per standard of care to minimize the risk of bleeding or developing clots. The therapeutic dose anticoagulation group will receive potent anticoagulation and thus may be at higher risk of bleeding.

A3.4.2 Known Potential Benefits

A recent study from patients with COVID-19 hospitalized in China found that patients with elevated D-dimer had the benefit of prophylactic dose anticoagulation versus no anticoagulation. Thus, there is a direct benefit of decreased clotting events in both arms – although this trial hypothesizes that the benefit in terms of decreasing adverse events will be superior in this therapeutic dose anticoagulation. All participants will be closely monitored by the study team and any changes will be discussed with the treating physicians and/or clinical team. There is a potential direct benefit of identifying clots or bleeding more rapidly based on this monitoring. This trial will contribute to the body of generalizable knowledge about the best anticoagulation strategy to use to minimize the risk of clotting in patients with COVID-19.

A3.5 *Study Enrollment*

A3.5.1 Inclusion Criteria

Same as the Master Protocol.

A3.5.2 Exclusion Criteria

Exclusion criteria are as follows:

- Contraindication to anticoagulation, including but not limited to:
    - known bleeding within the last 30 days requiring emergency room presentation or hospitalization

    - known history of an inherited or active acquired bleeding disorder
    - known history of heparin induced thrombocytopenia
    - recent ischemic stroke
- Indication for therapeutic anticoagulation in the case that it cannot be stopped
- Platelet count < 50x 10^9/L
- Hemoglobin < 8 g/dL
- Pregnancy
- Patient on dual antiplatelet therapy, when one of the agents cannot be stopped safely

A3.6 Event Adjudication

A subset of thrombotic events will be centrally adjudicated, with the proportion adjusted as needed based on agreement between the site and the event committee.

A3.7 ***Safety Analyses***

The safety event of importance for the therapeutic dose anticoagulation is major bleeding. The rates of ISTH major bleeding, ICH and fatal bleeds, and mortality will be monitored. The rates of bleeding will be directly compared to the control arm (prophylactic dose anticoagulation) as well as to any additional arms added to the platform trial subsequently if this arm continues. For ISTH major bleeding, ICH and fatal bleeds, and all cause mortality the DSMB will review the number of events, the event rates, and the posterior mean and 95% credible intervals for the event rates, difference between arms, and odds-ratios between arms will be summarized.

A3.8 *Statistical Analyses*

The therapeutic dose anticoagulation arm will be compared to the control arm (prophylactic dose anticoagulation) for efficacy on the primary analysis and the secondary endpoints. In addition, this arm will be compared to the control and may be stopped for futility if it does not improve the primary clinical outcome.

The primary Bayesian statistical model (see Master protocol) will be used for modeling this arm.

A3.8.1 Interim Analysis Schedule

Interim analyses will take place for this arm starting when 200 participants have been randomized to this arm and have 21-day follow-up. Analyses will continue with every 200 participants enrolled to this arm, at sample sizes of 400, 600, 800, and 1,000.

A3.9 *Adaptive Decision Rules*

At each analysis the following rules will be carried out:

1. **Superiority**: Within each subtype, if the posterior probability of superiority of the therapeutic dose anticoagulation arm compared to the prophylactic dose (control) anticoagulation arm is greater than 0.99, then the therapeutic dose anticoagulation arm will be declared superior to prophylactic dose anticoagulation in that subtype. If the prophylactic dose anticoagulation arm has not been discontinued in that disease subtype, then this result trigger should discontinue randomization within that stratum to the prophylactic dose anticoagulation arm.

If the therapeutic dose anticoagulation arm reaches 1,000 total participants enrolled without a declaration of superiority or futility within a subtype, this arm may be discontinued within these remaining subtypes. If the steering committee decides it is important to keep this arm

in the platform trial, it may expand beyond this 1,000 participants randomized and this plan will be amended.

A3.10 *Operating Characteristics*

See Arm-specific SAP for the operating characteristics for the therapeutic dose anticoagulation arm.

A3.11 References

1. Garcia D, Baglin T, Weitz J, et al. Parenteral Anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012 Feb;141(2 Suppl):e24S–e43S

Appendix 4: Prophylactic Dose Anticoagulation (Arm B)

Any of the following strategies are recommended for prophylactic dose anticoagulation:

A4.1 *Prophylactic Dose Anticoagulation**

CrCl	BMI	Enoxaparin	Dalteparin	Tinzaparin	Fondaparinux	Heparin
≥30	<40	40 mg SC q24h	5000 units SC q24h	4500 units SC q24h	2.5 mg SC q24h	5000 units SC q8-12h
	≥40	40 mg SC q12h	5000 units SC q12h	9000 units SC q24h	NA	7500 units SC q8h
<30	<40	Heparin 5000 units SC q8-12h				
	≥40	Heparin 7500 units SC q8h				

*All drugs are considered standard of care as an anticoagulant (1–2). Different drugs are used in different regions, countries, and hospital formularies. As a pragmatic trial of antithrombotic therapy in COVID-19, sites will use the anticoagulant that they typically use in the hospital setting.

It is recommended that participants be given prophylactic-dose parenteral anticoagulation daily for at least 14 days or until hospital discharge, whichever comes first. Treatment may continue beyond 14 days at the discretion of the most responsible physician.

The following measures are recommended during CRRT: regional citrate, heparin priming and prophylactic dose heparin administration (without measurable systemic anticoagulation)

Full therapeutic dose anticoagulation (therapeutic dose UFH or LMWH) is permitted as rescue therapy in the event of suspected or confirmed deep vein thrombosis, pulmonary embolism, systemic arterial thromboembolism, acute coronary syndrome, circuit or line thrombosis during continuous renal replacement therapy (despite regional measures) or sustained low-efficiency daily dialysis. Full therapeutic dose anticoagulation is also acceptable for intermittent hemodialysis. These are adherent to protocol. Full therapeutic anticoagulation is not recommended solely for clinical deterioration involving transfer to ICU-level care in this setting in the absence of suspected PE. If the team changes to therapeutic dose for other reasons (e.g., increasing D-dimer; team is not comfortable with prophylactic dose, minor increase in oxygen support), then this is not adherent to protocol and site PI will need to discuss this with the clinical team.

A4.2 *Discontinuation of study intervention*

Anticoagulation should be discontinued if there is clinical bleeding or another complication sufficient to warrant cessation in the opinion of the treating clinician. Major bleeding, including death due to bleeding, is an SAE. Assigned treatment may be resumed if deemed appropriate by the treating clinician.

Occurrence of HIT must result in the cessation of UFH or LMWH without recommencement regardless of treatment assignment. Use of an acceptable alternative agent is required in this instance as clinically indicated. Occurrence of HIT is an SAE.

Study interventions can be discontinued at any time by the treating clinician if doing so is

regarded as being in the best interests of the patient. Temporary cessation – for the shortest period of time possible, but not longer than 24 hours – such as to allow surgical or other procedures is not a protocol deviation.

Temporary or permanent cessation of study intervention for bleeding is not a protocol deviation.

A4.3 ***Study Schedule***

Activity	**Screening/ Enrollment**	**Hospital Duration**	**28 days and/or hospital discharge[+]**	**90 days post randomization[++]**
Eligibility				
Consent	X			
Demographic and Medical History	X			
Assessment of Inclusion/Exclusion criteria	X			
Self-reported race/ethnicity and sex	X			
Pregnancy Test, for women of childbearing potential	X			
Study Drug Administration				
Randomization	X			
Study treatment	X	X		
Study Procedures				
Height	X			
Weight	X			
Vital signs	X	X		
Concomitant medications	X	X		
WHO ordinal assessment	X	X	X^	X
Outcomes assessment		X	X	X[++]
SOC Laboratory Assessments				
Chemistry panel	X	X	X^	
CBC with platelet count	X	X	X^	
Blood Group*	X			
PT, PTT if known	X	X		
Anticoagulation Monitoring (ex, PTT/ Antifactor Xa level)**	X	X (site-specific)		
D-dimer***	X	X	X^	
Troponin****	X	X	X^	
Coagulation and inflammatory markers*****	X	X	X^	
Optional Biorepository	X	X		

*Blood group taken from hospital record or self report if that is not available.

** Frequency and mode (Anti-factor Xa/PTT) of testing will be based on site routine. Anti-factor Xa monitoring is preferred over PTT

*** Baseline D-dimer is required with SOC labs (sample needs to be obtained prior to randomization, but results do not need to be available at the time of randomization). All values collected should be recorded.

****Strongly recommended as part of routine care, all values collected should be recorded

*****Optional, listed in case report form

[+]Assessments indicated in the table above will be ascertained at discharge, or at 28 days, whichever comes first. Participants must be followed for vital status until discharged from the hospital or another care facility (if transferred on organ support) up to 90 days. To maximize retention, participants will be contacted intermittently (e.g. at one and two months post-discharge)

[++]Participants will be contacted to ascertain vital status and functional status and quality of life. (Instruments detailed in the manual of operations)

^ May be collected at hospital discharge and at 28 days in participants who remain in hospital at that time

A4.4 *Potential Risks & Benefits*

A4.4.1 Known Potential Risks

Participants are monitored as per standard of care to minimize the risk of bleeding or developing clots.

A4.4.2 Known Potential Benefits

A recent study from patients with COVID-19 hospitalized in China found that patients with elevated D-dimer had a benefit of prophylactic dose anticoagulation versus no anticoagulation. Thus, there is a direct benefit of decreased clotting events in both arms – although this trial hypothesizes that the benefit in terms of decreasing adverse events will be superior in this therapeutic dose anticoagulation. All participants will be closely monitored by the study team and any changes will be discussed with the treating physicians and/or clinical team. There is a potential direct benefit of identifying clots or bleeding more rapidly based on this monitoring. This trial will contribute to the body of generalizable knowledge about the best anticoagulation strategy to use to minimize the risk of clotting in patients with COVID-19.

A4.5 *Study Enrollment*

A4.5.1 Inclusion Criteria

Same as the Master Protocol.

A4.5.2 Exclusion Criteria

Exclusion criteria are as follows:

- Contraindication to anticoagulation, including but not limited to
    - known bleeding within the last 30 days requiring emergency room presentation or hospitalization
    - known history of a bleeding disorder of an inherited or active acquired bleeding

disorder
    - known history of heparin induced thrombocytopenia
    - recent ischemic stroke
- Indication for therapeutic anticoagulation in the case that it cannot be stopped safely
- Platelet count < 50x 10^9/L
- Hemoglobin < 8 g/dL
- Pregnancy
- Patient on dual antiplatelet therapy when one of the agents cannot be stopped safely

A4.6 Event Adjudication

A subset of thrombotic events will be centrally adjudicated, with the proportion adjusted as needed based on agreement between the site and the event committee.

A4.7 *Safety Analyses*

The safety event of importance for the prophylactic dose anticoagulation is serious thrombotic events. The risk is that with a sub therapeutic dose there may be elevated thrombotic events. The rates of serious thrombotic events and mortality will be monitored. The rates of serious thrombotic events will be directly compared to the therapeutic dose anticoagulation arm as well as to any additional arms added to the platform trial subsequently if this arm continues. For serious thrombotic events the DSMB will review the number of events, the event rates, and the posterior mean and 95% credible intervals for the event rates, difference between arms, and odds-ratios between arms will be summarized.

A4.8 *Statistical Analyses*

The prophylactic anticoagulation arm is intended as the initial control arm in the platform trial. This arm will be the referent arm in the Bayesian statistical model. This arm will not have any efficacy or futility stopping rules. This arm will function as a comparator within each of the subtypes and will continue in each until an arm demonstrates efficacy compared to this arm and it is discontinued in that subtype. This prophylactic dose anticoagulation arm is likely to be the safest of the arms in this platform trial and hence arms will have a need to demonstrate statistical superiority to this arm for it to be discontinued.

A4.9 Number of Participants

Approximately 1,000 participants will be randomized to this arm and have 90-day follow-up.

A4.10 References

1. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 suppl):e227S-277S.

2. Garcia D, Baglin T, Weitz J, et al. Parenteral Anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012 Feb;141(2 Suppl):e24S–e43S.

Appendix 5: ACTIV-4 Blood Sampling – proposed samples and times for sites participating in mechanistic studies and biorepository

The goal of the Mechanistic Studies Center and the Biorepository/Central Lab is to add significant value to the clinical trials by collecting high-quality blood samples for studies aimed at elucidating underlying disease mechanisms and insights into how the therapy modifies these underlying disease processes. A goal is to identify biomarkers that can identify pathological mechanisms, predict outcomes, direct therapy, and/or identify higher-risk patient subpopulations.

A5.1 *Inpatient sampling*

Blood collection times for inpatients:

- Days 1 (time of enrollment), 3, 7 and 14
- Samples should be coordinated with clinical lab blood draws when possible.

Standard samples to be collected & volumes at each time point:

- Citrate plasma
  - Two 4.5 mL Citrate tubes (BD # 369714)
- EDTA plasma
  - One 10 mL EDTA tube (BD# 366643)
- Serum
  - One 5.0 mL Serum tube (BD # 367814)

Note 1: *We anticipate that some sites may not be able to collect & process all the samples and time points listed above. We plan to work with those sites to identify more limited time points and/or discard samples that could be collected, processed and sent to the biorepository.*

Note 2: *We anticipate that some high-functioning sites may, in addition to the sample collections noted above, also participate in enhanced collections & studies, which may include:*

- Additional blood collection tubes such as:
  - HTI SCAT-144 plasma
  - Paxgene RNA whole blood
  - Cell Prep Tube (CPT)
- Whole blood assays:
  - Viscoelastic assays (thromboelastography or thromboelastometry)
  - Platelet aggregometry
  - Whole blood genomics

A5.2 *Sample processing*

A detailed Manual of Operations (MOP) will provide instructions to clinical lab and research personnel regarding sample processing including centrifugation, processing, freezing, storing, & shipping samples. Also, the following will be provided: training materials; sample processing kits with prelabeled transport and/or storage vials; sample tracking software; shipping materials.

A5.3 *Biorepository/Central Lab*

The Biorepository will archive biosamples from the clinical sites, and distribute them to the labs doing ACTIV-4 approved mechanistic studies and other research. If ACTIV-4 biosamples cannot be shipped to the Biorepository for some reason, the information will be captured and used to form a "Virtual Biorepository", so that those samples can contribute to the mechanistic studies as well.

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Appendix 6. Additional data inclusion from other trials merged under activ-4 platform

There are several clinical trials that have been testing safety and efficacy of Arm A and B regiments. Data collected in these trials will be included in the data analysis under this protocol provided that the subjects consented for the data to be shared or a waiver of consent and authorization had been granted by the reviewing IRB. The data will be labeled with subject ID and only include dates which are necessary to assess safety and efficacy endpoint events. All other private health information (PHI) will be removed. The data will be stored at the study coordinating center, University of Pittsburg, in HIPAA compliant electronic system and only coordinating center staff will have access to the data. The statistical analysis plan will account for this additional data.

Multi-platform Randomized-Controlled Trial (mpRCT) Analysis Plan for ACTIV-4, ATTACC, and REMAP-CAP (AARC)

Version 1.0
September 17, 2020

Background
Three operationally distinct trial platforms – ACTIV-4, ATTACC, and REMAP-CAP (*i.e.,* AARC) – are undertaking a jointly-developed, single multiplatform randomized controlled trial (mpRCT) evaluating the efficacy of antithrombotic strategies in patients hospitalized with COVID-19. Each of these platforms is randomizing a control arm (prophylactic-dose anticoagulation) against a therapeutic-dose anticoagulation through a common mpRCT. This document describes the agreed analytic plan across the three platforms for the question of efficacy related to therapeutic-dose anticoagulation.

Operational Separation
Each of the three platforms will operate individually but in coordination. The three trials will use closely harmonized protocols, and overlapping data collection, leadership, and oversight approaches. The decisions each platform makes based on the efficacy analyses may vary, but they agree on the joint efficacy analysis plan and will collaborate on making major decisions.

Inferential Synergy
The three platforms have agreed to prospectively federate patient-level data together to form a single mpRCT to evaluate the efficacy and safety of therapeutic-dose anticoagulation. This document describes the agreed analytic plan and an overview of the analysis implementation for the anticoagulation efficacy.

Interim Analysis Strategy
Interim analyses for anticoagulation efficacy will be conducted monthly with the first interim occurring upon finalization of this plan. At least 100 must be randomized across AARC between interims or the monthly interim will be skipped. The interim analyses will commence the first working day of each month. This will determine the time at which data are transferred for the interim analysis.

External events, such as other trials reporting positive/negative results of similar questions, may also trigger an analysis of the anticoagulation efficacy results. The same procedures, models, and analyses will take place, but at times dictated by the trials' leadership.

Implementation Plan
The efficacy analyses will be conducted by a Statistical Analysis Committee (SAC). The SAC is an independent group chartered to conduct interim analyses. The SAC members are unblinded to trial results. At the time of an interim analysis, each trial platform will send the necessary data for the interim analysis to the SAC. The format for this data delivery and the specifications for the data file necessary for the interim analyses will be set by the SAC. Each platform is responsible for the monitoring and quality of their data. The SAC receives this data and performs appropriate data investigation but does not change data nor have the responsibility to verify data or perform data cleaning or monitoring.

The SAC will conduct the efficacy analyses (described below) and will report the results of the interim analyses to the DSMBs for each of the trials (Figure 1). The DSMBs are then responsible

for the communication to each of the platforms' leadership/steering committees. The three platforms agree to jointly present and publicly disclose the outcome of the anticoagulation results.

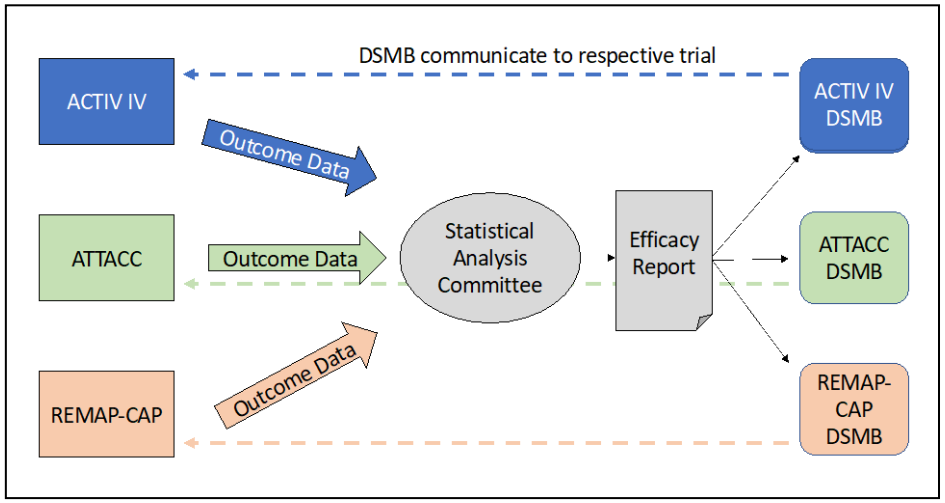

Figure 1: The communication plan across trials for the interim analyses

Response Adaptive Randomization

The REMAP-CAP and ATTACC trials utilize response adaptive randomization. At the interim analyses the response adaptive randomization proportions for the respective trials will be provided to their randomization services for their continued uses of response adaptive randomization. The ACTIV-4 trial is not currently utilizing response adaptive randomization.

The model run for REMAP-CAP for the response adaptive randomization will be different than the model run for the joint efficacy analysis. The REMAP-CAP model is conducted on all randomized patients within the REMAP-CAP trial, accounting for other interventions, to evaluate potential platform conclusions and set the randomization proportions. This *larger model* is not used to trigger success or futility, as the analysis detailed in this report is jointly used and agree upon to label superiority and futility of the anticoagulation domain. The RAR for REMAP-CAP will be updated at a REMAP-CAP specific interim.

The adaptive randomization proportions for the ATTACC platform will vary by d-dimer group and will be based on the mpRCT analysis outlined below.

Joint Efficacy Analysis Plan

Arms
Control Arm: The prophylactic-dose anticoagulation arm.
Treatment Arm: The therapeutic-dose anticoagulation arm.

Analysis Population
The joint efficacy analyses will be conducted on the joint anticoagulation PCR positive populations. This includes each patient who was randomized to either the control arm or the treatment arm who had one or more PCR positive test results.

If new arms are added to this joint analysis, this definition would include patients randomized to that additional arm. For clarity: REMAP-CAP is enrolling patients to other domains; a patient randomized to other domains but not the anticoagulation domain would not be included in this analysis. The alternative randomization to other arms will not be included in this joint analysis of efficacy for anticoagulation.

Primary Endpoint
The primary endpoint is an ordinal scale that is a composite of in-hospital mortality and organ support-free days (OSFD) through 21 days. Organ support is defined as delivery of one or more of the following while admitted to an ICU:

1. Receipt of invasive or non-invasive mechanical ventilatory support
2. High-flow nasal oxygen
3. Vasopressor therapy

The time on organ support is defined as the time from the start of organ support in ICU to the last use of organ support (intervening time off organ support between the first and last use are considered on organ support) during any and each ICU admission in the 21 days after randomization. Time out of ICU prior to the end of study day 21 is counted as organ support-free. The organ support "free-days" is defined as 21 days minus the time on organ support in ICU. If a patient dies in their acute hospital stay, then they are assigned the worst outcome value of –1. For patients that survive the hospital stay, they are assigned the number of organ support-free days, rounded to the nearest integer number of days. The best possible outcome of 22 is reserved for patients who survive and never have organ support in ICU. There are 24 possible outcomes for this ordinal outcome: all integers from –1 to 22. Higher values correspond to better patient outcomes.

Patient Subtypes
There are four patient subgroups – denoted *subtypes* – that have separate inferences for anticoagulation in this analysis. The subtypes are based on a cross classification of the baseline disease state severity (receiving organ support with ICU level of care vs not) and for those not receiving ICU organ support, the baseline d-dimer group, defined as low or high. Patients missing d-dimer level will be included in a separate subtype that will help inform the overall model through the Bayesian hierarchical structure, but no adaptive triggers for superiority or futility will be actionable for this subtype. For notation purposes we label the disease severity state, as s=1, for patients not receiving organ support in ICU at baseline, and s=2 for patients receiving organ support in ICU at baseline. For s=1, we have three d-dimer levels, labeled, d=1 (d-dimer low), d=2 (d-dimer high), and d=3 (d-dimer is missing). We refer to these using the s:d notation, where the 4 subtypes are 1:1, 1:2, 1:3, and 2:0 (we use the d-dimer notation d=0 for the organ support in ICU disease state). We use the term "severe" for the patients receiving

organ support in ICU at baseline and "moderate" for the patients not receiving organ support eg ICU level of care at baseline.

Adaptive Decision Rules

The following adaptive decision rules have been specified as labels for the efficacy outcomes. These rules are in place to determine the statistical triggers to label the treatment arm as superior to the control arm or to label the treatment arm as futile on the primary endpoint compared to the control arm. Each rule is separately evaluated within the three subtypes: moderate state: low d-dimer, moderate state: high d-dimer, and severe state. Efficacy conclusions will not be made for the subgroup of moderate patients with missing d-dimer levels.

1. **Superiority**

If the posterior probability of superiority within a subtype is greater than 99% then the treatment arm will be labeled as superior to the control arm for OSFDs.

2. **Futility**

If the posterior probability of at least an odds-ratio benefit of 1.2 is less than 5% then the treatment arm will be considered futile compared to the control arm.

Modeling of the Primary Endpoint

Let $Y_i = \{-1, 0, 1, \ldots, 21, 22\}$ denote the ordinal outcome (OSFD) for patient i. The probability of patient i, in state s, observing y OSFD or less is denoted as $\pi_{isy} = \Pr(Y_i \leq y)$. The model is a proportional odds model, where the log odds-ratio parameters in the model are structured so that a value > 0 implies treatment benefit, and an odds-ratio > 1 implies treatment benefit. The primary analysis model is formulated as follows:

$$\log\left(\frac{\pi_{isy}}{1 - \pi_{isy}}\right) = \alpha_{y,s} - \left[\gamma_P + \nu_{Site,s} + \lambda_{Time,s} + \theta_{a,s:d} + \beta_{Age,s} + \beta_{Sex,s} + \beta_d\right]$$

1. Each "platform," *P*, has a covariate adjustment in the model, *P*=1 is REMAP-CAP, *P*=2 is ATTACC, and *P*=3 is ACTIV-4.
2. The "site" variable is the clinical site within the trial. These will be set as distinct sites across all three trials. The site effects are estimated separately within the severe and moderate disease states, but do not vary by d-dimer level.
3. The "time" variable is an indicator of the time epoch in which a patient was enrolled in the trial, numbered increasing from the first most recent epoch to the earliest time for the analysis. Time epochs are two-week time periods, Time=1, and then every 2-week epoch, moving back in time throughout the enrollment in the trial, Time=2,3,4,…. The first two time periods are combined to form a 4-week category that serves as the referent. The time effects are modeled separately within the severe and moderate disease states, but do not vary by d-dimer level. The time epochs are defined to be the same time periods for both moderate and severe.
4. The "arm" to which a patient is randomized is labeled as *a* where *a*=1 is the control and *a*=2 is the treatment arm. The effects of arm vary by the disease state and the d-dimer level. The treatment effects for arm *a* within subtype *s*:*d* are modeled with the $\theta_{a,s:d}$ parameters.
5. The "age" variable is a categorical classification of age as ≤ 39, 40-49, 50-59, 60-69, 70-79, and 80+. The age effects will be estimated separately within the moderate and severe disease states, but do not vary by d-dimer level.
6. The "sex" variable is sex at birth. The sex effects will be estimated separately within the moderate and severe disease states, but do not vary by d-dimer level.
7. The additive effects of d-dimer levels are modeled with the β_d for d = 0, 1, 2, 3.

8. The $\alpha_{y,s}$ parameters determine the baseline rates of the ordinal outcome, which are modeled separately by disease state but not d-dimer level.

Model Priors

The ordinal endpoint rates are modeled using a Dirichlet prior where the individual probabilities for the 24 outcomes are based on one patient's weight on real-world evidence-based outcomes (details of the vector *P* in the Anticoagulation Domain Current State).

$$logit(\alpha_{y,s}) \sim Dirichlet(P)$$

For identifiability, the platform effect for ATTACC is defined such that $\gamma_2 \equiv 0$. The platform effects, $\gamma_P,\ P = 1, 3$, are modeled with independent N(0, 1) priors.

The site effects, ν_{Site}, are modeled using a hierarchical model where site is nested within the country of the site:

$$\nu_{Site,s} \sim N(\mu_{country,s}, \tau^2_{country,s}), site = 1, \dots, N_{Site}$$

$$\mu_{country,s} \sim N(0,1);\ \tau^2_{country,s} \sim IG(0.25, 0.1), s = 1,2$$

A referent country, the United States, will be set such that $\mu_{country,1} \equiv \mu_{country,2} \equiv 0$. The hyper-parameters of the site hierarchical model vary by disease state *s*.

The effect of age category is modeled with independent, normally distributed priors for each disease state. The prior mean for each age category effect is based on emerging data from external sources (specific details for the age prior in the Anticoagulation Domain Current State).

The effect of time (*Time=T*) is modeled using a second-order normal dynamic linear model separately by disease state, *s*. The two most recent time epochs are modeled as the referent time epochs with the time parameters set to 0. The preceding time epochs are modeled as a normal dynamic linear model as:

$$\lambda_1 = \lambda_2 \equiv 0$$

$$\lambda_3 \sim N(0, 0.15^2)$$

$$\lambda_T - 2\lambda_{T-1} + \lambda_{T-2} \sim N(0, \tau^2_{Time}), T \geq 4$$

The treatment effect parameters are relative to a control arm, which will be labeled in the arm-specific appendix. The treatment effect for the control arm, labeled as arm *a* = 1, will be set to 0 for each of the disease subtypes and d-dimer level:

$$\theta_{1,s:d} \equiv 0$$

The effects of the treatment arm are modeled hierarchically across disease subtype and d-dimer level. The treatment effects for each arm, *a*, are modeled as:

$$\theta_{a,2:0} \sim N(\mu_{a,1}, \tau^2_{a,1}),$$

$$\theta_{a,1} \sim N(\mu_{a,1}, \tau^2_{a,1}),$$

$$\theta_{a,s:d} \sim N\left(\theta_{a,1}, \tau^2_{a,2}\right), \qquad s:d = 1:1, 1:2, 1:3,$$

$$\mu_{a,1} \sim N(0,1);\ \tau^2_{a,1} \sim IG(0.25, 0.1),$$

$$\tau^2_{a,2} \sim IG(0.25, 0.0025)$$

The effect of d-dimer is modeled with a N(0, 1) prior for d = 2,3, and the parameters β_0 and β_1 are set to 0 for identifiability. Any additional covariates included in the model will have independent N(0, 1) priors unless otherwise specified.

Current State of the Statistical Model for the AARC Multi-Platform Randomized Clinical Trial Analysis Plan

Version 1.1 dated 19 November 2020

Version History:

Version 1.1 – Updated by Lindsay Berry; November 19, 2020

Version 1.1 is updated to replace Version 1.0 as the Current State document for the first analysis of the AARC mpRCT. The following edits were made to Version 1.0:

- The platform effects have been removed from the statistical model due to the possibility of non-identifiability of platform effects and site effects. On page 9, the table of parameters for platform effect has been deleted. On page 11 on Model Specification, the gamma parameters have been removed from the list of variables and the moderate and severe state likelihoods.

Version 1.0 - Written by Elizabeth Lorenzi, Lindsay Berry, and Scott Berry; September 26, 2020

Version 1.0 of this document was intended to be used for the first analysis of the anticoagulation mpRCT.

Terminology

Severe State is a patient that is receiving organ failure support in an ICU at baseline

Moderate State is defined by not being admitted to an ICU, or admitted to an ICU but not receiving organ failure support at baseline.

d-dimer is a baseline measure that will be classified into three groups: low, high, and missing. The definition of **high** is a value greater than or equal to 2 times the upper limit of normal.

Subtype is the smallest unit-of-analysis subgroup for this analysis

Modeling Conventions

Primary Endpoint

Composite of:	Definition	Notes
22	No organ support in an ICU	Not a possible outcome in the Severe state
0, 1, …, 21	Number of study days for which the subject is alive and not receiving organ support in an ICU up until the end of study day 21	Rounded to the nearest integer
−1	Death before discharge from an acute hospital	

Derivation Details

- Note that the SAC will receive the derived endpoint from data providers, and the derivation details below are provided solely for clarification purposes.
- Deriving this endpoint from hours
    - 0 organ support hours, OSFD = 22
    - Less than 12 hours on organ support, OSFD = 21
    - Off organ support for more than 12 hours, OSFD = 1
    - Less than 12 hours free of organ support, OSFD = 0
- Time of first organ support to time of last organ support within an ICU admission (intervening time free of organ support does not count)

Anticoagulation

- **2 Interventions**
- **Subgroups:** The anticoagulation domain includes pre-specified subtypes based on baseline d-dimer status. The subtypes are:
    - moderate state, low d-dimer;
    - moderate state, high d-dimer;
    - moderate state, missing d-dimer;
    - severe state
- **Statistical Triggers:** The domain allows superiority of the therapeutic dose anticoagulation over venous thromboprophylaxis and futility of therapeutic dose anticoagulation compared to the venous thromboprophylaxis. These conclusions apply individually to three of the four subtypes:
    - moderate state, low d-dimer;
    - moderate state, high d-dimer;
    - severe state

Intervention Name	Input Data File Code	Notes
Venous thromboprophylaxis	1	H1
Therapeutic anticoagulation	2	H2

Response Adaptive Randomization

The response adaptive randomization for the ATTACC trial should be set for the moderate/low d-dimer, and the moderate/high d-dimer groups. ATTACC does not “enroll” in a severe group, even if some are classified as ‘severe’ in the model. The Moderate group with missing d-dimer should remain equal randomization.

Adaptive randomization is based on the posterior probability that the odds-ratio for H2 is greater than 1 within each subtype. This probability should be truncated between 0.10 and 0.90.

MODEL TERMS SPECIFICATION

Model States and Notation	
State	Note
Moderate	Parameter s = 1
Severe	Parameter s = 2

Control rate probabilities by state			
Term	State	Prior	Note
$\alpha_{-1,s=1} \ldots \alpha_{22,s=1}$	Moderate	$\alpha_{k,s=1} = logit\left(\sum_{j=-1}^{k} p_{j,s=1}\right), k = -1, \ldots, 22$ where $(p_{-1,s=1}, \ldots, p_{22,s=1}) \sim Dirichlet(\hat{p}_{s=1})$ and $\hat{p}_{s=1}$ is a vector of the prior probabilities reported below.	Intercepts in ordinal model for moderate state
$\alpha_{-1,s=2} \ldots \alpha_{21,s=2}$	Severe	$\alpha_{k,s=2} = logit\left(\sum_{j=-1}^{k} p_{j,s=2}\right), k = -1, \ldots, 21$ where $(p_{-1,s=2}, \ldots, p_{21,s=2}) \sim Dirichlet(\hat{p}_{s=2})$ and $\hat{p}_{s=2}$ is a vector of the prior probabilities reported below. The severe model is constrained such that $p_{22,s=2} = 0$ and $\alpha_{21,s=2} = \infty$.	Intercepts in ordinal model for severe state

Notes:

- If there is an outcome in the ordinal scale that did not occur in the data for a state, then that outcome will be combined to a single outcome with a neighboring outcome for that state (the worse outcome).
- For example, if the outcome 11 never occurred in the moderate state, then a combined outcome of 10 & 11 will be modeled for the moderate state in this analysis.
- For the severe state, $\hat{p}_{s=2}$has 29.5% probability on –1, 22.5% on 0, 1.5% on each outcome from 1-10, and 3.0% on each outcome from 11-21. The sum of the Dirichlet prior concentration parameter is 1.
- For the moderate state, $\hat{p}_{s=1}$has 9.0% probability on –1, 7.1% on 0, 0.4% on each outcome from 1-10, 0.9% on each outcome from 11-21, and 70% probability on 22. The sum of the Dirichlet prior concentration parameter is 1.

Main Effects of Era by State

Term	Description	Prior	Note
$\lambda_{T=1,s}$	Most recent 4 weeks**	0	Set to 0
$\lambda_{T=2,s} - \lambda_{T=1,s}$	Difference for 2-week period after 1 months from most recent	N(0, 0.15^2)	
$\lambda_{T,s} - 2\lambda_{T-1,s} + \lambda_{T-2,s}$	Difference for each additional 2-week bucket	$N(0, \tau_\lambda^2)$ $\tau_\lambda^2 \sim IG(0.25, 0.00562)$	

Definition of Era Terms by State	
Term	Description
$\lambda_{T=1,s}$	Most recent 4 weeks** in state *s*
$\lambda_{T=2,s}$	4-6 week from time 0 in state *s*
$\lambda_{T=3,s}$	6-8 week from time 0 in state *s*
…	Continuation of buckets as time progresses

Notes:

- **Time 0: Time of randomization of the most recent subject with a complete outcome in the analysis dataset. Time 0 is the same for the severe and moderate state.
- The time era buckets are the same for each state, but we estimate time effects by state.
- Time buckets with <5 subjects in a state randomized within the bucket may be combined with a neighboring bucket for that state.

Main Effects of Site by state. Site modeled within Parent Country c_R where $c_R = 1, \dots, C$		
Term	Description	Prior
$\nu_{R=1,s}$	Site 1	$[\nu_{R,s}] \sim N(\mu_{C_R,s}, \tau^2_{C_R,s})\ R = 1, \dots, N_R,$ $[\mu_{C_R,s}] \sim N(0,1);\ [\tau^2_{C_R,s}] \sim IG(0.25,0.1),$ where c=2,…,C. s=1,2 $[\mu_{1,s}] = 0$
$\nu_{R=2,s}$	Site 2	
$\nu_{R=3,s}$ …	Site 3	
$\nu_{R=N_R,s}$	Site N_R	
Note: c=1 will represent the US.		

Notes:

- All sites within a country that have <5 subjects randomized in a state in the analysis population will be combined into a single site within that country.

Main Effects of Age Category			
Term	Description	Prior	Note
$\beta_{age=1,s}$	39 years old or less	N(1.5300, 1)	
$\beta_{age=2,s}$	40-49	N(1.2959, 1)	
$\beta_{age=3,s}$	50-59	N(0.6054, 1)	
$\beta_{age=4,s}$	60-69	0	Set to 0
$\beta_{age=5,s}$	70-79	N(−0.4837, 1)	
$\beta_{age=6,s}$	80+	N(−0.3900, 1)	

Main Effects of Sex at Birth Category by State			
Term	Description	Prior	Note
$\beta_{Sex=1,s}$	Male	Set to 0	Referent
$\beta_{Sex=2,s}$	Female	N(0, 1)	

Main Effects of D-Dimer Subgroup in Moderate State			
Term	Description	Prior	Note
$\beta_{D-Dimer=0}$	Missing baseline d-dimer	N(0, 1)	
$\beta_{D-Dimer=1}$	Low baseline d-dimer	Set to 0	Referent
$\beta_{D-Dimer=2}$	High baseline d-dimer	N(0, 1)	

Model Treatment Parameters:

Model Parameters	State (s)	Prior Distribution	Description of Parameter
$\theta_{1,s}$	1, 2	0	Effect of No Therapeutic Anticoagulation
$\theta_{2,2}$	2	$N(\mu_{\theta,1}, \tau^2_{\theta,1})$	Effect of Therapeutic Anticoagulation in severe state
$\theta_{2,1}$	1	$N(\mu_{\theta,1}, \tau^2_{\theta,1})$	Effect of Therapeutic Anticoagulation in moderate state
$\theta_{2,1:0}$	1	$N(\theta_{2,1}, \tau^2_{\theta,2})$	Effect of Therapeutic Anticoagulation in moderate state, missing baseline D-Dimer
$\theta_{2,1:1}$	1	$N(\theta_{2,1}, \tau^2_{\theta,2})$	Effect of Therapeutic Anticoagulation in moderate state, low baseline D-Dimer
$\theta_{2,1:2}$	1	$N(\theta_{2,1}, \tau^2_{\theta,2})$	Effect of Therapeutic Anticoagulation in moderate state, high baseline D-Dimer
$\mu_{\theta,1}$	1,2	N(0, 1)	Shared mean for nested parameters
$\tau^2_{\theta,1}$	1,2	IG(0.25, 0.1)	Shared variance for nested state parameters
$\tau^2_{\theta,2}$	1	IG(0.25, 0.0025)	Shared variance for nested moderate parameters

MODEL SPECIFICATION

Modeling Strategy for Disease States

- There are separate, independent covariate effects for the moderate and severe states. This includes the effects of site, age, sex, and time.
- The α parameters control the distribution of the ordinal outcome. There will two separate, independent vectors of α parameters: one for the moderate state and one for the severe state. In the severe state, it is not possible for a subject to have an outcome of 22 (no organ support). To adjust for this, we set the probability of a 22 equal to 0, effectively forcing $\alpha_{21,s=2} = \infty$.
- Intervention effects will vary by subtype and there will be borrowing between the subtypes.

Let the following variables be assigned for subject i:

- s_i = disease state
- r_i = site
- age_i = age group
- sex_i = biological sex at birth
- T_i = randomization era
- D_i= d-dimer subgroup. Possible values are 0 (missing), 1 (low), and 2 (high) for subjects in the moderate state. Severe patients have no baseline d-dimer subgroup.
- a_i = arm (intervention)

The ordinal outcomes are labeled $Y_{i,s} \in \{-1,0,1,\ldots,21,22\}$ for the OSFD outcome of patient i in state s. We model the probability of an outcome *y* or worse for patient i in state s as $\pi_{iys} = Pr(Y_i \leq y | s_i = s)$.

Severe State Likelihood:

For subjects that are in the Severe state, we model the ordinal outcome Y_i as:

$$log\left(\frac{\pi_{iy2}}{1-\pi_{iy2}}\right) = \alpha_{y,s=2} - (v_{r_i,s=2} + \beta_{age_i,s=2} + \beta_{sex_i,s=2} + \lambda_{T_i,s=2} + \theta_{a_i,2})$$

Moderate State Likelihood:

For subjects that are in the Moderate state, we model the ordinal outcome $Y_{i,s=1}$as follows:

$$log\left(\frac{\pi_{iy1}}{1-\pi_{iy1}}\right) = \alpha_{y,s=1} - (v_{r_i,s=1} + \beta_{D_i} + \beta_{age_i,s=1} + \beta_{sex_i,s=1} + \lambda_{T_i,s=1} + \theta_{a_i,1:D_i})$$

- The moderate state adjusts for the baseline d-dimer subgroup through the parameter β_D.

Transition from Moderate to Severe State:

This mpRCT analysis does not include any modeling of patients that transition from the moderate to severe state. A patient who transitions would only be included in the disease state in which they were randomized to an anticoagulation intervention.

Statistical Triggers

- For each intervention, we list all possible statistical triggers
- Triggers are made by subtype

Intervention	Subtype	Conclusion	Comparator	Decision quantity		Threshold
Therapeutic anticoagulation	S=2 Severe	Superiority	Venous thromboprophylaxis	Pr($exp(\theta_{2,2})$ >1)	>	0.99
Therapeutic anticoagulation	S=2 Severe	Futility	Venous thromboprophylaxis	Pr($exp(\theta_{2,2})$ >1.2)	<	0.05
Therapeutic anticoagulation	S=1,D=1 Moderate, Low D-Dimer	Superiority	Venous thromboprophylaxis	Pr($exp(\theta_{2,1:1})$ >1)	>	0.99
Therapeutic anticoagulation	S=1,D=1 Moderate, Low D-Dimer	Futility	Venous thromboprophylaxis	Pr($exp(\theta_{2,1:1})$ >1.2)	<	0.05
Therapeutic anticoagulation	S=1,D=2 Moderate, High D-Dimer	Superiority	Venous thromboprophylaxis	Pr($exp(\theta_{2,1:2})$ >1)	>	0.99
Therapeutic anticoagulation	S=1,D=2 Moderate, High D-Dimer	Futility	Venous thromboprophylaxis	Pr($exp(\theta_{2,1:2})$ >1.2)	<	0.05

Current State of the Statistical Model for the AARC Multi-Platform Randomized Clinical Trial Analysis Plan

Version 1.2 dated 5 January 2021

Version History:

Version 1.2 – Updated by Elizabeth Lorenzi; January 5, 2021

Version 1.2 is updated to replace Version 1.1 as the Current State document for the analysis of the AARC mpRCT. The following edits were made to Version 1.1:

- OSFD values of 21 and 22 are pooled together in the analysis model for the moderate state. This is an artifact of the use of study days to calculate OSFD by some platforms, where the value of 21 may not be calculable.
- Statistical triggers for the severe subtype are no longer available as possible platform conclusions. These have been grayed out in the table and text is displayed with a strikethrough.

Version 1.1 – Updated by Lindsay Berry; November 19, 2020

Version 1.1 is updated to replace Version 1.0 as the Current State document for the first analysis of the AARC mpRCT. The following edits were made to Version 1.0:

- The platform effects have been removed from the statistical model due to the possibility of non-identifiability of platform effects and site effects. On page 9, the table of parameters for platform effect has been deleted. On page 11 on Model Specification, the gamma parameters have been removed from the list of variables and the moderate and severe state likelihoods.

Version 1.0 - Written by Elizabeth Lorenzi, Lindsay Berry, and Scott Berry; September 26, 2020

Version 1.0 of this document was intended to be used for the first analysis of the anticoagulation mpRCT.

Terminology

Severe State is a patient that is receiving organ failure support in an ICU at baseline

Moderate State is defined by not being admitted to an ICU, or admitted to an ICU but not receiving organ failure support at baseline.

d-dimer is a baseline measure that will be classified into three groups: low, high, and missing. The definition of **high** is a value greater than or equal to 2 times the upper limit of normal.

Subtype is the smallest unit-of-analysis subgroup for this analysis

Modeling Conventions

Primary Endpoint

Composite of:	Definition	Notes
22	No organ support in an ICU	Not a possible outcome in the Severe state For moderate state will be pooled with the 21 outcomes
0, 1, …, 21	Number of study days for which the subject is alive and not receiving organ support in an ICU up until the end of study day 21	Rounded to the nearest integer
−1	Death before discharge from an acute hospital	

Derivation Details

- Note that the SAC will receive the derived endpoint from data providers, and the derivation details below are provided solely for clarification purposes.
- For moderate state, the outcome levels of 21 and 22 are combined into a single level of the ordinal outcome, labeled as a 21.

Anticoagulation

- **2 Interventions**
- **Subgroups:** The anticoagulation domain includes pre-specified subtypes based on baseline d-dimer status. The subtypes are:
    - moderate state, low d-dimer;
    - moderate state, high d-dimer;
    - moderate state, missing d-dimer;
    - severe state
- **Statistical Triggers:** The domain allows superiority of the therapeutic dose anticoagulation over venous thromboprophylaxis and futility of therapeutic dose anticoagulation compared to the venous thromboprophylaxis. These conclusions apply individually to three of the four subtypes:
    - moderate state, low d-dimer;
    - moderate state, high d-dimer;
    - severe state

Intervention Name	Input Data File Code	Notes
Venous thromboprophylaxis	1	H1
Therapeutic anticoagulation	2	H2

Response Adaptive Randomization

The response adaptive randomization for the ATTACC trial should be set for the moderate/low d-dimer, and the moderate/high d-dimer groups. ATTACC does not “enroll” in a severe group, even if some are classified as ‘severe’ in the model. The Moderate group with missing d-dimer should remain equal randomization.

Adaptive randomization is based on the posterior probability that the odds-ratio for H2 is greater than 1 within each subtype. This probability should be truncated between 0.10 and 0.90.

MODEL TERMS SPECIFICATION

Model States and Notation	
State	Note
Moderate	Parameter s = 1
Severe	Parameter s = 2

Control rate probabilities by state			
Term	State	Prior	Note
$\alpha_{-1,s=1} \ldots \alpha_{22,s=1}$	Moderate	$\alpha_{k,s=1} = logit\left(\sum_{j=-1}^{k} p_{j,s=1}\right), k = -1, \ldots, 21$ where $(p_{-1,s=1}, \ldots, p_{21,s=1}) \sim Dirichlet(\hat{p}_{s=1})$ and $\hat{p}_{s=1}$ is a vector of the prior probabilities reported below.	Intercepts in ordinal model for moderate state
$\alpha_{-1,s=2} \ldots \alpha_{21,s=2}$	Severe	$\alpha_{k,s=2} = logit\left(\sum_{j=-1}^{k} p_{j,s=2}\right), k = -1, \ldots, 21$ where $(p_{-1,s=2}, \ldots, p_{21,s=2}) \sim Dirichlet(\hat{p}_{s=2})$ and $\hat{p}_{s=2}$ is a vector of the prior probabilities reported below. The severe model is constrained such that $p_{22,s=2} = 0$ and $\alpha_{21,s=2} = \infty$.	Intercepts in ordinal model for severe state

Notes:

- If there is an outcome in the ordinal scale that did not occur in the data for a state, then that outcome will be combined to a single outcome with a neighboring outcome for that state (the worse outcome).
- For example, if the outcome 11 never occurred in the moderate state, then a combined outcome of 10 & 11 will be modeled for the moderate state in this analysis.
- For moderate state, the outcome levels of 21 and 22 are combined into a single level of the ordinal outcome, labeled 21.
- For the severe state, $\hat{p}_{s=2}$has 29.5% probability on –1, 22.5% on 0, 1.5% on each outcome from 1-10, and 3.0% on each outcome from 11-21. The sum of the Dirichlet prior concentration parameter is 1.
- For the moderate state, $\hat{p}_{s=1}$has 9.0% probability on –1, 7.1% on 0, 0.4% on each outcome from 1-10, 0.9% on each outcome from 11-20, and 70.9% probability on combined 21 and 22. The sum of the Dirichlet prior concentration parameter is 1.

Main Effects of Era by State			
Term	Description	Prior	Note
$\lambda_{T=1,s}$	Most recent 4 weeks**	0	Set to 0

$\lambda_{T=2,s} - \lambda_{T=1,s}$	Difference for 2-week period after 1 months from most recent	N(0, 0.15^2)	
$\lambda_{T,s} - 2\lambda_{T-1,s} + \lambda_{T-2,s}$	Difference for each additional 2-week bucket	$N(0, \tau_\lambda^2)$ $\tau_\lambda^2 \sim IG(0.25, 0.00562)$	

Definition of Era Terms by State	
Term	Description
$\lambda_{T=1,s}$	Most recent 4 weeks** in state *s*
$\lambda_{T=2,s}$	4-6 week from time 0 in state *s*
$\lambda_{T=3,s}$	6-8 week from time 0 in state *s*
…	Continuation of buckets as time progresses

Notes:

- **Time 0: Time of randomization of the most recent subject with a complete outcome in the analysis dataset. Time 0 is the same for the severe and moderate state.
- The time era buckets are the same for each state, but we estimate time effects by state.
- Time buckets with <5 subjects in a state randomized within the bucket may be combined with a neighboring bucket for that state.

Main Effects of Site by state. Site modeled within Parent Country c_R where $c_R = 1, \dots, C$		
Term	Description	Prior
$\nu_{R=1,s}$	Site 1	$[\nu_{R,s}] \sim N(\mu_{C_R,s}, \tau^2_{C_R,s})\ R = 1, \dots, N_R,$ $[\mu_{C_R,s}] \sim N(0,1);\ [\tau^2_{C_R,s}] \sim IG(0.25,0.1),$ where c=2,…,C. s=1,2 $[\mu_{1,s}] = 0$
$\nu_{R=2,s}$	Site 2	
$\nu_{R=3,s}$ …	Site 3	
$\nu_{R=N_R,s}$	Site N_R	
Note: c=1 will represent the US.		

Notes:

- All sites within a country that have <5 subjects randomized in a state in the analysis population will be combined into a single site within that country.

Main Effects of Age Category			
Term	Description	Prior	Note
$\beta_{age=1,s}$	39 years old or less	N(1.5300, 1)	
$\beta_{age=2,s}$	40-49	N(1.2959, 1)	
$\beta_{age=3,s}$	50-59	N(0.6054, 1)	
$\beta_{age=4,s}$	60-69	0	Set to 0
$\beta_{age=5,s}$	70-79	N(−0.4837, 1)	
$\beta_{age=6,s}$	80+	N(−0.3900, 1)	

Main Effects of Sex at Birth Category by State			
Term	Description	Prior	Note
$\beta_{Sex=1,s}$	Male	Set to 0	Referent
$\beta_{Sex=2,s}$	Female	N(0, 1)	

Main Effects of D-Dimer Subgroup in Moderate State			
Term	Description	Prior	Note
$\beta_{D-Dimer=0}$	Missing baseline d-dimer	N(0, 1)	
$\beta_{D-Dimer=1}$	Low baseline d-dimer	Set to 0	Referent
$\beta_{D-Dimer=2}$	High baseline d-dimer	N(0, 1)	

Model Treatment Parameters:

Model Parameters	State (s)	Prior Distribution	Description of Parameter
$\theta_{1,s}$	1, 2	0	Effect of No Therapeutic Anticoagulation
$\theta_{2,2}$	2	$N(\mu_{\theta,1}, \tau^2_{\theta,1})$	Effect of Therapeutic Anticoagulation in severe state
$\theta_{2,1}$	1	$N(\mu_{\theta,1}, \tau^2_{\theta,1})$	Effect of Therapeutic Anticoagulation in moderate state
$\theta_{2,1:0}$	1	$N(\theta_{2,1}, \tau^2_{\theta,2})$	Effect of Therapeutic Anticoagulation in moderate state, missing baseline D-Dimer
$\theta_{2,1:1}$	1	$N(\theta_{2,1}, \tau^2_{\theta,2})$	Effect of Therapeutic Anticoagulation in moderate state, low baseline D-Dimer
$\theta_{2,1:2}$	1	$N(\theta_{2,1}, \tau^2_{\theta,2})$	Effect of Therapeutic Anticoagulation in moderate state, high baseline D-Dimer
$\mu_{\theta,1}$	1,2	N(0, 1)	Shared mean for nested parameters
$\tau^2_{\theta,1}$	1,2	IG(0.25, 0.1)	Shared variance for nested state parameters
$\tau^2_{\theta,2}$	1	IG(0.25, 0.0025)	Shared variance for nested moderate parameters

MODEL SPECIFICATION

Modeling Strategy for Disease States

- There are separate, independent covariate effects for the moderate and severe states. This includes the effects of site, age, sex, and time.
- The α parameters control the distribution of the ordinal outcome. There will two separate, independent vectors of α parameters: one for the moderate state and one for the severe state. In the severe state, it is not possible for a subject to have an outcome of 22 (no organ support). To adjust for this, we set the probability of a 22 equal to 0, effectively forcing $\alpha_{21,s=2} = \infty$.
- Intervention effects will vary by subtype and there will be borrowing between the subtypes.

Let the following variables be assigned for subject i:

- s_i = disease state
- r_i = site
- age_i = age group
- sex_i = biological sex at birth
- T_i = randomization era
- D_i= d-dimer subgroup. Possible values are 0 (missing), 1 (low), and 2 (high) for subjects in the moderate state. Severe patients have no baseline d-dimer subgroup.
- a_i = arm (intervention)

The ordinal outcomes are labeled $Y_{i,S} \in \{-1,0,1,\ldots,21,22\}$ for the OSFD outcome of patient i in state s. We model the probability of an outcome *y* or worse for patient i in state s as $\pi_{iys} = Pr(Y_i \leq y | s_i = s)$.

Severe State Likelihood:

For subjects that are in the Severe state, we model the ordinal outcome Y_i as:

$$log\left(\frac{\pi_{iy2}}{1-\pi_{iy2}}\right) = \alpha_{y,s=2} - (v_{r_i,s=2} + \beta_{age_i,s=2} + \beta_{sex_i,s=2} + \lambda_{T_i,s=2} + \theta_{a_i,2})$$

Moderate State Likelihood:

For subjects that are in the Moderate state, we model the ordinal outcome $Y_{i,s=1}$as follows:

$$log\left(\frac{\pi_{iy1}}{1-\pi_{iy1}}\right) = \alpha_{y,s=1} - (v_{r_i,s=1} + \beta_{D_i} + \beta_{age_i,s=1} + \beta_{sex_i,s=1} + \lambda_{T_i,s=1} + \theta_{a_i,1:D_i})$$

- The moderate state adjusts for the baseline d-dimer subgroup through the parameter β_D.

Transition from Moderate to Severe State:

This mpRCT analysis does not include any modeling of patients that transition from the moderate to severe state. A patient who transitions would only be included in the disease state in which they were randomized to an anticoagulation intervention.

Statistical Triggers

- For each intervention, we list all possible statistical triggers
- Triggers are made by subtype

Intervention	Subtype	Conclusion	Comparator	Decision quantity		Threshold
~~Therapeutic anticoagulation~~	~~S=2 Severe~~	~~Superiority~~	~~Venous thromboprophylaxis~~	~~$\Pr(exp(\theta_{2,2}) > 1)$~~	~~>~~	~~0.99~~
~~Therapeutic anticoagulation~~	~~S=2 Severe~~	~~Futility~~	~~Venous thromboprophylaxis~~	~~$\Pr(exp(\theta_{2,2}) > 1.2)$~~	~~<~~	~~0.05~~
Therapeutic anticoagulation	S=1,D=1 Moderate, Low D-Dimer	Superiority	Venous thromboprophylaxis	$\Pr(exp(\theta_{2,1:1}) > 1)$	>	0.99
Therapeutic anticoagulation	S=1,D=1 Moderate, Low D-Dimer	Futility	Venous thromboprophylaxis	$\Pr(exp(\theta_{2,1:1}) > 1.2)$	<	0.05
Therapeutic anticoagulation	S=1,D=2 Moderate, High D-Dimer	Superiority	Venous thromboprophylaxis	$\Pr(exp(\theta_{2,1:2}) > 1)$	>	0.99
Therapeutic anticoagulation	S=1,D=2 Moderate, High D-Dimer	Futility	Venous thromboprophylaxis	$\Pr(exp(\theta_{2,1:2}) > 1.2)$	<	0.05

Statistical Analysis Plan for the Multi-Platform Randomized Clinical Trial of Therapeutic Anticoagulation for COVID-19

Version history

Version 1: Initiated December 21, 2020; Finalized January 5, 2021

SAP Authors

Ewan Goligher, University of Toronto, Toronto, CA

Patrick Lawler, University of Toronto, Toronto, CA

Scott Berry, Berry Consultants, Austin, TX, USA

Judith Hochman, NYU Grossman School of Medicine/NYU Langone Health, New York, NY

Matthew D. Neal, University of Pittsburgh, PA, USA

Bridget-Anne Kirwan, Socar Research, Nyon, Switzerland

Lindsay Berry, Berry Consultants, Austin, TX, USA

Elizabeth Lorenzi, Berry Consultants, Austin, TX, USA

Steven Webb, Monash University, Melbourne, Victoria, Australia

Colin McArthur, University of Auckland, Auckland, NZ

Derek C. Angus, University of Pittsburgh and UPMC Health System, PA, USA

Charlotte Bradbury, University Hospitals Bristol, Bristol, UK

Michael Farkouh, University of Toronto, Toronto, CA

Bryan McVerry, University of Pittsburgh and UPMC Health System, PA, USA

Jeff Berger, NYU Grossman School of Medicine/NYU Langone Health, NY, NY, USA

Michelle Ng Gong, Albert Einstein College of Medicine, NY, NY. USA

Anthony Gordon, Imperial College, London, UK

Ryan Zarychanski, University of Manitoba, Winnipeg, CA

SAP Introduction

This is the statistical plan for the analysis of the Covid-19 Therapeutic Anticoagulation Multi-Platform RCT (mpRCT). This plan has been prespecified by the investigators prior to unblinding of the data for the Severe state of the mpRCT.

mpRCT status at time of SAP preparation

Enrollment in the severe state was halted across platforms on December 18, 2020. The severe state-specific conclusion was publicly disclosed on December 22, 2020. The predefined statistical trigger for futility was met with data available to the Statistical Analytic Committee (SAC), and hence the results for the severe state will be unblinded and made public. This document prespecifies the analysis plan for this unblinding as well as future unblinding of the remaining subtypes. This SAP is relevant for the potential conclusions for the severe state and moderate states for comparing therapeutic anticoagulation to pharmacological venous thrombophrophylaxis. The first trigger for the severe state will utilize this analysis plan for reporting.

The authors of this document are blinded to all individual data. The authors are aware that the statistical trigger for futility has been reached for therapeutic anticoagulation in the severe state, have been advised of the primary model result for the interim analysis that prompted the trigger, along with the raw mortality rates and major bleeding event rates in the severe state. The moderate state is continuing randomization.

Prior analysis plan documents

There are three analysis plan documents that are the precursor to this statistical analysis plan:

1. **Multi-platform Randomized-Controlled Trial (mpRCT) Analysis Plan for ACTIV-4, ATTACC, and REMAP-CAP (AARC)** was created on September 17, 2020. This document described the creation of the AARC mpRCT and the agreed analysis plan.
2. Simulation Report for **Multi-platform Randomized-Controlled Trial (mpRCT) Analysis Plan for ACTIV-4, ATTACC, and REMAP-CAP** was created September 21, 2020. This document describes the clinical trial simulations conducted to characterize the operating characteristics of the analysis plan for the mpRCT.
3. The **Current State Document** dated November 19, 2020 is a complete specification of the statistical model and thresholds for the interim analyses to be conducted. This is a document created by the blinded joint steering committees as instructions to the Statistical Analysis Committee (SAC) for running interim analyses. This document can evolve as the mpRCT evolves incorporating the adaptations taking place in the three adaptive platform trials. The current state document referenced here is the current state document in place when the statistical trigger for futility in the severe state was met.

Reporting strategy

This SAP describes the planned analyses for the entire mpRCT. As outlined below, various subtypes within the mpRCT (defined below) are expected to report at different times. Moreover, given the complex process of federating data for analysis across platforms, multiple reports describing the results of analysis may be prepared and published to ensure expedited dissemination of mpRCT findings. It is anticipated that for each subtype, preliminary reports will describe key primary and secondary findings and limited subgroup analyses. Endpoints to be reported in the preliminary reports include:

- Organ support-free days to day 21 (primary endpoint)

- In-hospital mortality (co-primary endpoint)
- Major thrombotic events (key secondary endpoint)
- Major bleeding (key safety endpoint)

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

Design Considerations

The mpRCT is designed with a Bayesian analysis as the primary analysis method for the trial. There is one overarching Bayesian model, prespecified 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.

The mpRCT SAP is a joint analysis plan for three separate adaptive platform trials. The three platforms are ACTIV-4a, ATTACC, and REMAP-CAP. The three platforms have agreed to analyze the results of the comparison between two interventions, therapeutic anticoagulation and prophylactic anticoagulation, in a combined effort – labeled a multi-platform randomized-controlled trial (mpRCT). The three platform do not report their results separately–they have agreed this joint effort would be the primary method for analyzing these two interventions across the severe and moderate states. The analysis methods take the philosophy that the three platforms are essentially three multicenter randomized trials and hence combining the results together is a larger multicenter randomized trial. In this section we describe the basic defined structure of the analysis plan. This includes definitions for the patient subgroups, referred to as subtypes, the interventions, the primary endpoint, and the adaptive design. Italicized terms are defined terms by the mpRCT for these analyses.

Patient Subgroups

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

The primary analysis for the mpRCT creates four distinct populations to analyze potential differential benefit of the interventions. In this mpRCT these distinct groups are labeled as *subtypes*. The four subtypes in this mpRCT are: 1) patients in the severe state; 2) patients in the moderate state with a high baseline d-dimer; 3) patients in the moderate state with a low baseline d-dimer; 4) patients in the moderate state with unknown baseline d-dimer.

A baseline d-dimer level more than 2 times the upper limit of normal is defined as being a *high* d-dimer. Any value less than two times the upper limit of normal is defined as a *low* d-dimer.

Interventions

The two interventions for this mpRCT are labeled as *therapeutic anticoagulation* (TAC), which plays the inferential role of the investigational treatment and *venous thromboprophylaxis* (VTP) (referred to as Control), which plays the inferential role of the control arm. These interventions are defined as:

1. **TAC**: systemic anticoagulation using unfractionated or low molecular weight heparin to achieve the degree of anticoagulation generally required for the treatment of venous thromboembolism in accordance with usual local practice.
2. **VTP**: usual care strategies, including anticoagulation with lower doses of unfractionated or low molecular weight heparin or other anticoagulant as prophylaxis against the development of venous thromboembolism in accordance with usual local practice.

Primary Endpoint

The primary endpoint for the mpRCT 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. If a patient dies during their acute hospitalization they are coded as having –1 OSFDs, which is the worst outcome for the measure. Any patient on ICU-level organ support for 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 1, …, 21 refer to the number of days alive and free of organ support, with smaller values being worse outcomes. The value of *22* is reserved for a patient that is alive and never on ICU-level organ support in the first 21 days. Therefore, the primary outcome OSFDs is an ordinal outcome with 24 possible outcomes for each patient, –1, 0, 1, 2, …, 21, 22. The details for the calculation of the endpoint is detailed in the mpRCT SAC data dictionaries versions 20201210A (ATTACC and ACTIV) and 10.1 (REMAP-CAP).

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. In REMAP-CAP and ATTACC, high flow nasal cannula is considered to be ICU-level organ support when applied inspiratory flow is 30 L/min or higher at an $FiO_2 \geq 0.4$. In ACTIV-4, 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-4 defines any hospitalized area able to deliver the above organ-support as an ICU. ATTACC and REMAP-CAP specifically define regions as ICUs and non-ICUs. These matters are documented in detail in the SAC data dictionaries (see ATTACC/ACTIV version 20201210A).

This primary endpoint is an ordinal outcome and the primary analysis model analyzes the outcome as ordinal, with a cumulative logistic proportional effects 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 TAC an OR > 1 implies improved outcomes on OSFDs for the TAC intervention compared to the VTP intervention.

Adaptive Design

There is a prospective adaptive analysis plan for the mpRCT. The plan is to have approximately monthly analyses of the mpRCT 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 TAC to VTP is defined as a high probability of an OR greater than 1 for TAC and hence improved outcomes in OSFDs for the TAC

intervention. Futility will be declared if there is a high probability that the effect of TAC 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 mpRCT defines two statistical triggers within the trial that, at any analysis of the trial, would result in a declaration of superiority or futility as multi-platform conclusions.

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

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

For the purpose of this analysis plan, *inferiority* for TAC is defined as an OR<1.

At each analysis of the mpRCT each statistical trigger would be checked for three of the subtypes:

1. Severe state subtype
2. Moderate state, high d-dimer subtype
3. Moderate state, low d-dimer subtype

The fourth subtype, moderate state with unknown d-dimer, the same conclusions will be investigated when the two moderate state subtypes have reached a conclusion but would not trigger a declaration at an interim point. The fourth analysis subtype is part of the primary analysis model but does not have adaptive statistical triggers.

Endpoint adjudication

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

Unblinding

On December 18-19, 2020, the DSMBs advised that the statistical trigger for futility was met in the Severe state. The investigators have been unblinded to this statistical trigger in the Severe state with respect to the OR for the primary endpoint, organ support-free days, mortality rates, and rates of major bleeding.

Analysis Populations

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

1. **mpRCT confirmed (Primary)**. The mpRCT primary analysis population includes all enrolled patients with laboratory-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 all patients from all four subtypes. This analysis population will remain primary even if one subtype has a trigger before the other subtypes. The primary analysis will be conducted by the unblinded statistical

analysis committee and the results for the subtypes with statistical triggers will be reported.

The following analysis groups will be defined for each public disclosure corresponding to each subtype being unblinded.

2. **mpRCT confirmed unblinded.** The subset of patients in the mpRCT confirmed population that belong to the subtype(s) being reported (i.e. those specific subtype(s) that have been unblinded for reporting). This population consists entirely of patients with laboratory-confirmed COVID-19 randomized to therapeutic anticoagulation or prophylactic anticoagulation and analyzed according to the intention-to-treat principle.
3. **mpRCT confirmed and suspected unblinded** (exploratory sensitivity analyses only)**.** The mpRCT severe state population including patients in REMAP-CAP with suspected but unconfirmed Covid-19 who belong to the subtypes that are unblinded for reporting.
4. **mpRCT per protocol.** This consists of the patients in the mpRCT confirmed unblinded population who have been treated as per protocol. In this analysis that is defined as 1) patients randomized to TAC and who received at least 1 dose of anticoagulation at therapeutic doses on the first full study after randomization **or** within 48 hours of randomization, **and** 2) patients randomized to VTP and who did not receive anticoagulants at therapeutic doses on the first or second full study day after randomization.

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 mpRCT, 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.
   - Detailed definitions for OSFDs are specified in the mpRCT SAC data dictionary
   - Missing values for organ support-free days will be treated as “missing and ignored”. 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. **Mortality**
   - This is a time-to-event endpoint through 28 days and 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.

- 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.

4. **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.
   - 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

5. **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.
   - 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.

6. **Renal replacement-free days to day 28**
   - An ordinal outcome of the number of days free of renal replacement therapy.
   - All platforms 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

7. **ECMO utilization on or before day 28**
   - A dichotomous endpoint of use of extracorporeal membrane oxygenation.

8. **Duration of ICU stay**
   - A time-to-event endpoint of leaving the ICU alive. If a patient is known to leave the ICU and return to the ICU within 21 days that intervening time will be ignored.
   - 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.

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.

10. **ICU readmission**
    - A dichotomous endpoint of readmission to ICU.

11. **Major bleeding on or before day 14**
    - A dichotomous endpoint of major bleeding as defined according to International Society of Thrombosis and Hemostasis (ISTH) criteria in non-surgical patients.
    - The endpoint is censored at 14 days to correspond with the intervention duration.

12. **Fatal bleeding on or before day 14**
    - 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 censored at 14 days to correspond with the intervention duration.

13. **Heparin-induced thrombocytopenia (HIT)**
    - A dichotomous endpoint of laboratory-confirmed HIT.
    - The endpoint is censored at 14 days to correspond with the intervention duration.

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

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

16. **Ischemic cerebrovascular event**
    - A dichotomous endpoint of ischemic cerebrovascular event (stroke).

17. **Acute myocardial infarction**
    - A dichotomous endpoint of acute myocardial infarction defined according to the universal definition of myocardial infarction.

18. **Systemic arterial thromboembolism**
    - A dichotomous endpoint of clinically diagnosed systemic arterial thrombosis or embolism
    - In REMAP-CAP, this endpoint is captured as “other thrombotic event including mesenteric ischemia and limb ischemia”

- In ACTIV IV, this endpoint is captured as “systemic arterial thromboembolism”
- In ATTACC, this endpoint was not specified in the original protocol (v1.0 April 27, 2020); the updated protocol (v3.0, September 29, 2020) specifies this endpoint as “systemic arterial thromboembolism”

19. **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

20. **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

21. **Intracranial hemorrhage**
    - A dichotomous endpoint of ischemic cerebrovascular event (stroke).

22. **Hospital re-admission**
    - A dichotomous endpoint of readmission to hospital.
    - This endpoint will be reported descriptively using proportions.

23. **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

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 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.

Descriptive Statistics

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

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 high-flow nasal oxygenation, non-invasive

ventilation, invasive mechanical ventilation, ECMO, vasopressors/inotropes, renal replacement therapy, and miscellaneous physiological values and inflammatory biomarker laboratory values (see Appendix A). Anticoagulation dosing on day 1 will be compared between groups. Additionally, exposure to relevant drugs (e.g., antiplatelet agents, steroids, immunomodulatory therapies) prior to hospitalization, at baseline, and during the treatment period will be compared between groups.

Adherence

Adherence will be assessed based on the proportion of patients receiving anticoagulants at doses consistent with their randomly assigned anticoagulation strategy (TAC vs VTP) on the first full study day after randomization.

- In REMAP-CAP this will be study day 2
- In ACTIV-4 and ATTACC this will be study day 1

Treatment will be classified as adherent or non-adherent based on the following dosing equivalents categorization: (1) standard prophylactic, (2) intermediate prophylactic, (3) subtherapeutic, and (4) therapeutic; dosing equivalents (1) and (2) will be considered "prophylactic," and (3) and (4) will be considered "therapeutic" for the purposes of per-protocol analyses. The criteria for each categorization for each anticoagulant are given in Appendix B.

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.

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 for the severe state has 22 possible ordered outcomes. Let the outcome for a patient by labeled as Y_i, with possible values, –1 (death), 0, 1, …, 21, 22. The outcome of 22 for the severe state (never received organ support) is not possible. A cumulative logistic model is specified. The model is structured so that an OR >1 implies clinical benefit. The full details of the model are specified in the Current State Document, Version 1.1 dated November 19, 2020. 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 binds of time working backwards from the last enrolled patient, with the most recent epoch being 4 weeks.
6. Within moderate state an effect for d-dimer level
7. An effect for each intervention; the effects for TAC are nested across subtypes
8. All sites within a country that have <5 patients randomized will be combined into a single site within that country.
9. 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 with a neighboring outcome (the 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.

10. If there is a single subtype or a set of subtypes that don't allow 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.

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 is conducted.

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).

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.

Analytical Approach for Subgroup Analyses

The analyses for subgroup use 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 subgroup. 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.

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.

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.

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.

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.

Definition of times

Adherence and per protocol analyses will rely on assessment of drug administration on post-randomization day 1. In REMAP-CAP, post-randomization day 1 is referred to as study day 2; the 24-hour period defining study day 2 (e.g., midnight to midnight, 7 am to 7 am) is defined according to local site practice. In ATTACC and ACTIV-4, 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.

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., antiplatelet agents, corticosteroids, IL6 antagonists) may modify the benefit or harm of therapeutic anticoagulation. 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.

List of Pre-Specified Analyses

Prospectively defined primary, sensitivity, secondary, and safety analyses are summarized in Table 1. Prospectively planned subgroup analyses are summarized in Table 2. All models are described in detail below.

Table 1. Primary, sensitivity, secondary, safety, and per protocol analyses

#	Status	Population	Endpoint	Notes
14.1	Primary	mpRCT confirmed	OSFDs	Primary ordinal model
14.2	Primary	mpRCT confirmed	In-hospital mortality	Primary dichotomous model
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)]
14.13	Sensitivity	mpRCT confirmed unblinded	OSFDs	Treats missing data for OSFDs using "last known status carried forward" instead of "missing and ignored"
14.14	Secondary	mpRCT confirmed unblinded	Major thrombotic events or death	Primary dichotomous model
14.15	Secondary	mpRCT confirmed unblinded	All thrombotic events (major + DVT) or death	Primary dichotomous model
14.16	Secondary	mpRCT confirmed unblinded	Deep venous thrombosis	Primary dichotomous model
14.17	Secondary	mpRCT confirmed unblinded	Pulmonary embolism	Primary dichotomous model
14.18	Secondary	mpRCT confirmed unblinded	90-day mortality	Primary time to event model
14.19	Secondary	mpRCT confirmed unblinded	Vasopressor/inotrope-free days to day 28	Primary ordinal model
14.20	Secondary	mpRCT confirmed unblinded	Ventilator-free days to day 28	Primary ordinal model
14.21	Secondary	mpRCT confirmed unblinded	Renal replacement-free days to day 28	Primary ordinal model
14.22	Secondary	mpRCT confirmed unblinded restricted to patients not on ECMO at baseline	ECMO utilization on or before day 28	Primary dichotomous model
14.23	Secondary	mpRCT confirmed unblinded	ICU length-of-stay	Primary time to event model
14.24	Secondary	mpRCT confirmed unblinded	Hospital length-of-stay	Primary time to event model
14.25	Secondary	mpRCT confirmed unblinded	ICU readmission	Primary dichotomous model
14.26	Secondary	mpRCT confirmed unblinded	Ischemic cerebrovascular event	Primary dichotomous model
14.27	Secondary	mpRCT confirmed unblinded	Systemic arterial thromboembolism	Primary dichotomous model
14.28	Secondary	mpRCT confirmed unblinded	Acute myocardial infarction	Primary dichotomous model
14.29	Secondary	mpRCT confirmed unblinded	WHO scale	Primary ordinal 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
14.32	Safety	mpRCT confirmed unblinded	Laboratory-confirmed heparin-induced thrombocytopenia	Primary dichotomous model
14.33	Safety*	mpRCT confirmed unblinded	Fatal bleeding	Primary dichotomous model
14.34	Safety	mpRCT confirmed unblinded	Symptomatic bleeding into critical organ	Primary dichotomous model
14.35	Safety	mpRCT confirmed unblinded	Intracranial hemorrhage	Primary dichotomous model

14.36	Safety	mpRCT confirmed unblinded	Bleeding causing a ≥20 g/L drop in hemoglobin	Primary dichotomous model
14.37	Safety	mpRCT confirmed unblinded	Bleeding leading to ≥2 RBC unit transfusion	Primary dichotomous model
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
14.41	Sensitivity	mpRCT per protocol	All thrombotic events (major + DVT) or death	Primary dichotomous model
14.42	Secondary	mpRCT per protocol	Deep venous thrombosis	Primary dichotomous model
14.43	Secondary	mpRCT per protocol	Pulmonary embolism	Primary dichotomous model
14.44	Secondary	mpRCT per protocol	90-day mortality	Primary time to event model
14.45	Secondary	mpRCT per protocol	Vasopressor/inotrope-free days to day 28	Primary ordinal model
14.46	Secondary	mpRCT per protocol	Ventilator-free days to day 28	Primary ordinal model
14.47	Secondary	mpRCT per protocol	Renal replacement-free days to day 28	Primary ordinal model
14.48	Secondary	mpRCT per protocol restricted to patients not on ECMO at baseline	ECMO utilization on or before day 28	Primary dichotomous model
14.49	Secondary	mpRCT per protocol	ICU length-of-stay	Time to event model
14.50	Secondary	mpRCT per protocol	Hospital length-of-stay	Time to event model
14.51	Secondary	mpRCT per protocol	ICU readmission	Primary dichotomous model
14.52	Secondary	mpRCT per protocol	Ischemic cerebrovascular event	Primary dichotomous model
14.53	Secondary	mpRCT per protocol	Systemic arterial thromboembolism	Primary dichotomous model
14.54	Secondary	mpRCT per protocol	Acute myocardial infarction	Primary dichotomous model
14.55	Secondary	mpRCT per protocol	WHO scale	Primary ordinal model

Table 2. Prospectively defined subgroup analyses

Subgroup	**Specification of subgroup**	**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

*Pre-specified in REMAP-CAP domain specific appendix; DSA also specifies “all remaining potentially evaluable treatment-by-treatment interactions with other domains”

Table 3. Other exploratory subgroups of interest

Subgroup	**Specification of subgroup**	**Endpoint – Model #**

		OSFDs (efficacy)	Hospital mortality (efficacy)	Major thrombotic event or death (efficacy)	Major bleeding (safety)
Race	Categorical	16.1.1	16.1.2	16.1.3	16.1.4
D-dimer	Quintiles	16.2.1	16.2.2	16.2.3	16.2.4
Baseline troponin*	Terciles	16.3.1	16.3.2	16.3.3	16.3.4
Therapeutic anticoagulation strategy: LMWH vs. UFH (site classification strategy)*	Dichotomous	16.4.1	16.4.2	16.4.3	16.4.4
Therapeutic anticoagulation strategy: LMWH vs. UFH (day 1 patient classification strategy)*	Dichotomous	16.5.1	16.5.2	16.5.3	16.5.4
Proven concomitant bacterial co-infection*	Dichotomous	16.6.1	16.6.2	16.6.3	16.6.4
Randomization status in steroid domain (within REMAP only)	Dichotomous (steroid or control)	16.7.1	16.7.2	16.7.3	16.7.4
Randomization status in immunomodulatory domain (within REMAP only, restricted to patients with unblinded data in IM domain)	Dichotomous (immunomodulatory therapy or control)	16.8.1	16.8.2	16.8.3	16.8.4
Body mass index	Terciles	16.9.1	16.9.2	16.9.3	16.9.4
Severity of illness	Terciles	16.10.1	16.10.2	16.10.3	16.10.4
Shock (use of vasopressors or inotropes at baseline)*	Dichotomous	16.11.1	16.11.2	16.11.3	16.11.4
Baseline chronic kidney disease	Dichotomous	16.12.1	16.12.2	16.12.3	16.12.4
Steroid administration for COVID-19 at baseline	Dichotomous	16.13.1	16.13.2	16.13.3	16.13.4
Statin use at baseline	Dichotomous	16.14.1	16.14.2	16.14.3	16.14.4
Usual care practice: low vs intermediate (patient classification strategy)[1]	Dichotomous	16.15.1	16.15.2	16.15.3	16.15.4
Usual care practice: low vs intermediate (day 1 site classification strategy)[2]	Dichotomous	16.16.1	16.16.2	16.16.3	16.16.4

*Pre-specified in REMAP-CAP domain specific appendix; DSA also specifies "all remaining potentially evaluable treatment-by-treatment interactions with other domains"

[1]Patients will be classified as receiving low dose VTP if they receive a low dose anticoagulant (according to criteria given in Appendix B) on both of the first two full study days following randomization. Patients will be classified as receiving intermediate

dose VTP if they receive an intermediate dose anticoagulant (according to criteria given in Appendix B) on either of the first two full study days following randomization.
[2]Sites will be classified as “low dose” usual practice if >50% of patients randomized to the VTP at that site received low dose VTP; otherwise, sites will be classified as “intermediate dose” usual practice.

Models for urgent reporting

Primary analysis of OSFDs

Population	mpRCT confirmed
Endpoint	Organ support-free days
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the unblinded SAC

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Primary analysis of in-hospital mortality

Population	mpRCT confirmed
Endpoint	Hospital mortality (censored at day 90 or time of snapshot)
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the unblinded SAC

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Sensitivity analysis for OSFDs – proportional odds assumptions

Population	mpRCT confirmed
Endpoint	Organ support-free days
Model	Primary dichotomous model
Factors	Intervention, age, sex, site, time
Analysis	Conducted by the unblinded SAC

Notes

1. For this analysis, the primary dichotomous model will be fit to each dichotomization of OSFDs and the summaries of the odds ratio of therapeutic anticoagulation will be reported.

The following summaries will be reported for the therapeutic anticoagulation odds ratios:

OSFD Dichotomization	**Mean**	**SD**	**Median**	**95% Credible Interval**
-1 vs ≥0				
≤0 vs ≥1				
≤1 vs ≥2				
≤2 vs ≥3				
≤3 vs ≥4				
≤4 vs ≥5				
≤5 vs ≥6				
≤6 vs ≥7				
≤7 vs ≥8				
≤8 vs ≥9				
≤9 vs ≥10				
≤10 vs ≥11				
≤11 vs ≥12				
≤12 vs ≥13				
≤13 vs ≥14				
≤14 vs ≥15				
≤15 vs ≥16				
≤16 vs ≥17				
≤17 vs ≥18				
≤18 vs ≥19				
≤19 vs ≥20				
≤20 vs 21				

Sensitivity analysis of OSFDs in unblinded population

Population	mpRCT confirmed unblinded
Endpoint	Organ support-free days
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Sensitivity analysis of in-hospital mortality in unblinded population

Population	mpRCT confirmed unblinded
Endpoint	Hospital mortality (censored at day 90 or time of snapshot)
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Sensitivity analysis for OSFDs – include suspected but not confirmed patients

Population	mpRCT confirmed and suspected unblinded
Endpoint	Organ support-free days
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Sensitivity analysis for in-hospital mortality – include suspected but not confirmed patients

Population	mpRCT confirmed and suspected unblinded
Endpoint	Hospital mortality (censored at day 90 or time of snapshot)
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Sensitivity analysis for OSFDs – site and time effects removed

Population	mpRCT confirmed unblinded
Endpoint	Organ support-free days
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Therapeutic anticoagulation				

Sensitivity analysis for in-hospital mortality – site and time effects removed

Population	mpRCT confirmed unblinded
Endpoint	Hospital mortality (censored at day 90 or time of snapshot)
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Therapeutic anticoagulation				

Sensitivity analysis excluding patients on antiplatelet agents at baseline

Population	mpRCT confirmed unblinded excluding patients on antiplatelet agents at baseline or who are randomized in the antiplatelet domain in REMAP-CAP
Endpoint	Organ support-free days
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Sensitivity analysis excluding patients on antiplatelet agents at baseline or during treatment

Population	mpRCT confirmed unblinded excluding patients on antiplatelet agents at baseline or who are randomized in the antiplatelet domain in REMAP-CAP
Endpoint	Hospital mortality (censored at day 90 or time of snapshot)
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Sensitivity analysis of OSFDs specifying a prior describing enthusiasm or skepticism for benefit

Population	mpRCT confirmed unblinded
Endpoint	Hospital mortality (censored at day 90 or time of snapshot)
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

Notes

1. The enthusiastic prior distribution for the intervention effect will be set to N(0.56, 0.44) (equivalent a 50% posterior probability of OR≥1.75 and 10% posterior probability of OR<1). OR=1.75 is equivalent to an approximately 10% absolute risk reduction in mortality assuming a baseline mortality rate of 35%. This is deemed to represent reasonable enthusiasm for the effect of treatment.
2. The skeptical prior distribution for the intervention effect will be set to N(0, 0.44) (equivalent to a 50% posterior probability of OR≤1 and a 66% posterior probability of futility (OR≤1.2). This is deemed to represent reasonable skepticism for the effect of treatment.

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Sensitivity analysis of OSFDs treating missing OSFDs based on last known status carried forward

Population	mpRCT confirmed unblinded
Endpoint	Organ support-free days where missing data are handled based on last known status carried forward
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Secondary analysis of major thrombotic events or death

Population	mpRCT confirmed unblinded
Endpoint	Major thrombotic events or in-hospital death
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Secondary analysis of all thrombotic events or death

Population	mpRCT confirmed unblinded
Endpoint	All thrombotic events or death
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Secondary analysis of deep venous thrombosis

Population	mpRCT confirmed unblinded
Endpoint	Deep venous thrombosis
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Secondary analysis of pulmonary embolism

Population	mpRCT confirmed unblinded
Endpoint	Acute pulmonary embolism
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Secondary analysis of 90-day mortality

Population	mpRCT confirmed unblinded
Endpoint	Mortality at 90 days
Model	Time to event model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

A secondary analysis of days free of vasopressors or inotropes

Population	mpRCT confirmed unblinded
Endpoint	Days free of vasopressors and inotropes to day 28
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

A secondary analysis of days free of invasive or non-invasive ventilation

Population	mpRCT confirmed unblinded
Endpoint	Days free of invasive or non-invasive ventilation to day 28
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Days free of renal-replacement therapy

Population	mpRCT confirmed unblinded
Endpoint	Days free of renal replacement therapy to day 28
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

ECMO utilization

Population	mpRCT confirmed unblinded excluding patients on ECMO at baseline
Endpoint	ECMO utilization to day 28
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

A secondary analysis of ICU length-of-stay

Population	mpRCT confirmed unblinded
Endpoint	ICU length-of-stay (event=ICU discharge); patients who die in hospital are assigned a value of 90 days
Model	Primary time-to-event model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

A secondary analysis of hospital length-of-stay

Population	mpRCT confirmed unblinded
Endpoint	Hospital length-of-stay (event=hospital discharge); patients who die in hospital are assigned a value of 90 days
Model	Primary time-to-event model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

ICU readmission

Population	mpRCT confirmed unblinded
Endpoint	ICU readmission during index hospitalization
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Ischemic cerebrovascular event

Population	mpRCT confirmed unblinded
Endpoint	Ischemic cerebrovascular event
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Systemic arterial thromboembolism

Population	mpRCT confirmed unblinded
Endpoint	Systemic arterial thromboembolism
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Acute myocardial infarction

Population	mpRCT confirmed unblinded
Endpoint	Acute myocardial infarction
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

World Health Organization Ordinal Scale

Population	mpRCT confirmed unblinded
Endpoint	WHO scale on day 14
Model	Ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Safety analysis of major bleeding

Population	mpRCT confirmed unblinded
Endpoint	Major bleeding by ISTH criteria
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Sensitivity analysis of major bleeding – exclude patients on antiplatelet therapy at baseline

Population	mpRCT confirmed unblinded excluding patients on antiplatelet therapy at baseline or who are randomized in the antiplatelet domain of REMAP-CAP
Endpoint	Major bleeding by ISTH criteria
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Safety analysis of laboratory-confirmed heparin-induced thrombocytopenia

Population	mpRCT confirmed unblinded
Endpoint	Heparin-induced thrombocytopenia
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Safety analysis of fatal bleeding

Population	mpRCT confirmed unblinded
Endpoint	Fatal bleeding (subcomponent of major bleeding event definition)
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Safety analysis of symptomatic bleeding into critical organ

Population	mpRCT confirmed unblinded
Endpoint	Symptomatic bleeding into critical organ (subcomponent of major bleeding event definition)
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Safety analysis of intracranial hemorrhage

Population	mpRCT confirmed unblinded
Endpoint	Intracranial hemorrhage (subcomponent of major bleeding event definition)
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Safety analysis of bleeding leading to a ≥20 g/L drop in hemoglobin

Population	mpRCT confirmed unblinded
Endpoint	Bleeding to a ≥20 g/L drop in hemoglobin (subcomponent of major bleeding event definition)
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Safety analysis of bleeding leading to ≥2 red blood cell unit transfusion

Population	mpRCT confirmed unblinded
Endpoint	Bleeding leading to a ≥2 red blood cell unit transfusion (subcomponent of major bleeding event definition)
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Per protocol analysis of OSFDs

Population	mpRCT confirmed per protocol
Endpoint	Organ support-free days
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Per protocol analysis of in-hospital mortality

Population	mpRCT confirmed per protocol
Endpoint	Hospital mortality (censored at day 90 or time of snapshot)
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Per protocol analysis of major thrombotic events

Population	mpRCT confirmed per protocol
Endpoint	Major thrombotic events or death
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Per protocol analysis of all thrombotic events

Population	mpRCT confirmed per protocol
Endpoint	All thrombotic events or death
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Per protocol analysis of deep venous thrombosis

Population	mpRCT confirmed per protocol
Endpoint	Deep venous thrombosis
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Per protocol analysis of pulmonary embolism

Population	mpRCT confirmed per protocol
Endpoint	Acute pulmonary embolism
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Per protocol analysis of 90-day mortality

Population	mpRCT per protocol
Endpoint	Mortality at 90 days
Model	Time to event model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Per protocol analysis of days free of vasopressors or inotropes

Population	mpRCT per protocol
Endpoint	Days free of vasopressors and inotropes to day 28
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Per protocol analysis of days free of invasive or non-invasive ventilation

Population	mpRCT per protocol
Endpoint	Days free of invasive or non-invasive ventilation to day 28
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Per protocol analysis of days free of renal-replacement therapy

Population	mpRCT per protocol
Endpoint	Days free of renal replacement therapy to day 28
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

ECMO utilization

Population	mpRCT per protocol excluding patients on ECMO at baseline
Endpoint	ECMO utilization to day 28
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Per protocol analysis of ICU length-of-stay

Population	mpRCT per protocol
Endpoint	ICU length-of-stay (event=ICU discharge); patients who die in hospital are assigned a value of 90 days
Model	Primary time-to-event model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Per protocol analysis of hospital length-of-stay

Population	mpRCT per protocol
Endpoint	Hospital length-of-stay (event=hospital discharge); patients who die in hospital are assigned a value of 90 days
Model	Primary time-to-event model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

ICU readmission

Population	mpRCT per protocol
Endpoint	ICU readmission during index hospitalization
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Per protocol analysis of ischemic cerebrovascular event

Population	mpRCT per protocol
Endpoint	Ischemic cerebrovascular event
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Per protocol analysis of systemic arterial thromboembolism

Population	mpRCT per protocol
Endpoint	Systemic arterial thromboembolism
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Per protocol analysis of acute myocardial infarction

Population	mpRCT per protocol
Endpoint	Acute myocardial infarction
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Per protocol analysis of World Health Organization Ordinal Scale

Population	mpRCT per protocol
Endpoint	WHO scale on day 14
Model	Ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

Prospectively defined subgroup analyses

Age

OSFDs by age subgroup

Population	mpRCT confirmed unblinded
Endpoint	Organ support-free days
Model	Primary analysis ordinal model
Subgroups	Age categories (<50, 50-70, >70 years)
Factors	Age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**		
	Superiority	Futility	Inferiority
Therapeutic anticoagulation in 1st age subgroup			
Therapeutic anticoagulation in 2nd age subgroup			
Therapeutic anticoagulation in 3rd age subgroup			
Probability effect in 1st group > 2nd group			
Probability effect in 1st group > 3rd group			
Probability effect in 2nd group > 3rd group			

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				
Therapeutic anticoagulation in 1st age subgroup				
Therapeutic anticoagulation in 2nd age subgroup				
Therapeutic anticoagulation in 3rd age subgroup				

In-hospital mortality by age subgroup

Population	mpRCT confirmed unblinded
Endpoint	In-hospital mortality
Model	Dichotomous model

Subgroups	Age categories (<50, 50-70, >70 years)
Factors	Age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**		
	Superiority	Futility	Inferiority
Therapeutic anticoagulation in 1st age subgroup			
Therapeutic anticoagulation in 2nd age subgroup			
Therapeutic anticoagulation in 3rd age subgroup			
Probability effect in 1st group > 2nd group			
Probability effect in 1st group > 3rd group			
Probability effect in 2nd group > 3rd group			

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				
Therapeutic anticoagulation in 1st age subgroup				
Therapeutic anticoagulation in 2nd age subgroup				
Therapeutic anticoagulation in 3rd age subgroup				

Major thrombotic events by age subgroup

Population	mpRCT confirmed unblinded
Endpoint	Major thrombotic events or death
Model	Dichotomous model
Subgroups	Age categories (<50, 50-70, >70 years)
Factors	Age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**		
	Superiority	Futility	Inferiority
Therapeutic anticoagulation in 1st age subgroup			
Therapeutic anticoagulation in 2nd age subgroup			
Therapeutic anticoagulation in 3rd age subgroup			
Probability effect in 1st group > 2nd group			
Probability effect in 1st group > 3rd group			
Probability effect in 2nd group > 3rd group			

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				
Therapeutic anticoagulation in 1st age subgroup				
Therapeutic anticoagulation in 2nd age subgroup				
Therapeutic anticoagulation in 3rd age subgroup				

Major bleeding by age subgroup

Population	mpRCT confirmed unblinded
Endpoint	Major bleeding
Model	Dichotomous model
Subgroups	Age categories (<50, 50-70, >70 years)
Factors	Age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**		
	Superiority	Futility	Inferiority
Therapeutic anticoagulation in 1st age subgroup			
Therapeutic anticoagulation in 2nd age subgroup			
Therapeutic anticoagulation in 3rd age subgroup			
Probability effect in 1st group > 2nd group			
Probability effect in 1st group > 3rd group			
Probability effect in 2nd group > 3rd group			

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				
Therapeutic anticoagulation in 1st age subgroup				
Therapeutic anticoagulation in 2nd age subgroup				
Therapeutic anticoagulation in 3rd age subgroup				

Other exploratory subgroups of interest

Each model output for the additional subgroup analyses in Section 15, Tables 2 and 3 follow the forms in 15.1.1, 15.1.2, 15.1.3, and 15.1.4.

Graphical summaries

1. All ordinal endpoints will be graphed using stacked cumulative bar plots
2. All time-to-event endpoints will be plotted using Kaplan-Meier plots
3. All dichotomous endpoints will be plotted using bar plots
4. Thrombotic events will be plotted using Kaplan-Meier plots

COVID-19 Therapeutic Anticoagulation Multi-Platform RCT SAP Version 1.1

The version is in this document's header and on the cover page.

1.1. Version history

Version 1: Initiated December 21, 2020; Finalized January 5, 2021
Version 1.1: Initiated January 18, 2021; Finalized February 16, 2021

1.2. Amendment details

Summary of amendments in version 1.1

Page(s)	Section	Amendment	Rationale
15	Section 7 and Model 14.23	Changing truncation in hospital length of stay from 90 to 28 days	Alignment with data collection
17	Section 7 and Section 14.57	Addition of an 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	Prespecified in trial protocol but not included in SAP (administrative oversight)
17	Section 7 and Section 14.58	Addition of a dichotomous endpoint based on the proportion of patients who progressed to require organ support through 28 day	Additional secondary efficacy endpoint
81	Section 14.59	Specification of 3 component OSFDs (no organ support, organ support, death) in mpRCT confirmed	Additional sensitivity analysis to test the proportional odds assumption
82	Section 14.60	Sensitivity analysis removing moderate patients enrolled after January 7th, 2021	Sensitivity analysis excluding patients who may not have had 14 days of treatment at the time of trial stopping announcement

83	Section 14.38-14.47	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.	Changed to reflect dosing practices.
88	Section 15.1	Prespecification of subgroup analyses based on categorical level of respiratory support (none, nasal cannula, facemask, NFNO/NIV/invasive MV) and categorical region (North America, South America, Europe/UK, other)	Prespecification of subgroups relevant to moderate analysis.

2. SAP Authors

Ewan Goligher, University of Toronto, Toronto, CA

Patrick Lawler, University of Toronto, Toronto, CA

Scott Berry, Berry Consultants, Austin, TX, USA

Judith Hochman, NYU Grossman School of Medicine/NYU Langone Health, New York, NY

Matthew Neal, University of Pittsburgh, PA, USA

Bridget-Anne Kirwan, Socar Research, Nyon, Switzerland

Lindsay Berry, Berry Consultants, Austin, TX, USA

Elizabeth Lorenzi, Berry Consultants, Austin, TX, USA

Steven Webb, Monash University, Melbourne, Victoria, Australia

Colin McArthur, University of Auckland, Auckland, NZ

Derek C. Angus, University of Pittsburgh and UPMC Health System, PA, USA

Charlotte Bradbury, University Hospitals Bristol, Bristol, UK

Michael Farkouh, University of Toronto, Toronto, CA

Bryan McVerry, University of Pittsburgh and UPMC Health System, PA, USA

Jeff Berger, NYU Grossman School of Medicine/NYU Langone Health, NY, NY, USA

Michelle Ng Gong, Albert Einstein College of Medicine, NY, NY. USA

Anthony Gordon, Imperial College, London, UK
Ryan Zarychanski, University of Manitoba, Winnipeg, CA

3. Introduction

This is the statistical plan for the analysis of the Covid-19 Therapeutic Anticoagulation Multi-Platform RCT (mpRCT). This plan has been prespecified by the investigators prior to unblinding of the data for the Severe state of the mpRCT.

3.1. mpRCT status at time of SAP preparation

Enrolment in the severe state was halted across platforms on December 18, 2020. The severe state-specific conclusion was publicly disclosed on December 22, 2020. The predefined statistical trigger for futility was met with data available to the Statistical Analytic Committee (SAC), and hence the results for the severe state will be unblinded and made public. This document prespecifies the analysis plan for this unblinding as well as future unblinding of the remaining subtypes. This SAP is relevant for the potential conclusions for the severe state and moderate states for comparing therapeutic anticoagulation to pharmacological venous thrombophrophylaxis. The first trigger for the severe state will utilize this analysis plan for reporting.

The authors of this document are blinded to all individual data. The authors are aware that the statistical trigger for futility has been reached for therapeutic anticoagulation in the severe state, have been advised of the primary model result for the interim analysis that prompted the trigger, along with the raw mortality rates and major bleeding event rates in the severe state. The moderate state is continuing randomization.

3.2. Prior analysis plan documents

There are three analysis plan documents that are the precursor to this statistical analysis plan:

1. **Multi-platform Randomized-Controlled Trial (mpRCT) Analysis Plan for ACTIV-4, ATTACC, and REMAP-CAP (AARC)** was created on September 17, 2020. This document described the creation of the AARC mpRCT and the agreed analysis plan.
2. Simulation Report for **Multi-platform Randomized-Controlled Trial (mpRCT) Analysis Plan for ACTIV-4, ATTACC, and REMAP-CAP** was created September 21, 2020. This document describes the clinical trial simulations conducted to characterize the operating characteristics of the analysis plan for the mpRCT.
3. The **Current State Document** dated November 19 2020 is a complete specification of the statistical model and thresholds for the interim analyses to be conducted. This is a document created by the blinded joint steering committees as instructions to the Statistical Analysis Committee (SAC) for running interim analyses. This document can evolve as the mpRCT evolves incorporating the adaptations taking place in the three adaptive platform trials. The current state document referenced here is the current state document in place when the statistical trigger for futility in the severe state was met.

3.3. Reporting strategy

This SAP describes the planned analyses for the entire mpRCT. As outlined below, various subtypes within the mpRCT (defined below) are expected to report at different times. Moreover, given the complex process of federating data for analysis across platforms,

multiple reports describing the results of analysis may be prepared and published to ensure expedited dissemination of mpRCT findings. It is anticipated that for each subtype, preliminary reports will describe key primary and secondary findings and limited subgroup analyses. Endpoints to be reported in the preliminary reports include:

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

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

4. Design Considerations

The mpRCT is designed with a Bayesian analysis as the primary analysis method for the trial. There is one overarching Bayesian model, prespecified 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.

The mpRCT SAP is a joint analysis plan for three separate adaptive platform trials. The three platforms are ACTIV-4a, ATTACC, and REMAP-CAP. The three platforms have agreed to analyze the results of the comparison between two interventions, therapeutic anticoagulation and prophylactic anticoagulation, in a combined effort – labeled a multi-platform randomized-controlled trial (mpRCT). The three platform do not report their results separately–they have agreed this joint effort would be the primary method for analyzing these two interventions across the severe and moderate states. The analysis methods take the philosophy that the three platforms are essentially three multicenter randomized trials and hence combining the results together is a larger multicenter randomized trial. In this section we describe the basic defined structure of the analysis plan.This includes definitions for the patient subgroups, referred to as subtypes, the interventions, the primary endpoint, and the adaptive design. Italicized terms are defined terms by the mpRCT for these analyses.

4.1. Patient Subgroups

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

The primary analysis for the mpRCT creates four distinct populations to analyze potential differential benefit of the interventions. In this mpRCT these distinct groups are labeled as *subtypes*. The four subtypes in this mpRCT are: 1) patients in the severe state; 2) patients in the moderate state with a high baseline d-dimer; 3) patients in the moderate state with a low baseline d-dimer; 4) patients in the moderate state with unknown baseline d-dimer.

A baseline d-dimer level more than 2 times the upper limit of normal is defined as being a *high* d-dimer. Any value less than two times the upper limit of normal is defined as a *low* d-dimer.

4.2. Interventions

The two interventions for this mpRCT are labeled as *therapeutic anticoagulation* (TAC), which plays the inferential role of the investigational treatment and *venous thromboprophylaxis* (VTP) (referred to as Control), which plays the inferential role of the control arm. These interventions are defined as:

1. **TAC**: systemic anticoagulation using unfractionated or low molecular weight heparin to achieve the degree of anticoagulation generally required for the treatment of venous thromboembolism in accordance with usual local practice.
2. **VTP**: usual care strategies, including anticoagulation with lower doses of unfractionated or low molecular weight heparin or other anticoagulant as prophylaxis against the development of venous thromboembolism in accordance with usual local practice.

4.3. Primary Endpoint

The primary endpoint for the mpRCT 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. If a patient dies during their acute hospitalization they are coded as having –1 OSFDs, which is the worst outcome for the measure. Any patient on ICU-level organ support for 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 1, …, 21 refer to the number of days alive and free oforgan support, with smaller values being worse outcomes. The value of *22* is reserved for a patient that is alive and never on ICU-level organ support in the first 21 days. Therefore, theprimary outcome OSFDs is an ordinal outcome with 24 possible outcomes for each patient, –1, 0, 1, 2, …, 21, 22. The details for the calculation of the endpoint is detailed in the mpRCT SAC data dictionaries versions 20201210A (ATTACC and ACTIV) and 10.1 (REMAP-CAP).

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. In REMAP-CAP and ATTACC, high flow nasal cannulais considered to be ICU-level organ support when applied inspiratory flow is 30 L/min or higher at an $FiO_2 \geq 0.4$. In ACTIV-4, 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-4 defines any hospitalized area able to deliver the above organ-support as an ICU. ATTACC and REMAP-CAP specifically define regions as ICUs and non-ICUs. These matters are documented in detail in the SAC data dictionaries (see ATTACC/ACTIV version 20201210A).

This primary endpoint is an ordinal outcome and the primary analysis model analyzes the outcome as ordinal, with a cumulative logistic proportional effects 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 TAC an OR > 1 implies improved outcomes on OSFDs for the TAC intervention compared to the VTP intervention.

4.4. Adaptive Design

There is a prospective adaptive analysis plan for the mpRCT. The plan is to have approximately monthly analyses of the mpRCT 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 TAC to VTP is defined as a high probability of an OR greater than 1 for TAC and hence improved outcomes in OSFDs for the TAC intervention. Futility will be declared if there is a high probability that the effect of TAC 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 mpRCT defines two statistical triggers within the trial that, at any analysis of the trial, would result in a declaration of superiority or futility as multi-platform conclusions.

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

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

For the purpose of this analysis plan, *inferiority* for TAC is defined as an OR<1.

At each analysis of the mpRCT each statistical trigger would be checked for three of the subtypes:

1. Severe state subtype
2. Moderate state, high d-dimer subtype
3. Moderate state, low d-dimer subtype

The fourth subtype, moderate state with unknown d-dimer, the same conclusions will be investigated when the two moderate state subtypes have reached a conclusion but would not trigger a declaration at an interim point. The fourth analysis subtype is part of the primary analysis model but does not have adaptive statistical triggers.

4.5. Endpoint adjudication

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

5. Unblinding

On December 18-19, 2020, the DSMBs advised that the statistical trigger for futility was met in the Severe state. The investigators have been unblinded to this statistical trigger in the Severe state with respect to the OR for the primary endpoint, organ support-free days, mortality rates, and rates of major bleeding.

6. Analysis Populations

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

1. **mpRCT confirmed (Primary)**. The mpRCT primary analysis population includes all enrolled patients with laboratory-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 all patients from all four subtypes. This analysis population will remain primary even if one subtype has a trigger before the other subtypes. The primary analysis will be conducted by the unblinded statistical analysis committee and the results for the subtypes with statistical triggers will be reported.

The following analysis groups will be defined for each public disclosure corresponding to each subtype being unblinded.

2. **mpRCT confirmed unblinded.** The subset of patients in the mpRCT confirmed population that belong to the subtype(s) being reported (i.e. those specific subtype(s) that have been unblinded for reporting). This population consists entirely of patients with laboratory-confirmed COVID-19 randomized to therapeutic anticoagulation or prophylactic anticoagulation and analyzed according to the intention-to-treat principle.
3. **mpRCT confirmed and suspected unblinded** (exploratory sensitivity analyses only)**.** The mpRCT severe state population including patients in REMAP-CAP with suspected but unconfirmed COVID-19 who belong to the subtypes that are unblinded for reporting.
4. **mpRCT per protocol.** This consists of the patients in the mpRCT confirmed unblinded population who have been treated as per protocol. In this analysis that is defined as 1) patients randomized to TAC and who received at least 1 dose of anticoagulation at therapeutic doses on the first full study after randomization **or** within 48 hours of randomization, **and** 2) patients randomized to VTP and who did not receive anticoagulants at therapeutic doses on the first or second full study day after randomization.

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 mpRCT, 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.
    - Detailed definitions for OSFDs are specified in the mpRCT SAC data dictionary
    - Missing values for organ support-free days will be treated as "missing and ignored". We will conduct a sensitivity analysis on the primary endpoint treatingmissing 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. **Mortality**
    - This is a time-to-event endpoint through 28 days and 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.
    - 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.

4. **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.
    - 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

5. **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.
    - 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 whichpatients are not on ventilatory support will be ignored.

6. **Renal replacement-free days to day 28**
    - An ordinal outcome of the number of days free of renal replacement therapy.
    - All platforms 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

7. **ECMO utilization on or before day 28**
    - A dichotomous endpoint of use of extracorporeal membrane oxygenation.

8. **Duration of ICU stay**
    - A time-to-event endpoint of leaving the ICU alive. If a patient is known to leave the ICU and return to the ICU within 21 days that intervening time will be ignored.
    - 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.

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 28 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.

10. **ICU readmission**
    - A dichotomous endpoint of readmission to ICU.

11. **Major bleeding on or before day 14**
    - A dichotomous endpoint of major bleeding as defined according to International Society of Thrombosis and Hemostasis (ISTH) criteria in non-surgical patients.
    - The endpoint is censored at 14 days to correspond with the intervention duration.

12. **Fatal bleeding on or before day 14**
    - 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 censored at 14 days to correspond with the intervention duration.

13. **Heparin-induced thrombocytopenia (HIT)**
    - A dichotomous endpoint of laboratory-confirmed HIT.
    - The endpoint is censored at 14 days to correspond with the intervention duration.

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

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

16. **Ischemic cerebrovascular event**
    - A dichotomous endpoint of ischemic cerebrovascular event (stroke).

17. **Acute myocardial infarction**
    - A dichotomous endpoint of acute myocardial infarction defined according to the universal definition of myocardial infarction.

18. **Systemic arterial thromboembolism**
    - A dichotomous endpoint of clinically diagnosed systemic arterial thrombosis or embolism
    - In REMAP-CAP, this endpoint is captured as “other thrombotic event including mesenteric ischemia and limb ischemia”
    - In ACTIV IV, this endpoint is captured as “systemic arterial thromboembolism”
    - In ATTACC, this endpoint was not specified in the original protocol (v1.0 April 27, 2020); the updated protocol (v3.0, September 29, 2020) specifies this endpoint as “systemic arterial thromboembolism”

19. **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

20. **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

21. **Intracranial hemorrhage**
    - A dichotomous endpoint of ischemic cerebrovascular event (stroke).

22. **Hospital re-admission**
    - A dichotomous endpoint of readmission to hospital.
    - This endpoint will be reported descriptively using proportions.

23. **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 therapy4 = Oxygen by
mask or nasal prongs
5 = Non-invasive ventilation or high-flow oxygen6 = Intubation
and mechanical ventilation
7 = Ventilation + additional organ support: vasopressors, renal replacementtherapy (RRT), ECMO
8 = Death

24. **Progression to require intubation or die on or before day 28**
    - An 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.

25. **Progression to require organ support on or before 28 days**
    - A dichotomous endpoint based on the proportion of patients who progressed to require organ support through 28 day.

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 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 25th, 50th, and 75th 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 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 high-flow nasal oxygenation, non-invasive ventilation, invasive mechanical ventilation, ECMO, vasopressors/inotropes, renal replacement therapy, and miscellaneous physiological values and inflammatory biomarker laboratory values (see Appendix A). Anticoagulation dosing on day 1 will be compared between groups. Additionally, exposure to relevant drugs (e.g., antiplatelet agents, steroids,

immunomodulatory therapies) 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 anticoagulants at doses consistent with their randomly assigned anticoagulation strategy (TAC vs VTP) on the first full study day after randomization.

- In REMAP-CAP this will be study day 2
- In ACTIV-4 and ATTACC this will be study day 1

Treatment will be classified as adherent or non-adherent based on the following dosing equivalents categorization: (1) standard prophylactic, (2) intermediate prophylactic, (3) subtherapeutic, and (4) therapeutic; dosing equivalents (1) and (2) will be considered "prophylactic," and (3) and (4) will be considered "therapeutic" for the purposes of per-protocol analyses. The criteria for each categorization for each anticoagulant are given in Appendix B.

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 for the severe state has 22 possible ordered outcomes. Let the outcome for a patient by labeled as Y_i, with possible values, –1 (death), 0, 1, …, 21, 22. The outcome of 22 for the severe state (never received organ support) is not possible. A cumulative logistic model is specified. The model is structured so that an OR >1 implies clinical benefit. The full details of the model are specified in the Current State Document, Version 1.1 dated November 19, 2020. 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 binds of time working backwards from the last enrolled patient, with the most recent epoch being 4 weeks.
6. Within moderate state an effect for d-dimer level
7. An effect for each intervention; the effects for TAC are nested across subtypes
8. All sites within a country that have <5 patients randomized will be combined into a single site within that country.
9. 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 with a neighboring outcome (the worse outcome). This is done for model stability. For example, if the

outcome 11 never occurred, then a combined outcome of 10 & 11 will bemodeled for the analysis.

10. If there is a single subtype or a set of subtypes that don't allow 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 is 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 Subgroup Analyses

The analyses for subgroup use 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 subgroup. 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 thresholdof 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.

12.10. Definition of times

Adherence and per protocol analyses will rely on assessment of drug administration on post-randomization day 1. In REMAP-CAP, post-randomization day 1 is referred to as study day 2; the 24-hour period defining study day 2 (e.g., midnight to midnight, 7 am to 7 am) is defined according to local site practice. In ATTACC and ACTIV-4, post-randomization day 1 isreferred 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., antiplatelet agents, corticosteroids, IL6 antagonists) may modify the benefit or harm of therapeutic anticoagulation. 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.

13. List of Pre-Specified Analyses

Prospectively defined primary, sensitivity, secondary, and safety analyses are summarized in Table 1. Prospectively planned subgroup analyses are summarized in Table 2. All models are described in detail below.

Table 1. Primary, sensitivity, secondary, safety, and per protocol analyses

#	Status	Population	Endpoint	Notes
14.1	Primary	mpRCT confirmed	OSFDs	Primary ordinal model
14.2	Primary	mpRCT confirmed	In-hospital mortality	Primary dichotomous model
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)]
14.13	Sensitivity	mpRCT confirmed unblinded	OSFDs	Treats missing data for OSFDs using "last known status carried forward" instead of "missing and ignored"
14.14	Secondary	mpRCT confirmed unblinded	Major thrombotic events or death	Primary dichotomous model
14.15	Secondary	mpRCT confirmed unblinded	All thrombotic events (major + DVT) or death	Primary dichotomous model
14.16	Secondary	mpRCT confirmed unblinded	Deep venous thrombosis	Primary dichotomous model
14.17	Secondary	mpRCT confirmed unblinded	Pulmonary embolism	Primary dichotomous model
14.18	Secondary	mpRCT confirmed unblinded	90-day mortality	Primary time to event model
14.19	Secondary	mpRCT confirmed unblinded	Vasopressor/inotrope -free days to day 28	Primary ordinal model
14.20	Secondary	mpRCT confirmed unblinded	Ventilator-free days to day 28	Primary ordinal model
14.21	Secondary	mpRCT confirmed unblinded	Renal replacement-free days to day 28	Primary ordinal model
14.22	Secondary	mpRCT confirmed unblinded restricted to patients not on ECMO at baseline	ECMO utilization on or before day 28	Primary dichotomous model
14.23	Secondary	mpRCT confirmed unblinded	ICU length-of-stay	Primary time to event model
14.24	Secondary	mpRCT confirmed unblinded	Hospital length-of-stay	Primary time to event model
14.25	Secondary	mpRCT confirmed unblinded	ICU readmission	Primary dichotomous model
14.26	Secondary	mpRCT confirmed unblinded	Ischemic cerebrovascular event	Primary dichotomous model
14.27	Secondary	mpRCT confirmed unblinded	Systemic arterial thromboembolism	Primary dichotomous model
14.28	Secondary	mpRCT confirmed unblinded	Acute myocardial infarction	Primary dichotomous model
14.29	Secondary	mpRCT confirmed unblinded	WHO scale	Primary ordinal 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
14.32	Safety	mpRCT confirmed unblinded	Laboratory-confirmed heparin-induced thrombocytopenia	Primary dichotomous model
14.33	Safety*	mpRCT confirmed unblinded	Fatal bleeding	Primary dichotomous model
14.34	Safety	mpRCT confirmed unblinded	Symptomatic bleeding into critical organ	Primary dichotomous model
14.35	Safety	mpRCT confirmed unblinded	Intracranial hemorrhage	Primary dichotomous model
14.36	Safety	mpRCT confirmed unblinded	Bleeding causing a	Primary dichotomous model

			≥20 g/L drop in hemoglobin	
14.37	Safety	mpRCT confirmed unblinded	Bleeding leading to ≥2 RBC unit transfusion	Primary dichotomous model
14.38	Sensitivity	mpRCT per protocol	OSFDs	Primary ordinal model
14.39	Sensitivity	mpRCT per protocol	In-hospital mortality	Primary dichotomous model
14.40	Secondary	mpRCT per protocol	Major thrombotic events or death	Primary dichotomous model
14.41	Secondary	mpRCT per protocol	All thrombotic events (major + DVT) or death	Primary dichotomous model
14.42	Secondary	mpRCT per protocol	Deep venous thrombosis	Primary dichotomous model
14.43	Secondary	mpRCT per protocol	Pulmonary embolism	Primary dichotomous model
14.44	Secondary	mpRCT per protocol	90-day mortality	Primary time to event model
14.45	Secondary	mpRCT per protocol	Vasopressor/inotrope -free days to day 28	Primary ordinal model
14.46	Secondary	mpRCT per protocol	Ventilator-free days to day 28	Primary ordinal model
14.47	Secondary	mpRCT per protocol	Renal replacement-free days to day 28	Primary ordinal model
14.48	Secondary	mpRCT per protocol restricted to patients not on ECMO at baseline	ECMO utilization on or before day 28	Primary dichotomous model
14.49	Secondary	mpRCT per protocol	ICU length-of-stay	Time to event model
14.50	Secondary	mpRCT per protocol	Hospital length-of-stay	Time to event model
14.51	Secondary	mpRCT per protocol	ICU readmission	Primary dichotomous model
14.52	Secondary	mpRCT per protocol	Ischemic cerebrovascular event	Primary dichotomous model
14.53	Secondary	mpRCT per protocol	Systemic arterial thromboembolism	Primary dichotomous model
14.54	Secondary	mpRCT per protocol	Acute myocardial infarction	Primary dichotomous model
14.55	Secondary	mpRCT per protocol	WHO scale	Primary ordinal model

Table 2. Prospectively defined subgroup analyses

Subgroup	**Specification of subgroup**	**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

*Pre-specified in REMAP-CAP domain specific appendix; DSA also specifies “all remaining potentially evaluable treatment-by-treatment interactions with other domains”

Table 3. Other exploratory subgroups of interest

Subgroup	**Specification of subgroup**	**Endpoint – Model #**			
		OSFDs (efficacy)	Hospital mortality (efficacy)	Major thrombotic	Major bleeding (safety)

				event or death (efficacy)	
Race	Categorical	16.1.1	16.1.2	16.1.3	16.1.4
D-dimer	Quintiles	16.2.1	16.2.2	16.2.3	16.2.4
Baseline troponin*	Terciles	16.3.1	16.3.2	16.3.3	16.3.4
Therapeutic anticoagulation strategy: LMWH vs. UFH (site classification strategy)*	Dichotomous	16.4.1	16.4.2	16.4.3	16.4.4
Therapeutic anticoagulation strategy: LMWH vs. UFH (day 1 patient classification strategy)*	Dichotomous	16.5.1	16.5.2	16.5.3	16.5.4
Proven concomitant bacterial co-infection*	Dichotomous	16.6.1	16.6.2	16.6.3	16.6.4
Randomization status in steroid domain (within REMAP only)	Dichotomous (steroid or control)	16.7.1	16.7.2	16.7.3	16.7.4
Randomization status in immunomodulatory domain (within REMAP only, restricted to patients with unblinded data in IM domain)	Dichotomous (immunomodulatory therapy or control)	16.8.1	16.8.2	16.8.3	16.8.4
Body mass index	Terciles	16.9.1	16.9.2	16.9.3	16.9.4
Severity of illness	Terciles	16.10.1	16.10.2	16.10.3	16.10.4
Shock (use of vasopressors or inotropes at baseline)*	Dichotomous	16.11.1	16.11.2	16.11.3	16.11.4
Baseline chronic kidney disease	Dichotomous	16.12.1	16.12.2	16.12.3	16.12.4
Steroid administration for COVID-19 at baseline	Dichotomous	16.13.1	16.13.2	16.13.3	16.13.4
Statin use at baseline	Dichotomous	16.14.1	16.14.2	16.14.3	16.14.4
Usual care practice: low vs intermediate (patient classification strategy)[1]	Dichotomous	16.15.1	16.15.2	16.15.3	16.15.4
Usual care practice: low vs intermediate (day 1 site classification strategy)[2]	Dichotomous	16.16.1	16.16.2	16.16.3	16.16.4

*Pre-specified in REMAP-CAP domain specific appendix; DSA also specifies “all remaining potentially evaluable treatment-by-treatment interactions with other domains”

[1]Patients will be classified as receiving low dose VTP if they receive a low dose anticoagulant (according to criteria given in Appendix B) on both of the first two full study days following randomization. Patients will be classified as receiving intermediate dose VTP if they receive an intermediate dose anticoagulant (according to criteria given in Appendix B) on either of the first two full study days following randomization.
[2]Sites will be classified as “low dose” usual practice if >50% of patients randomized to the VTP at that site received low dose VTP; otherwise, sites will be classified as “intermediate dose” usual practice.

14. Primary and secondary analyses

14.1. Primary analysis of OSFDs

Population	mpRCT confirmed
Endpoint	Organ support-free days
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the unblinded SAC

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.2. Primary analysis of in-hospital mortality

Population	mpRCT confirmed
Endpoint	Hospital mortality (censored at day 90 or time of snapshot)
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the unblinded SAC

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.3. Sensitivity analysis for OSFDs – proportional odds assumptions

Population	mpRCT confirmed
Endpoint	Organ support-free days
Model	Primary dichotomous model
Factors	Intervention, age, sex, site, time
Analysis	Conducted by the unblinded SAC

Notes

1. For this analysis, the primary dichotomous model will be fit to each dichotomization of OSFDs and the summaries of the odds ratio of therapeutic anticoagulation will be reported.

The following summaries will be reported for the therapeutic anticoagulation odds ratios:

OSFD Dichotomization	**Mean**	**SD**	**Median**	**95% Credible Interval**
-1 vs ≥0				
≤0 vs ≥1				
≤1 vs ≥2				
≤2 vs ≥3				
≤3 vs ≥4				
≤4 vs ≥5				
≤5 vs ≥6				
≤6 vs ≥7				
≤7 vs ≥8				
≤8 vs ≥9				
≤9 vs ≥10				
≤10 vs ≥11				
≤11 vs ≥12				
≤12 vs ≥13				
≤13 vs ≥14				
≤14 vs ≥15				
≤15 vs ≥16				
≤16 vs ≥17				
≤17 vs ≥18				
≤18 vs ≥19				
≤19 vs ≥20				
≤20 vs 21				

14.4. Sensitivity analysis of OSFDs in unblinded population

Population	mpRCT confirmed unblinded
Endpoint	Organ support-free days
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.5. Sensitivity analysis of in-hospital mortality in unblinded population

Population	mpRCT confirmed unblinded
Endpoint	Hospital mortality (censored at day 90 or time of snapshot)
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.6. Sensitivity analysis for OSFDs – include suspected but not confirmed patients

Population	mpRCT confirmed and suspected unblinded
Endpoint	Organ support-free days
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.7. Sensitivity analysis for in-hospital mortality – include suspected but not confirmed patients

Population	mpRCT confirmed and suspected unblinded
Endpoint	Hospital mortality (censored at day 90 or time of snapshot)
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.8. Sensitivity analysis for OSFDs – site and time effects removed

Population	mpRCT confirmed unblinded
Endpoint	Organ support-free days
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Therapeutic anticoagulation				

14.9. Sensitivity analysis for in-hospital mortality – site and time effects removed

Population	mpRCT confirmed unblinded
Endpoint	Hospital mortality (censored at day 90 or time of snapshot)
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Therapeutic anticoagulation				

14.10. Sensitivity analysis excluding patients on antiplatelet agents at baseline

Population	mpRCT confirmed unblinded excluding patients on antiplatelet agents at baseline or who are randomized in the antiplatelet domain in REMAP-CAP
Endpoint	Organ support-free days
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.11. Sensitivity analysis excluding patients on antiplatelet agents at baseline or during treatment

Population	mpRCT confirmed unblinded excluding patients on antiplatelet agents at baseline or who are randomized in the antiplatelet domain in REMAP-CAP
Endpoint	Hospital mortality (censored at day 90 or time of snapshot)
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.12. Sensitivity analysis of OSFDs specifying a prior describing enthusiasm or skepticism for benefit

Population	mpRCT confirmed unblinded
Endpoint	Hospital mortality (censored at day 90 or time of snapshot)
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

Notes

1. The enthusiastic prior distribution for the intervention effect will be set to N(0.56, 0.44) (equivalent a 50% posterior probability of OR≥1.75 and 10% posterior probability of OR<1). OR=1.75 is equivalent to an approximately 10% absolute risk reduction in mortality assuming a baseline mortality rate of 35%. This is deemed to represent reasonable enthusiasm for the effect of treatment.
2. The skeptical prior distribution for the intervention effect will be set to N(0, 0.44) (equivalent to a 50% posterior probability of OR≤1 and a 66% posterior probability of futility (OR≤1.2). This is deemed to represent reasonable skepticism for the effect of treatment.

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.13. Sensitivity analysis of OSFDs treating missing OSFDs based on last known status carried forward

Population	mpRCT confirmed unblinded
Endpoint	Organ support-free days where missing data are handled based on last known status carried forward
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.14. Secondary analysis of major thrombotic events or death

Population	mpRCT confirmed unblinded
Endpoint	Major thrombotic events or in-hospital death
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.15. Secondary analysis of all thrombotic events or death

Population	mpRCT confirmed unblinded
Endpoint	All thrombotic events or death
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.16. Secondary analysis of deep venous thrombosis

Population	mpRCT confirmed unblinded
Endpoint	Deep venous thrombosis
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.17. Secondary analysis of pulmonary embolism

Population	mpRCT confirmed unblinded
Endpoint	Acute pulmonary embolism
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.18. Secondary analysis of 90-day mortality

Population	mpRCT confirmed unblinded
Endpoint	Mortality at 90 days
Model	Time to event model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.19. A secondary analysis of days free of vasopressors or inotropes

Population	mpRCT confirmed unblinded
Endpoint	Days free of vasopressors and inotropes to day 28
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.20. A secondary analysis of days free of invasive or non-invasive ventilation

Population	mpRCT confirmed unblinded
Endpoint	Days free of invasive or non-invasive ventilation to day 28
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.21. Days free of renal-replacement therapy

Population	mpRCT confirmed unblinded
Endpoint	Days free of renal replacement therapy to day 28
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.22. ECMO utilization

Population	mpRCT confirmed unblinded excluding patients on ECMO at baseline
Endpoint	ECMO utilization to day 28
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.23. A secondary analysis of ICU length-of-stay

Population	mpRCT confirmed unblinded
Endpoint	ICU length-of-stay (event=ICU discharge); patients who die in hospital are assigned a value of 90 days
Model	Primary time-to-event model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.24. A secondary analysis of hospital length-of-stay

Population	mpRCT confirmed unblinded
Endpoint	Hospital length-of-stay (event=hospital discharge); patients who die in hospital are assigned a value of 90 days
Model	Primary time-to-event model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.25. ICU readmission

Population	mpRCT confirmed unblinded
Endpoint	ICU readmission during index hospitalization
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.26. Ischemic cerebrovascular event

Population	mpRCT confirmed unblinded
Endpoint	Ischemic cerebrovascular event
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.27. Systemic arterial thromboembolism

Population	mpRCT confirmed unblinded
Endpoint	Systemic arterial thromboembolism
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.28. Acute myocardial infarction

Population	mpRCT confirmed unblinded
Endpoint	Acute myocardial infarction
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.29. World Health Organization Ordinal Scale

Population	mpRCT confirmed unblinded
Endpoint	WHO scale on day 14
Model	Ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.30. Safety analysis of major bleeding

Population	mpRCT confirmed unblinded
Endpoint	Major bleeding by ISTH criteria
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.31. Sensitivity analysis of major bleeding – exclude patients on antiplatelet therapy at baseline

Population	mpRCT confirmed unblinded excluding patients on antiplatelet therapy at baseline or who are randomized in the antiplatelet domain of REMAP-CAP
Endpoint	Major bleeding by ISTH criteria
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.32. Safety analysis of laboratory-confirmed heparin-induced thrombocytopenia

Population	mpRCT confirmed unblinded
Endpoint	Heparin-induced thrombocytopenia
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.33. Safety analysis of fatal bleeding

Population	mpRCT confirmed unblinded
Endpoint	Fatal bleeding (subcomponent of major bleeding event definition)
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.34. Safety analysis of symptomatic bleeding into critical organ

Population	mpRCT confirmed unblinded
Endpoint	Symptomatic bleeding into critical organ (subcomponent of major bleeding event definition)
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.35. Safety analysis of intracranial hemorrhage

Population	mpRCT confirmed unblinded
Endpoint	Intracranial hemorrhage (subcomponent of major bleeding event definition)
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.36. Safety analysis of bleeding leading to a ≥20 g/L drop in hemoglobin

Population	mpRCT confirmed unblinded
Endpoint	Bleeding to a ≥20 g/L drop in hemoglobin (subcomponent of major bleeding event definition)
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.37. Safety analysis of bleeding leading to ≥2 red blood cell unit transfusion

Population	mpRCT confirmed unblinded
Endpoint	Bleeding leading to a ≥2 red blood cell unit transfusion (subcomponent of major bleeding event definition)
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.38. Per protocol analysis of OSFDs

Population	mpRCT confirmed per protocol
Endpoint	Organ support-free days
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.39. Per protocol analysis of in-hospital mortality

Population	mpRCT confirmed per protocol
Endpoint	Hospital mortality (censored at day 90 or time of snapshot)
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.40. Per protocol analysis of major thrombotic events

Population	mpRCT confirmed per protocol
Endpoint	Major thrombotic events or death
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.41. Per protocol analysis of all thrombotic events

Population	mpRCT confirmed per protocol
Endpoint	All thrombotic events or death
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.42. Per protocol analysis of deep venous thrombosis

Population	mpRCT confirmed per protocol
Endpoint	Deep venous thrombosis
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.43. Per protocol analysis of pulmonary embolism

Population	mpRCT confirmed per protocol
Endpoint	Acute pulmonary embolism
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.44. Per protocol analysis of 90-day mortality

Population	mpRCT per protocol
Endpoint	Mortality at 90 days
Model	Time to event model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.45. Per protocol analysis of days free of vasopressors or inotropes

Population	mpRCT per protocol
Endpoint	Days free of vasopressors and inotropes to day 28
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.46. Per protocol analysis of days free of invasive or non-invasive ventilation

Population	mpRCT per protocol
Endpoint	Days free of invasive or non-invasive ventilation to day 28
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.47. Per protocol analysis of days free of renal-replacement therapy

Population	mpRCT per protocol
Endpoint	Days free of renal replacement therapy to day 28
Model	Primary analysis ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.48. ECMO utilization

Population	mpRCT per protocol excluding patients on ECMO at baseline
Endpoint	ECMO utilization to day 28
Model	Primary analysis dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.49. Per protocol analysis of ICU length-of-stay

Population	mpRCT per protocol
Endpoint	ICU length-of-stay (event=ICU discharge); patients who die in hospital are assigned a value of 90 days
Model	Primary time-to-event model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.50. Per protocol analysis of hospital length-of-stay

Population	mpRCT per protocol
Endpoint	Hospital length-of-stay (event=hospital discharge); patients who die in hospital are assigned a value of 90 days
Model	Primary time-to-event model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.51. ICU readmission

Population	mpRCT per protocol
Endpoint	ICU readmission during index hospitalization
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.52. Per protocol analysis of ischemic cerebrovascular event

Population	mpRCT per protocol
Endpoint	Ischemic cerebrovascular event
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.53. Per protocol analysis of systemic arterial thromboembolism

Population	mpRCT per protocol
Endpoint	Systemic arterial thromboembolism
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.54. Per protocol analysis of acute myocardial infarction

Population	mpRCT per protocol
Endpoint	Acute myocardial infarction
Model	Dichotomous model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.55. Per protocol analysis of World Health Organization Ordinal Scale

Population	mpRCT per protocol
Endpoint	WHO scale on day 14
Model	Ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.56. Not used

14.57. Secondary analysis of progression to intubation or death through 28 days

Population	mpRCT per protocol
Endpoint	Progression to intubation or death
Model	Ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.58. Secondary analysis of progression to requiring organ support through 28 days

Population	mpRCT per protocol
Endpoint	Progression to requiring organ support
Model	Ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.59. Sensitivity analysis of OSFDs as 3-component OSFDs (no organ support, organ support, death)

Population	mpRCT per protocol
Endpoint	Categorized, 3-component OSFDs
Model	Ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	Posterior Probability
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

14.60. Sensitivity analysis of OSFDs removing moderate patients enrolled after January 7th, 2021

Population	mpRCT per protocol
Endpoint	Sensitivity analysis of primary OSFDs endpoint removing moderate patients enrolled after January 7th, 2021
Model	Ordinal model
Factors	Intervention, age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

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

Quantity of Interest	**Posterior Probability**
Therapeutic anticoagulation is superior to control	
Therapeutic anticoagulation is futile	
Therapeutic anticoagulation 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+				
D-dimer high (for moderate)				
D-dimer missing (for moderate)				
Female				
Time epoch 1				
…				
Time epoch k-1				
Therapeutic anticoagulation				

15. Prospectively defined subgroup analyses

15.1. Age

15.1.1. OSFDs by age subgroup

Population	mpRCT confirmed unblinded
Endpoint	Organ support-free days
Model	Primary analysis ordinal model
Subgroups	Age categories (<50, 50-70, >70 years)
Factors	Age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**		
	Superiority	Futility	Inferiority
Therapeutic anticoagulation in 1st age subgroup			
Therapeutic anticoagulation in 2nd age subgroup			
Therapeutic anticoagulation in 3rd age subgroup			
Probability effect in 1st group > 2nd group			
Probability effect in 1st group > 3rd group			
Probability effect in 2nd group > 3rd group			

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				
Therapeutic anticoagulation in 1st age subgroup				
Therapeutic anticoagulation in 2nd age subgroup				
Therapeutic anticoagulation in 3rd age subgroup				

15.1.2. In-hospital mortality by age subgroup

Population	mpRCT confirmed unblinded
Endpoint	In-hospital mortality
Model	Dichotomous model
Subgroups	Age categories (<50, 50-70, >70 years)
Factors	Age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**		
	Superiority	Futility	Inferiority
Therapeutic anticoagulation in 1st age subgroup			

Therapeutic anticoagulation in 2nd age subgroup			
Therapeutic anticoagulation in 3rd age subgroup			
Probability effect in 1st group > 2nd group			
Probability effect in 1st group > 3rd group			
Probability effect in 2nd group > 3rd group			

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				
Therapeutic anticoagulation in 1st age subgroup				
Therapeutic anticoagulation in 2nd age subgroup				
Therapeutic anticoagulation in 3rd age subgroup				

15.1.3. Major thrombotic events by age subgroup

Population	mpRCT confirmed unblinded
Endpoint	Major thrombotic events or death
Model	Dichotomous model
Subgroups	Age categories (<50, 50-70, >70 years)
Factors	Age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**		
	Superiority	Futility	Inferiority
Therapeutic anticoagulation in 1st age subgroup			
Therapeutic anticoagulation in 2nd age subgroup			
Therapeutic anticoagulation in 3rd age subgroup			
Probability effect in 1st group > 2nd group			
Probability effect in 1st group > 3rd group			
Probability effect in 2nd group > 3rd group			

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				
Therapeutic anticoagulation in 1st age subgroup				
Therapeutic anticoagulation in 2nd age subgroup				
Therapeutic anticoagulation in 3rd age subgroup				

15.1.4. Major bleeding by age subgroup

Population	mpRCT confirmed unblinded
Endpoint	Major bleeding
Model	Dichotomous model
Subgroups	Age categories (<50, 50-70, >70 years)
Factors	Age, sex, site, time, d-dimer (moderate)
Analysis	Conducted by the mpRCT analysis team

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**		
	Superiority	Futility	Inferiority
Therapeutic anticoagulation in 1st age subgroup			
Therapeutic anticoagulation in 2nd age subgroup			
Therapeutic anticoagulation in 3rd age subgroup			
Probability effect in 1st group > 2nd group			
Probability effect in 1st group > 3rd group			
Probability effect in 2nd group > 3rd group			

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				
Therapeutic anticoagulation in 1st age subgroup				
Therapeutic anticoagulation in 2nd age subgroup				
Therapeutic anticoagulation in 3rd age subgroup				

16. Other exploratory subgroups of interest

Each model output for the additional subgroup analyses in Section 15, Tables 2 and 3 follow the forms in 15.1.1, 15.1.2, 15.1.3, and 15.1.4. Additionally, subgroup analyses based on level or respiratory support at baseline, additional D-dimer categories, and region, will be examined.

17. Graphical summaries

1. All ordinal endpoints will be graphed using stacked cumulative bar plots
2. All time-to-event endpoints will be plotted using Kaplan-Meier plots
3. All dichotomous endpoints will be plotted using bar plots
4. Thrombotic events will be plotted using Kaplan-Meier plots

18. Appendix A: Baseline Characteristics to Report

To be updated.

19. Appendix B: Criteria for Classifying Anticoagulation Dosing

To be updated

mpRCT SAP Summary of Changes from Version 1.0

1.1. Amendment details

Summary of amendments in version 1.1

Page(s)	Section	Amendment	Rationale
15	Section 7 and Model 14.23	Changing truncation in hospital length of stay from 90 to 28 days	Alignment with data collection
17	Section 7 and Section 14.57	Addition of an 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	Prespecified in trial protocol but not included in SAP (administrative oversight)
17	Section 7 and Section 14.58	Addition of a dichotomous endpoint based on the proportion of patients who progressed to require organ support through 28 day	Additional secondary efficacy endpoint
81	Section 14.59	Specification of 3 component OSFDs (no organ support, organ support, death) in mpRCT confirmed	Additional sensitivity analysis to test the proportional odds assumption
82	Section 14.60	Sensitivity analysis removing moderate patients enrolled after January 7th, 2021	Sensitivity analysis excluding patients who may not have had 14 days of treatment at the time of trial stopping announcement

83	Section 14.38-14.47	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.	Changed to reflect dosing practices.
88	Section 15.1	Prespecification of subgroup analyses based on categorical level of respiratory support (none, nasal cannula, facemask, NFNO/NIV/invasive MV) and categorical region (North America, South America, Europe/UK, other)	Prespecification of subgroups relevant to moderate analysis.

Statistical Analysis Plan for Report of Moderate Subtypes ofmpRCT 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 today 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			

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			

Addendum for the analysis of REMAP-CAP Severe State Data for Interactions between IL-6R antagonists and therapeutic anticoagulation.

Version

Version 1.0, Created May 13, 2021. Scott Berry, Lindsay Berry, Elizabeth Lorenzi.

Background

This addendum to the SAP is based on a request from NEJM to explore the interaction of IL-6Ra inhibitors and therapeutic anticoagulation and agreement from the REMAP-CAP ITSC to use the data from REMAP-CAP for this question. This analysis plan has been created before running any analyses on the interaction between the two interventions, but after analyzing the individual data for anticoagulation and IL-6Ra inhibitors. Therefore, this analysis is considered "post-hoc" and exploratory in nature.

The REMAP-CAP trial, among severe state patients, was simultaneously enrolling and randomizing patients to the immune modulation and anticoagulation domains. Within the immune modulation domain were 5 interventions:

1. No immune modulation
2. Interferon-beta-1a (IFN-β1a)
3. Anakinra (IL-1Ra)
4. Tocilizumab (IL-6Ra)
5. Sarilumab (IL-6Ra)

Additionally, patients were randomized to the anticoagulation domain, with interventions:

1. Local standard venous thromboprophylaxis
2. Therapeutic anticoagulation

During this time, some patients were randomized to both of these domains. The Immune Modulation domain declared tocilizumab superior to no immune modulation on November 19, 2020. After this date no patients were randomized to the no immune modulation intervention.

IL-6Ra/Anticoagulation Interaction Population

The analysis population for this analysis will be all PISOP severe state patients that were randomized the therapeutic anticoagulation domain. The classification of the immune modulation status will be:

1. Did not get an immune modulation therapy not randomized versus IL-6Ra
2. Eligible for an IL-6Ra randomization and randomized to no immune modulation
3. Eligible for an IL-6Ra randomization and randomized to IL-6Ra

This analysis population is then restricted to patients randomized on or before November 19, 2020. The assignment to each treatment for each domain will be the randomized assignment (intent-to-treat) in each domain, where no distinction is made between Tocilizumab or Sarilumab, they are pooled as an IL-6Ra intervention.

Analyses

#	Status	Population	Endpoint	Notes
14.1	Exploratory	IL-6Ra/Anticoagulation Interaction	OSFDs	Primary ordinal model, with interactions
14.2	Exploratory	IL-6Ra/Anticoagulation Interaction	In-hospital mortality	Primary dichotomous model with interactions

The primary analysis model for the severe state mpRCT will be adopted for each of the two analyses defined. The same covariates from the primary analysis model will be fit. The model adds in the pooled IL-6Ra interventions and an interaction between the IL-6Ra intervention and the therapeutic anticoagulation intervention. The following model parameters and prior distributions are utilized:

The coefficient for the pooled IL-6Ra intervention is, θ_{6}, and has prior distribution

$$\theta_{6} \sim N(0,1).$$

The interaction between therapeutic anticoagulation and IL-6Ra is labeled as δ. The prior distribution of which is

$$\delta \sim N(0,1).$$

The effect is included for those possibly randomized to Il-6Ra (a parameter in the REMAP-CAP analyses) has a prior distribution of

$$\zeta \sim N(0,1).$$

The following summaries of the model will be presented:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval	Pr(OR > 1)
Age < 39					--
Age 40, 49					--
Age 50, 59					--
Age 70-79					--
Age 80+					--
Female					--
Time Bucket 1					--
…					--

Time Bucket k-1					--
Randomized to IL-6Ra					
Therapeutic Anticoagulation					
IL-6Ra					
Therapeutic Anticoagulation * IL-6Ra combination					
Therapeutic Anticoagulation * IL-6Ra interaction					

The posterior probability that each of the four combinations is the optimal combination will be presented.

Descriptive Summaries

Descriptive summaries of OSFDs and In-hospital mortality will be summarized by the four combinations of treatment interventions.

1. OSFDs will be summarized by the cumulative frequency of each outcome. The 25th, 50th, and 75th percentiles will be summarized.
2. Dichotomous endpoints will be summarized by the proportion in each category.
3. OSFDs will be graphed using stacked cumulative bar plots and cumulative frequency graphs