

REMAP-CAP

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

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



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 Appendix to Core (PA_TC).

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	<ul style="list-style-type: none"> 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	<p>Patients will be eligible for this domain if:</p> <ul style="list-style-type: none"> 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	<p>Patients will be excluded from this domain if they have any of the following:</p> <ul style="list-style-type: none"> 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	<p>Primary REMAP endpoint: as defined in an operational document specified from the Pandemic Appendix to the Core Protocol Section 7.5.1</p> <p>Secondary REMAP endpoints: as defined in an operational document specified from Pandemic Appendix to the Core Protocol Section 7.5.2</p> <p>Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment):</p> <ul style="list-style-type: none">• Serious Adverse Events (SAE) as defined in Core Protocol
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Not for IRB submission

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
PA _t C	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

Not for IRB submission

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 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 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 Gordon
Dr. Patrick Lawler
Professor Robert Fowler
Professor Anand Kumar
Dr. Patrick Lawless
Dr. Sylvain Lothier
Professor John Marshall
Dr. Zoe McQuilten
Dr. Alexis Turgeon
Professor Simon Stanworth
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4.2. Contact Details

Chair: Dr. Ryan Zarychanski

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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 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

20th April 2020

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-\(2019-ncov\)](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>).

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 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.

5.2.2.2. 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 the possibility 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 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.

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 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.

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 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).

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 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 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 (odds ratio 0.88 (95% CI, 0.77 to 1.00; I² = 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 LMWH 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.

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 requires close 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 of polymeric 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 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).

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 medical-surgical ICU patients is approximately 0.3 to 0.6% (Group et al., 2011).

6. 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-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
- 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 on D-dimer strata status.

7. 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 Core Protocol 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.

7.3.1.1. *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.

7.3.2. 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

7.3.2.1. *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.

7.3.2.2. *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.

7.3.2.3. *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 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.

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 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 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 a protocol 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 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.

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. 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 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 the treating clinician.

7.5. Endpoints

7.5.1. 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.

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 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.

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-CAP trial.

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 Protocol Section 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 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 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 be 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.

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 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.

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 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

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 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.

10.2. 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).

10.3. 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.GOVERNANCE ISSUES

11.1. 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.

11.2. 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.

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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13.APPENDIX 1. OVERVIEW OF DESIGN AND INITIAL RESULTS FOR THE THERAPEUTIC ANTICOAGULATION 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 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.

13.1.1. Treatment Arms

The main effect for therapeutic anticoagulation in this domain will be modeled as specified in the PATC.

13.1.2. 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.

13.2. 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??).

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 is 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 this domain. 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 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.

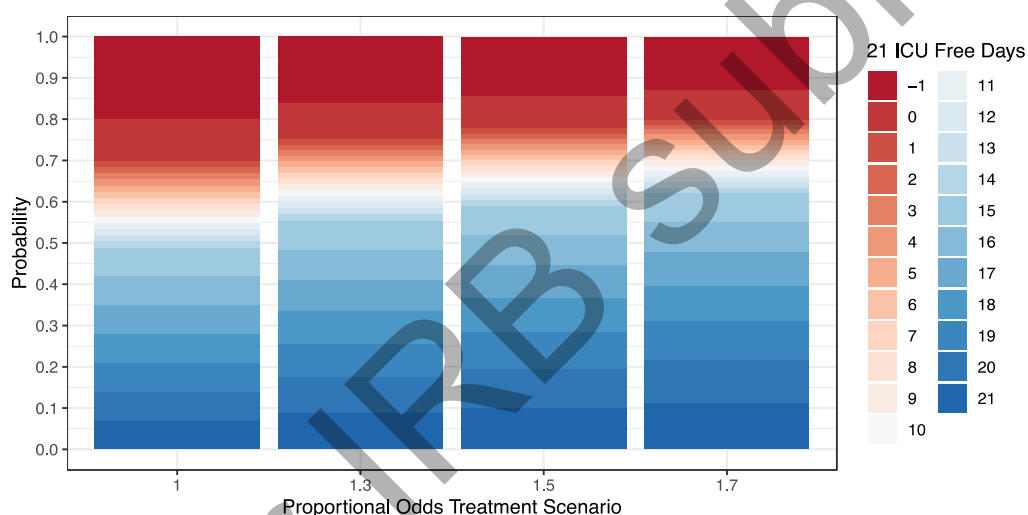


Figure 1. Control outcome probabilities for the ICU-free day end point (left panel) and then the probabilities for treatment effects of odds ratios of 1.3, 1.5, and 1.7.

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.

13.4. 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).

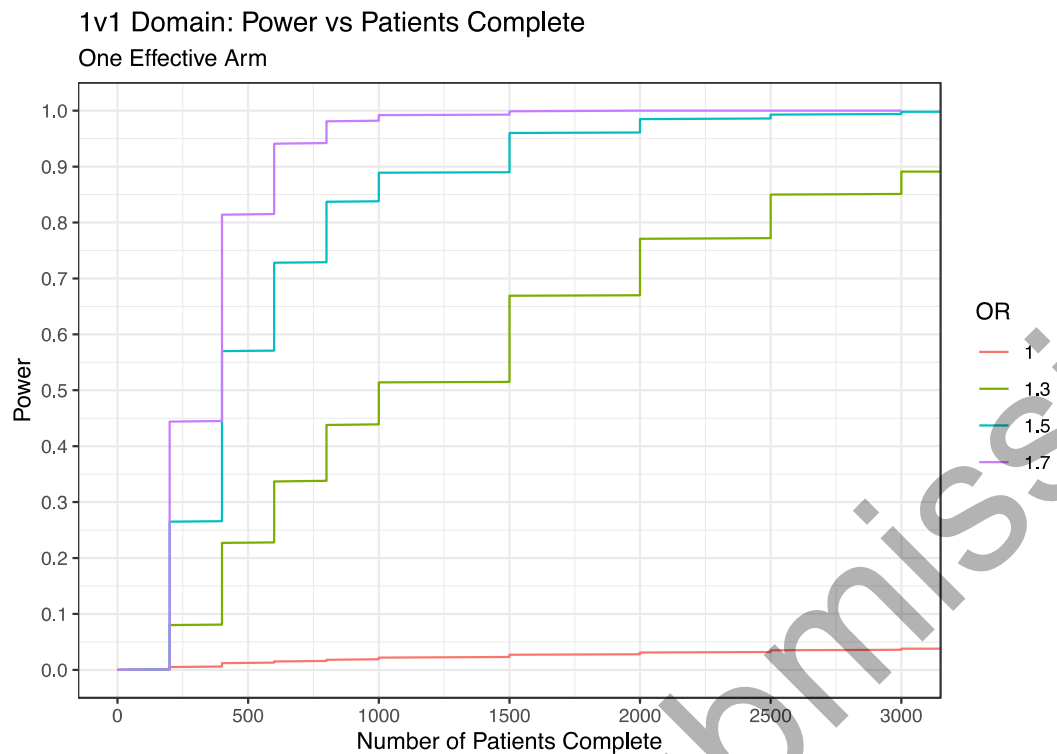


Figure 2: The cumulative power for each of the explored treatment effects (odds ratios of 1.3, 1.5, and 1.7). The cumulative type I error is shown as the red line (effect size of 1).

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 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%.