# Domain-Specific Appendix: COVID-19 Anticoagulation

(formerly known as the COVID-19 Therapeutic Anticoagulation Domain)

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

Anticoagulation Domain-Specific Appendix Version 3.0 27th February, 2021

**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 up to three interventions:

- Conventional low dose thromboprophylaxis
- Intermediate dose thromboprophylaxis
- Continuation of therapeutic dose anticoagulation (only in the Prior Therapeutic Anticoagulation Stratum)

At this participating site the following interventions have been selected within this domain for patients in the No Prior Therapeutic Anticoagulation stratum:

☐ Conventional low dose thromboprophylaxis

☐ Intermediate dose thromboprophylaxis

At this participating site the following interventions have been selected within this domain for patients in the Prior Therapeutic Anticoagulation stratum:

☐ Conventional low dose thromboprophylaxis

☐ Intermediate dose thromboprophylaxis

☐ Continuation of therapeutic dose anticoagulation

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 |
| Domain-specific Stratum | N/A | No Prior Therapeutic Anticoagulation | Prior Therapeutic Anticoagulation | N/A |
| Interventions specified in this DSA | Not available | Conventional low dose Intermediate dose | Conventional low dose Intermediate dose Continuation of therapeutic dose anticoagulation | Not available |
| Interventions submitted for approval in this jurisdiction | Not available | ☐ Conventional low dose ☐ Intermediate dose | ☐ Conventional low dose ☐ Intermediate dose ☐ Continuation of therapeutic dose anticoagulation | Not available |
| | Ward | ICU | ICU | ICU | ICU |
| Interventions offered at this site | Not available | Not available | ☐ Conventional low dose ☐ Intermediate dose | ☐ Conventional low dose ☐ Intermediate dose ☐ Continuation of therapeutic dose anticoagulation | Not available |

| REMAP-CAP: COVID-19 Anticoagulation Domain Summary | |
|---|---|
| Interventions | • Conventional low dose thromboprophylaxis<br>• Intermediate dose thromboprophylaxis<br>• Continuation of therapeutic dose anticoagulation (Prior Therapeutic Anticoagulation Stratum only) |
| Unit of Analysis, Strata, and State | This domain is analyzed only in the pandemic statistical model.<br><br>The pandemic statistical model includes only patients who are in the Pandemic Infection Suspected or Proven (PISOP) stratum. Within the Anticoagulation Domain there is a 'domain-specific' strata that categorizes patients at time of randomization as either Prior Therapeutic Anticoagulation or No Prior Therapeutic Anticoagulation. The unit-of-analysis is defined by illness severity state at time of enrollment, defined as Severe State, and by Prior Therapeutic Anticoagulation strata status. Borrowing is permitted between 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 Prior Therapeutic Anticoagulation strata status. |
| Evaluable treatment-by-treatment Interactions | Interactions with the Antiplatelet Domain will be modeled. |
| 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:<br>• COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing<br>• 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:<br>• More than 48 hours has elapsed since ICU admission, unless the patient has already been assigned a treatment in another domain in the Moderate State in which case exclusion will occur if more than 48 hours has elapsed since commencement of sustained organ failure support in an ICU<br>• A clinical indication to commence or continue therapeutic dose anticoagulation<br>• Intention to continue or commence dual antiplatelet therapy<br>• Enrollment 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<br>• Known or suspected previous adverse reaction to UFH or LMWH including heparin induced thrombocytopenia (HIT).<br>• The treating clinician believes that participation in the domain would not be in the best interests of the patient<br><br>Additional stratum specific exclusion criteria are applied.<br>In the Prior Therapeutic Anticoagulation Stratum patients will be excluded if they have:<br>• Clinical or laboratory bleeding risk or both that is sufficient to contraindicate continuation of therapeutic dose anticoagulation<br><br>In the No Prior Therapeutic Anticoagulation Stratum patients will be excluded if they have any of the following:<br>• Clinical or laboratory bleeding risk or both that is sufficient to contraindicate intermediate dose thromboprophylaxis |

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| | • The patient is receiving non-heparin anticoagulation medication (such as a direct acting oral anticoagulant) and the treating clinician believes that cessation and substitution with conventional low-dose thromboprophylaxis is either inappropriate or not possible. |
| Intervention-Specific Exclusions | None |
| Outcome measures | Primary REMAP endpoint: refer to REMAP-CAP Core Protocol + Pandemic Appendix and REMAP-COVID Core Protocol<br><br>Secondary REMAP endpoints: refer to REMAP-CAP Core Protocol + Pandemic Appendix and REMAP-COVID Core Protocol<br><br>Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment):<br>• Confirmed deep venous thrombosis<br>• Confirmed pulmonary embolism<br>• Confirmed ischemic cerebrovascular event<br>• Total red cell blood cell units transfused between randomization and the end of study day 15<br>• Acute myocardial infarction<br>• Peak troponin<br>• Major bleeding<br>• Other thrombotic events including mesenteric ischemia and limb ischemia<br>• Serious Adverse Events (SAE) as defined in relevant core protocol documents and this DSA |

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# 1. ABBREVIATIONS

| | |
|---|---|
| ACE2 | Angiotensin-Converting Enzyme 2 |
| aPTT | Activated partial thromboplastin time |
| ARDS | Acute Respiratory Distress Syndrome |
| CCP | Clinical Characterization Protocol |
| CrCl | Creatinine clearance |
| DSA | Domain-Specific Appendix |
| DIC | Disseminated Intravascular Coagulation |
| DSMB | Data Safety and Monitoring Board |
| DSWG | Domain-Specific Working Group |
| HIT | Heparin Induced Thrombocytopenia |
| HTE | Heterogeneity of Treatment Effect |
| ICU | Intensive Care Unit |
| ISIG | International Statistics Interest Group |
| ITSC | International Trial Steering Committee |
| LMWH | Low Molecular Weight Heparin |
| LSVT | Local Standard Venous Thromboprophylaxis |
| MERS-CoV | Middle East respiratory syndrome coronavirus |
| mpRCT | Multi-platform RCT |
| 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 ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION

The version of the COVID-19 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

Version 3:    Approved by the COVID-19 Anticoagulation DSWG on 27th February 2021

## 4. COVID-19 ANTICOAGULATION DOMAIN GOVERNANCE

### 4.1. Domain members

**Chair:**             Dr. Ryan Zarychanski

**Deputy Chair:**    Dr. Charlotte Bradbury (Version 3 adaptation lead)

**Members:**

Prof. Derek Angus

Dr. Diptesh Aryal

Dr. Scott Berry

Dr. Shailesh Bihari

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## 4.2. Contact Details

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## 4.3. *Interaction with ATTACC and ACTIV-IV platform trials*

Both ATTACC and ACTIV-IV are trials also evaluating the treatment effect of anticoagulation in patients with COVID-19. There is overlap between the leadership of the ATTACC and ACTIV-IV (inpatient) trials and the leadership of this domain. ATTACC and ACTIV-IV have been designed to be complementary with previous versions of this domain including pre-specified plans in relation to methods of analysis. Data from this domain, ATTACC, and ACTIV-IV may be incorporated into a statistical model that is separate from the pandemic statistical model of REMAP-CAP. The protocol, governance, and data management of ATTACC and ACTIV-IV are separate from REMAP-CAP. The REMAP-CAP DSMB will have overlapping membership with the DSMB for the ATTACC trial. ACTIV-IV functions with a separate independent DSMB. All three trials 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.

# 5. COVID-19 ANTICOAGULATION DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

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

**Chair**                          Date          27th February 2021

Dr. Ryan Zarychanski

# 6. BACKGROUND AND RATIONALE

## 6.1. *Domain definition*

This is a domain within the REMAP-CAP platform to test the effectiveness of different anticoagulation strategies for patients with acute illness due to suspected or proven COVID-19.

## 6.2. Domain-specific background

### 6.2.1. COVID-19 infection

COVID-19 is caused by a novel coronavirus designated SARS-CoV-2. In December 2019, COVID-19 was first reported when a cluster of patients with severe pneumonia of unknown cause was identified in Wuhan, China. SARS-CoV-2 quickly spread across the globe and the WHO declared COVID-19 a pandemic in March 2020 (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf). The spectrum of illness due to SARS-CoV-2 ranges from asymptomatic infection through to severe pneumonia, respiratory distress, multiorgan dysfunction, and death. A substantial proportion of patients admitted to hospital because of COVID-19 require provision of organ failure support in an Intensive Care Unit (ICU) and in-hospital mortality within this group is high (Tan et al., 2021). Early clinical management recommendations focus on supportive care, including organ support as needed, and the prevention of complications. Effective treatments are urgently needed. The WHO have recommended that "investigational anti-COVID-19 therapeutics should be used only in approved, randomized, controlled trials" (https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf).

### 6.2.2. Clinical trials for COVID-19 infection

Observational data cannot determine treatment effects reliably due to the risk of systematic bias (Califf et al., 2020). Clinical trials to identify effective COVID-19 treatments are needed and a large number of trials are underway. Early in the pandemic, the WHO provided guidance regarding both trial design and prioritization of candidate therapies. With regards to trial design, the WHO noted that initially there were no treatments with proven efficacy in patients with COVID-19. Therefore, the recommended 'standard of care' comparator was a control group that did 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). As effective COVID-19 treatments are identified, it is anticipated that 'standard of care', both inside and outside of a clinical trial, will continue to change to incorporate the use of agents with proven efficacy. REMAP-CAP randomizes COVID-19 patients to a range of therapeutic interventions across different domains. Up to date information regarding active and inactive interventions and domains is available at www.remapcap.org.

It is recognized that in patients with COVID-19 the effect of treatments can be different depending on stage or progression and severity of illness (Recovery Collaborative Group et al., 2020). As such,

therapies should be evaluated independently in pre-defined patient groups e.g. those who are critically ill, those who are admitted to hospital but are not critically ill, and those who have COVID-19 but have not been admitted to hospital. 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 influence the balance between beneficial and adverse effects of a particular intervention, reinforcing 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 anticoagulation strategies for patients with acute illness due to suspected or proven COVID-19. If at, any stage, external evidence of harm or definitive evidence of absence of effectiveness 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. Venous thromboprophylaxis is standard care for hospitalized patients who do not have COVID-19

For hospitalized patients (without COVID), particularly those with reduced mobility, it is long-standing clinical practice to administer some form of pharmacological anticoagulation thromboprophylaxis to prevent VTE. There is evidence that routine conventional low dose thromboprophylaxis, most commonly with heparin, reduces morbidity, mortality and health service costs in hospitalized patients, as highlighted in national and international guidelines (https://www.nice.org.uk/guidance/ng89, https://www.sign.ac.uk/media/1060/sign122.pdf, https://ashpublications.org/bloodadvances/article/2/22/3198/16115/American-Society-of-Hematology-2018-guidelines-for). As a result, virtually all patients admitted to hospital who do not have contraindications are administered thromboprophylaxis, most frequently with heparin.

### 6.2.5. Thrombotic complications are common in patients admitted to hospital with COVID-19

Patients admitted to hospital with COVID-19 are at high risk of thrombotic complications, in spite of conventional low dose thromboprophylaxis (Spyropoulos et al., 2020, Bikdeli et al., 2020a, Helms et

al., 2020, Klok et al., 2020, Bilaloglu et al., 2020, Al-Samkari et al., 2020). Patients at highest thrombotic risk are those with severe COVID-19 in ICU. COVID-19 related thrombotic complications are diverse and have been reported within the venous circulation i.e. VTE such as Pulmonary Embolism (PE); arterial circulation, i.e. ischemic cardiac events or strokes or mesenteric ischemia, peripheral vascular ischemia; microvascular circulation, which may contribute to organ dysfunction; and extracorporeal circuits, such as clotting within hemofiltration circuits. Microvascular injury, activation, inflammation and thrombosis are also central to the pathogenesis of the viral pneumonitis and development of acute respiratory distress syndrome (ARDS) seen in severe COVID19 infection (Perlman and Dandekar, 2005, Blondonnet et al., 2016). Autopsies and histology from those who have died from COVID-19, have revealed widespread thrombosis in large and small blood vessels of the pulmonary vasculature (Buja et al., 2020, Menter et al., 2020, Wichmann et al., 2020, Lax et al., 2020). Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19 (Rapkiewicz et al., 2020). It is now widely recognized that thrombosis is a key contributor to clinical deterioration and death in patients with COVID-19 and that a vasculopathy underlies the acute lung injury.

Multiple studies have looked at thrombotic rates in hospitalized patients with COVID-19 infection. For example, a multicenter, retrospective study in the US described the rate and severity of hemostatic and thrombotic complications in 400 hospital-admitted COVID-19 patients, including 144 critically ill patients (Al-Samkari et al., 2020). These patients primarily received standard-dose prophylactic heparin anticoagulation, yet the overall incidence of thrombotic complications was reported as 9.5% (95%CI 6.8-12.8%). The incidence of bleeding and major bleeding was 4.8% (95%CI 2.9-7.3%) and 2.3% (95%CI 1.0-4.2%) respectively. The incidence of thrombotic complications is higher in patients with COVID-19 who are treated in an ICU. In the presence of conventional low dose thromboprophylaxis, VTE events occur in approximately 30% (most commonly PE) and arterial events in 4% (Klok et al., 2020, Helms et al., 2020). Similar rates of thrombosis (25%) in patients admitted to an ICU have also been reported in China where patients do not receive thromboprophylaxis routinely (Cui et al., 2020). Data from patients with severe COVID-19 admitted to an ICU in the UK, where routine thromboprophylaxis is used, showed an overt thrombotic rate of 43% (n=81/187), with PE the commonest site (22.5%), serious arterial thrombotic events in 13% and major bleeding in 5% (Shah et al., 2020). Two studies reported that thrombotic complications were much higher than those previously observed in patients admitted to an ICU with non-COVID infective ARDS of 6 to 8% (Helms et al., 2020, Poissy et al., 2020).

Pre-existing comorbid cardiovascular disease, diabetes and hypertension are distinct risk factors for COVID-19 associated mortality (Zhou et al., 2020). Regarding the incidence of arterial thrombotic events. Data from a large US cohort (Bilaloglu et al., 2020) of 3334 patients admitted to hospital with COVID-19, reported that thrombotic complications occurred in 16% of all patients and in 29.4% of patients treated in an ICU. In this cohort, acute myocardial infarction (AMI) was the commonest thrombotic event occurring in 8.9% overall and 13.9% in the ICU cohort. All-cause mortality was 24.5% and there was an association between occurrence of thrombotic events and mortality (43.2% vs 21.0%; P < .001).

Acute cardiac injury (troponin >99th percentile of upper limit of normal) is a common feature of COVID-19 infection and associated with a poor prognosis (Shi et al., 2020a, Shi et al., 2020b). The underlying mechanism of cardiac injury includes direct infection via ACE2 of cardiac myocytes and coronary endothelium resulting in coronary and microvascular thrombosis as well as myocarditis. Elevated Troponin-I and arrhythmia are both associated with poor outcome (Guo et al., 2020). Of 416 hospitalized patients with COVID-19, approximately 20% had cardiac injury and cardiac injury was associated with an increased risk of complications including renal failure, as well as a 3.4-fold increase in mortality (Shi et al., 2020b).

Patients with COVID-19 are also at increased risk of other arterial events including mesenteric ischemia, peripheral vascular ischemia and stroke. Stroke occurred in 2.8% (6 out of 214 patients, 41% male, mean age 53 years) in a cohort from Wuhan, China (Mao et al., 2020). From New York City, over a 2-week period from March 23 to April 7, 2020, a total of five patients below the age of 50 years presented with new-onset symptoms of large-vessel ischemic stroke. All five patients tested positive for COVID-19. By comparison, every 2 weeks over the previous 12 months, the same service treats on average, 0.73 patients below the age of 50 years with large-vessel stroke (Oxley et al., 2020). Ischemic injury of the fingers and toes has also been reported in patients with severe COVID-19 (Li et al., 2020).

### 6.2.6. Pathogenesis of thrombotic complications in patients with COVID-19

There is direct viral infection of the vascular endothelium via ACE2 with resulting injury, activation and local vascular inflammation (Varga et al., 2020, Escher et al., 2020, Goshua et al., 2020, O'Sullivan et al., 2020). There is also hypercoagulability which is driven by the profound inflammatory response to COVID-19 and is an exaggerated version of the acute phase response commonly seen in patients unwell with infection, cancer or inflammatory disorders. Hypercoagulable changes include high levels of fibrinogen, factor VIII, Von Willibrand factor, D-

dimers, platelet activation, impaired fibrinolysis, low antithrombin and antiphospholipid antibodies (Helms et al., 2020, Shah et al., 2020, Panigada et al., 2020, Ranucci et al., 2020, Tang et al., 2020b, Hasan Ali et al., 2020, Amezcua-Guerra et al., 2020, Zhang et al., 2020).

Laboratory analysis of COVID-19 patients' blood demonstrates overt prothrombotic changes beyond the normal range and also beyond what is considered "normal" for non-COVID hospitalized patients with markedly hypercoagulable thromboelastography traces (Panigada et al., 2020). Derangements in coagulation laboratory parameters are strongly associated with worse outcomes and various lines of evidence suggest that the prothrombotic state is causally related to poor outcomes. In multiple large case series, elevated D-dimer is consistently associated with a higher risk of developing ARDS and death (Wu and McGoogan, 2020, Zhou et al., 2020). However, in the majority of patients with COVID-19, raised D-dimers are not associated low fibrinogen levels or thrombocytopenia or prolonged prothrombin times (Panigada et al., 2020, Shah et al., 2020). Therefore, although there is microvascular thrombosis, the COVID-19 coagulopathy is very rarely associated with disseminated intravascular coagulation (DIC).

### 6.2.7. Rationale for evaluation of anticoagulation strategies in patients with COVID-19

#### 6.2.7.1. Introduction

Given that thrombotic complications are a potentially preventable cause of significant number of COVID-19 related deaths and of morbidity in survivors, more intensive antithrombotic prevention strategies may have the potential to improve clinical outcomes.

The two predominant clinical strategies for thrombosis prevention are anticoagulation and antiplatelet therapy. Anticoagulation is generally used for prevention of VTE and antiplatelet agents for prevention of arterial events. In addition, there are some clinical conditions, such as acute coronary syndrome, where a combination of anticoagulation and antiplanet agents has shown synergistic efficacy, albeit with an increased bleeding risk.

#### 6.2.7.2. Current treatment guidelines for prevention of thrombotic complications

Many sets of thrombosis prophylaxis guidelines have been published that are specific for patients admitted to hospital with COVID-19. While all guidelines recommend thromboprophylaxis, unless there is a clear contraindication, there is substantial variation in the recommended approach for thromboprophylaxis including dose (Table 1). Broadly, there are two strategies. One strategy, referred to as conventional low dose thromboprophylaxis, is to administer the same low dose of anticoagulation medications that are used in patients who do not have COVID-19. The other

strategy, referred to as intermediate dose, is to administer approximately twice as much as low dose (and approximately half as much as therapeutic dose). The effectiveness of low dose is well established in patients without COVID-19. Adoption of intermediate dose in clinical practice, and guidelines, for COVID-19 is not based on high-quality evidence, but was driven by observational data reporting high rates of thrombosis in spite of conventional low dose thromboprophylaxis, particularly in patients corresponding to the Severe State. As such, these guidelines are based on expert consensus and observational data rather than high-quality randomized evidence. Both variation in guidelines, as well as variation in practice, occur as a consequence of the absence of high-quality evidence. In some countries, including the UK, it has become standard practice for patients who are critically ill with COVID-19 to receive 'intermediate dose'. In other countries such as US, practice has been to use conventional low dose. Although not recommended in guidelines, some hospitals declined to participate in Version 2 of this domain because the site had adopted the use of therapeutic anticoagulation as routine therapy.

*Table 1. Summary of published statements on thromboprophylaxis in COVID-19, available as of January 2021.*

| Organization | Severe COVID-19 patients (ICU) | Moderate COVID-19 patients (ward) |
|---|---|---|
| British Thoracic Society (brit-thoracic.org.uk) | Conventional low dose thromboprophylaxis Consider higher doses of LMWH in a proportion of patients<br><br>D-dimer may indicate risk | Not specifically discussed |
| International Society on Thrombosis and Haemostasis PMID: 32459046 | Conventional low dose thromboprophylaxis after considering the bleeding risk<br><br>Consider intermediate dose LMWH (50% of panel) | Conventional low dose thromboprophylaxis after considering the bleeding risk<br><br>Consider intermediate dose LMWH (30% of panel) |

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|---|---|---|
| American College of Chest Physicians<br><br>PMID: 32502594 | Conventional low dose thromboprophylaxis preferred over intermediate or higher doses | Conventional low dose thromboprophylaxis during in-patient stay only |
| Global COVID-19 Thrombosis Collaborative Group<br><br>PMID: 32311448 | Conventional low dose thromboprophylaxis Insufficient data to recommend intermediate or therapeutic doses | Conventional low dose thromboprophylaxis Insufficient data to recommend intermediate or therapeutic doses |
| Faculty of Intensive Care Medicine<br><br>(icmanaesthesiacovid-19.org) | Intermediate or higher doses of LMWH | Conventional low dose LMWH<br><br>D-dimer levels alone should not be used to guide LMWH dosing |
| American society of Haematology<br><br>(hematology.org/covid-19/covid-19-and-vte-anticoagulation) | Conventional low dose thromboprophylaxis | Conventional low dose thromboprophylaxis |
| NICE<br><br>https://www.nice.org.uk/guidance/ng186/chapter/Rationales | Consider Intermediate dose LMWH | Conventional low dose LMWH |
| WHO COVID-10 Clinical management guidelines<br>https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-clinical-2021-1 | Conventional low dose thromboprophylaxis | Conventional low dose thromboprophylaxis |

*6.2.7.3. Results of clinical trials of routine therapeutic anticoagulation*

On the basis of observational studies that reported possible benefit, in association with an acceptable bleeding profile (Paranjpe et al., 2020, Tang et al., 2020b, Tang et al., 2020a), as well as the possibility that heparin drugs may inhibit the binding of the SARS-CoV2 virus to ACE2 receptors (Vicenzi et al., 2004, Lang et al., 2011) (https://www.biorxiv.org/content/10.1101/2020.02.29.971093v1), the REMAP-CAP platform, in association with the ATTACC and ACTIV-4a trials, evaluated the treatment effect of therapeutic anticoagulation with heparin compared with local standard venous thromboprophylaxis. The protocol for the REMAP-CAP component of this multi-platform RCT (mpRCT) was the previous

version, Version 2, of this DSA. Pre-specified statistical triggers occurred for the mpRCT in December 2020 and January 2021. The results that resulted in occurrence of these statistical triggers have been placed in the public domain (www.remapcap.org), and at the time of writing of this DSA are being prepared for submission for peer-review and publication. The adaptation of this DSA, from Version 2 to Version 3, is based on the results reported by the mpRCT. The REMAP-CAP platform is also evaluating the treatment effect of different antiplatelet agents and this domain of the platform is ongoing.

The mpRCT randomized eligible patients to local standard venous thromboprophylaxis (LSVT) or therapeutic anticoagulation with heparin. The design of the mpRCT permitted separate evaluation of treatment effect in patients in the Severe State and, in the Moderate State, patients with a d-dimer that was less than twice the upper limit of normal and patients with a d-dimer that was more than twice the upper limit of normal. The range of intensity of anticoagulation permitted within the local standard venous thromboprophylaxis intervention included low dose, as well as intermediate dose (as outlined in section 6.2.7)

On December 18th 2020 randomization between therapeutic anticoagulation and local standard venous thromboprophylaxis was ceased based on a recommendation from the trial DSMB. This recommendation was based on the occurrence of a pre-specific statistical trigger for futility for therapeutic anticoagulation compared with LSVT in the Severe State. The most recent analysis, in the Severe State, indicates a high probability of inferiority of therapeutic anticoagulation compared with LSVT (posterior probability = 0.89) with a mean odds ratio = 0.87 (95% credible interval of 0.70 to 1.08). Odds ratio below 1 indicate a worse outcome with respect to the pandemic primary outcome which is a composite of in-hospital mortality and the duration of organ failure support in survivors.

The identification of futility, with a high probability of inferiority, was not an expected finding. As indicated above, a range of intensity of anticoagulation medication administration was permitted within the LSVT intervention. The decision as to whether low or intermediate dose was administered was made by the treating clinician and could be varied between patients at the same participating site. This choice of control intervention was appropriate, in the context of a trial that compared therapeutic anticoagulation with local standard venous thromboprophylaxis, but the variability within the local standard venous thromboprophylaxis intervention leaves uncertainty for clinicians regarding optimal intensity of anticoagulation administration, when used for prophylaxis for patients that correspond to the Severe State.

On 21st January 2021, the DSMB recommended stopping recruitment to the anticoagulation domain for patients in the Moderate State. In these patients, therapeutic dose heparin reached the pre-specified statistical threshold for superiority compared with standard of care thromboprophylaxis in both the low D-dimer stratum and the high D-dimer stratum. The probability of superiority (odds ratio is higher than 1) in the low D-dimer stratum was 0.997 and in the high D-dimer stratum was 0.991. This corresponded to mean odds ratios of 1.57, 1.53, and 1.51 for the low D-dimer, high D-dimer, and missing D-dimer stratum, respectively. This is a treatment effect in the opposite direction in the Moderate State to that observed in the Severe State. The protocol of all three trials that contributed to the mpRCT specified continuation of therapeutic anticoagulation in patients enrolled in the Moderate State, if the patients progressed to the Severe State, during the treatment period.

There are several possible reasons for the divergent treatment effect that was observed in different States. One possible explanation is heterogeneity of treatment effect (HTE) according to severity (Iwashyna et al., 2015). While not attempting to provide a mechanism by which this difference in treatment effect occurs, the observed results are consistent with HTE. The possibility of HTE was the rationale for the trial design that permitted separate estimates of treatment effect in the Moderate State and the Severe State, and HTE has been observed with other treatments that are effective for patients with severe COVID-19 (Recovery Collaborative Group et al., 2020). Another possible explanation relates to differences within the LSVT control intervention in the Moderate compared with the Severe State. It appears likely that most patients randomized to LSVT in the Moderate State received conventional low dose whereas intermediate dose was more common for patients randomized to LSVT in the Severe State. It is possible that intermediate dose is sufficient to prevent thrombotic complications and higher doses add risk without further benefit, at least in patients enrolled in the Severe State.

There is one RCT that compared low and intermediate dose that has announced results, although at the time of writing this DSA amendment, this trial has not been published (Bikdeli et al., 2020b). The INSPIRATION trial, conducted in Iran, recruited patients who were critically ill. This trial reported that there was no benefit of intermediate compared to low dose, but the reported confidence intervals do not exclude clinically relevant benefit and the dose chosen for intermediate was higher and once daily rather than the lower dose twice daily regimens most commonly used in standard care including the LSVT intervention in the mpRCT. There are also several publications, albeit derived from non-randomized data, that suggest intermediate dose heparin improves outcomes in critically ill patients with COVID-19. These data suggest that compared to conventional low dose, intermediate dose heparin reduces thrombotic rates, without an increase in major bleeding rates

(Tacquard et al., 2021, Atallah et al., 2021). Therefore, the optimal dose of heparin in critically ill patients with COVID-19 remains to be established.

The following conclusions have been made by the REMAP-CAP investigators:

- For patients who are admitted to hospital with COVID-19 and are not critically ill (i.e. corresponding to the Moderate State in REMAP-CAP) therapeutic anticoagulation may become a widely adopted therapy. However, in such patients there is substantial uncertainty as to the appropriate anticoagulant treatment strategy should the patient become critically ill. While the mpRCT protocols that specified continuation of therapeutic anticoagulation have reported benefit, there is independent evidence from the mpRCT Severe State platform conclusion that, in patients receiving ICU-level support, commencement of therapeutic anticoagulation is likely harmful. Therefore, there is uncertainty as to whether the optimal treatment strategy for patients who become critically ill is continuation of full dose therapeutic anticoagulation or de-escalation and, if de-escalated, whether this should occur to conventional low or intermediate dose.

- For patients who are receiving ICU-level support (i.e. corresponding to the Severe State in REMAP-CAP) who have not received prior therapeutic anticoagulation there is evidence that therapeutic anticoagulation should not be provided but there is uncertainty as to whether patients should receive low (conventional) or intermediate dose thromboprophylaxis.

This version of the DSA, Version 3, adapts the domain to compare conventional low dose thromboprophylaxis with intermediate dose in patients in the Severe State who have not previously received therapeutic heparin and it compares continuation of therapeutic dose anticoagulation to de-escalation to conventional low dose and intermediate dose thromboprophylaxis in patients who received therapeutic dose heparin previously.

### 6.2.8. 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.

### 6.2.9. 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).

### 6.2.10. 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). Overall, patients receiving therapeutic anticoagulation with these agents have a 1 to 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).

In patients admitted to hospital with COVID-19, clinically manifest bleeding is less common than identified thrombosis. In a study of 429 patients from Boston, major bleeding (WHO grade 3-4) rate was 2.3% (95% CI, 1.0-4.2), or 1.96 per 100 patient-weeks (Al-Samkari et al., 2020) for a rate of 5.6% (95% CI, 2.4-10.7), or 3.46 per 100 patient-weeks, whereas, thrombotic events occurred 9.5% (virtually all patients were on conventional low dose or higher doses of heparin). All but 1 major bleed occurred in the critically ill. Helms et al specifically assessed the severe COVID-19 cohort (70% on prophylactic heparin and 30% on therapeutic dose) and reported a 2.3% incidence of major bleeding (Helms et al., 2020). Another study assessed thrombotic and hemorrhagic complications in critically ill patients with COVID-19, with the majority on standard of care thromboprophylaxis (prophylactic or intermediate dose) and demonstrated an overall rate of bleeding of 8% with major bleeding in 5% compared to an incidence of thrombotic complications in 43% (Shah et al., 2020).

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% (Protect Investigators for the Canadian Critical Care Trials 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 different anticoagulation strategies 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 strategies. The following interventions will be available:

- Conventional low dose thromboprophylaxis
- Intermediate dose thromboprophylaxis
- Continuation of therapeutic dose anticoagulation (only in the Prior Therapeutic Anticoagulation Stratum)

We hypothesize that the treatment effect of different anticoagulation strategies is different depending on whether SARS-CoV-2 infection is confirmed to be present or absent.

We hypothesize that the treatment effect of different anticoagulation strategies is different depending on whether prior therapeutic anticoagulation is present or absent.

We hypothesize that the treatment effect of different anticoagulation strategies is different depending on allocation status in the Antiplatelet Domain. This is a treatment-by-treatment interaction between interventions in the Anticoagulation Domain and the Antiplatelet Domain.

# 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.

### 8.1.1. State

This domain is available for patients who have acute illness due to suspected or proven pandemic infection in the Severe State.

### 8.1.2. Domain-specific strata

Domain-specific strata are applied to patients in the Severe State at the time of assessment for this domain.

#### 8.1.2.1. Prior Therapeutic Anticoagulation Stratum

Patients in the Severe State who are currently receiving therapeutic dose anticoagulation with heparin for the treatment of COVID-19 infection will be categorized as members of the Prior Therapeutic Anticoagulation Stratum.

#### 8.1.2.2. No Prior Therapeutic Anticoagulation Stratum

Patients in the Severe State who are not currently receiving therapeutic dose anticoagulation with heparin for the treatment of COVID-19 infection will be categorized as members of the No Prior Therapeutic Anticoagulation Stratum.

## 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 Anticoagulation Domain.

### 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, unless the patient has already been assigned a treatment in another domain in the Moderate State in which case exclusion will occur if more than 48 hours has elapsed since commencement of sustained organ failure support in an ICU
- A clinical indication to commence or continue therapeutic dose anticoagulation

- Intention to continue or commence dual antiplatelet therapy

- Enrollment 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. Stratum-specific domain exclusion criteria

In the Prior Therapeutic Anticoagulation Stratum, patients will be excluded from this domain if they have any of the following:

- Clinical or laboratory bleeding risk or both that is sufficient to contraindicate continuation of therapeutic dose anticoagulation with heparin

In the No Prior Therapeutic Anticoagulation Stratum, patients will be excluded from this domain if they have any of the following:

- Clinical or laboratory bleeding risk or both that is sufficient to contraindicate intermediate dose thromboprophylaxis

- The patient is receiving non-heparin anticoagulation medication (such as a direct acting oral anticoagulant) and the treating clinician believes that cessation and substitution with conventional low-dose thromboprophylaxis is either inappropriate or not possible

### 8.2.4. Intervention exclusion criteria

Nil.

### 8.2.5. Eligibility for Antiplatelet Domain

Eligible patients in the Prior Therapeutic Anticoagulation Stratum will be excluded from the Antiplatelet Domain if their age is more than 75 years.

Eligible patients in the No Prior Therapeutic Anticoagulation Stratum are eligible for the Antiplatelet Domain irrespective of age.

## 8.3. Interventions

### 8.3.1. Anticoagulation interventions

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

☐ Conventional low dose thromboprophylaxis

☐ Intermediate dose thromboprophylaxis

☐ Continuation of therapeutic dose anticoagulation (only in the Prior Therapeutic Anticoagulation Stratum)

In the Prior Therapeutic Anticoagulation stratum randomization occurs to continuation of therapeutic dose anticoagulation with heparin or de-escalation to one of two intensities of thromboprophylaxis. In the Prior Therapeutic Anticoagulation stratum a site must participate in at least two interventions. Sites may be given the option of participating in only one or both of the two domain-specific stratum.

### 8.3.2. Conventional low dose thromboprophylaxis

Low dose thromboprophylaxis will be administered for 14 days following randomization or until hospital discharge, whichever occurs first. Dosing should be according to the dosing tables in Appendix 1. LMWH is recommended in preference to UFH for patients with an estimated creatinine clearance (CrCl) of greater than or equal to 30 ml/min. For patients with an estimated CrCl less than 30 ml/min, see options outlined in dosing tables (Appendix 1). After 14 days or hospital discharge decisions regarding thromboprophylaxis are at the discretion of the treating clinician.

#### 8.3.2.1. Use of therapeutic dose anticoagulation in patients assigned to conventional low dose thromboprophylaxis

Any patient who develops an accepted clinical indication for therapeutic dose 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 systemic therapeutic dose anticoagulation for renal replacement therapy. Alternatives to systemic therapeutic dose anticoagulation for renal replacement therapy are encouraged and include regional citrate, heparin priming and low-dose

heparin administration (without measurable systemic anticoagulation). Administration of intermediate dose thromboprophylaxis is a protocol deviation.

### 8.3.3. Intermediate dose thromboprophylaxis

Intermediate dose thromboprophylaxis will be administered for 14 days following randomization or until hospital discharge, whichever occurs first. Dosing should be according to the dosing tables in Appendix 1. LMWH is recommended in preference to UFH for patients with CrCl greater than or equal to 30 ml/min. For patients with an estimated CrCl less than 30 ml/min, see options outlined in dosing tables (Appendix 1). After 14 days or hospital discharge decisions regarding thromboprophylaxis are at the discretion of the treating clinician. In the absence of bleeding complications, administration of conventional low dose thromboprophylaxis is considered a protocol deviation.

#### 8.3.3.1. *Use of therapeutic anticoagulation in patients assigned to intermediate dose thromboprophylaxis*

Any patient who develops an accepted clinical indication for therapeutic dose 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 systemic therapeutic dose anticoagulation for renal replacement therapy. Alternatives to systemic therapeutic dose anticoagulation for renal replacement therapy are encouraged and include regional citrate, heparin priming and low-dose heparin administration (without measurable systemic anticoagulation).

### 8.3.4. Continuation of therapeutic dose anticoagulation

The patient will be administered either UFH by IV infusion or LMWH to achieve systemic anticoagulation according to local practice for acute VTE treatment for 14 days following randomization or until hospital discharge, whichever occurs first. Either agent may be used and the same patient may be switched between UFH and LMWH at the discretion of the treating clinician. After 14 days or hospital discharge decisions regarding thromboprophylaxis or anticoagulation are at the discretion of the treating clinician.

#### 8.3.4.1. *Therapeutic dose 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.

### 8.3.4.2. Therapeutic dose 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 measured or estimated weight of the patient.

Adjustment for impairment of renal function should be according to dosing tables in Appendix 1.

### 8.3.4.3. Duration of therapeutic dose 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. Therapeutic dose anticoagulation may be ceased at ICU discharge at the discretion of the treating clinician. In the absence of clinically significant bleeding complications, cessation of therapeutic dose anticoagulation before the end of 14 days while the patient is receiving invasive mechanical ventilation is a protocol deviation.

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

### 8.3.5. Discontinuation of study intervention

The assigned anticoagulation strategy may be discontinued if there is clinically significant bleeding or other complication sufficient to warrant cessation in the opinion of the treating clinician. The assigned anticoagulation strategy 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, such as to allow surgical or other procedures is not a protocol deviation if the cessation is for less than 24 hours.

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

### 8.3.6. Anticoagulation strategy in patients negative for COVID-19 infection

Patients with suspected COVID-19 infection who receive an allocation status in this domain but who subsequently test negative for COVID-19 infection may have treatment changed to standard of care at the discretion of the treating clinician. 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

Commencement of any new agent that inhibits platelet function or is an anticoagulant medication is not permitted unless there is an accepted clinical indication such as an acute coronary syndrome, ischemic stroke or transient ischemic event, or where the agent that inhibits platelet function has been specified in another domain of this platform. A patient who receives an agent that acts to inhibit platelet function as a usual medication may have this medication continued.

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:

- 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 Hemostasis definition)

- Mesenteric Ischemia, limb ischemia, and other thrombotic 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 domain has adapted as a consequence of separate Platform Conclusions in the Moderate and Severe States. This amendment specifies three new interventions. Two of these interventions are within the spectrum of the intervention that was previously specified as 'local standard venous thromboprophylaxis' in Version 2 of this DSA. The third intervention is continuation of previously commenced therapeutic dose anticoagulation with heparin, which differs only from the intervention previously specified as 'therapeutic anticoagulation' in Version 2 of this DSA in that it is only available to patients who have already commenced therapeutic dose anticoagulation with heparin.

While the conventional low dose and intermediate dose thromboprophylaxis interventions are within the spectrum of the previous 'local standard thromboprophylaxis' intervention these two new strategies will be considered to be new interventions independent of the previous intervention. Similarly, the continuation of therapeutic dose anticoagulation intervention will be considered a new intervention, independent of the previous arm. No modeling of the relationship between the previous 'local standard thromboprophylaxis' intervention and these new interventions will be created.

Although no recruitment of patients in the Moderate State will occur in this domain at sites with approval for Version 3 of this DSA, analysis of patients recruited previously in the Moderate State continues.

The following Platform Conclusions are possible in the Prior Therapeutic Anticoagulation Stratum and in combination with the Antiplatelet Domain:

- Superiority of any intervention

- Inferiority of any intervention

- Futility of:

    o Continuation of therapeutic dose anticoagulation compared to either conventional low dose thromboprophylaxis or intermediate dose thromboprophylaxis or both

    o Intermediate dose thromboprophylaxis compared with conventional low dose thromboprophylaxis.

- Superiority of any combination of any intervention in the Anticoagulation Domain and any Antiplatelet Domain intervention compared with all other possible combinations in both domains

- Effectiveness:

    o Intermediate dose thromboprophylaxis compared to conventional low dose thromboprophylaxis

    o Continuation of therapeutic dose anticoagulation compared to conventional low dose thromboprophylaxis

    o Intermediate dose thromboprophylaxis in the Anticoagulation Domain in combination with any active intervention in the Antiplatelet Domain compared to the combination of low dose thromboprophylaxis and no antiplatelet intervention in the Antiplatelet Domain

    o Continuation of therapeutic anticoagulation in the Anticoagulation Domain in combination with any active intervention in the Antiplatelet Domain compared with the combination of low dose thromboprophylaxis and no antiplatelet intervention in the Antiplatelet Domain

- Harm from either intervention in the Anticoagulation Domain in combination with each active intervention in the Antiplatelet Domain compared with the combination of any other

intervention in the Anticoagulation Domain and no antiplatelet intervention in the Antiplatelet Domain.

The following Platform Conclusions are possible in the No Prior Therapeutic Anticoagulation stratum and in combination with the Antiplatelet Domain:

- Superiority of either intervention

- Superiority of any combination of either intervention in the Anticoagulation Domain and any Antiplatelet Domain intervention compared with all possible combinations in both domains

- Futility of intermediate dose thromboprophylaxis compared to conventional low dose thromboprophylaxis

- Effectiveness of:

  o Intermediate dose thromboprophylaxis compared to conventional low dose thromboprophylaxis

  o Intermediate dose thromboprophylaxis in the Anticoagulation Domain in combination with any active intervention in the Antiplatelet Domain compared with the combination of the low dose thromboprophylaxis and no antiplatelet interventions

  o Either intervention in the Anticoagulation Domain in combination with each active intervention in the Antiplatelet Domain compared with the combination of the other intervention in the Anticoagulation Domain and no antiplatelet intervention in the Antiplatelet Domain.

- Harm from either intervention in the Anticoagulation Domain in combination with each active antiplatelet intervention compared with the combination of the other intervention in the Anticoagulation Domain and no antiplatelet intervention in the Antiplatelet Domain

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 Severe State.

Unit-of-analysis will be defined by Prior Therapeutic Anticoagulation Strata status and may also be defined by SARS-CoV-2 infection strata. Borrowing is permitted between strata. If the SARS-CoV-2 strata is applied in analysis, Response Adaptive Randomization will be applied to all PISOP patients using probabilities derived from the SARS-CoV-2 confirmed stratum. Randomization proportions will be balanced at initiation, within each stratum.

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 following domains is considered possible and will be incorporated into the statistical model used to analyze this domain:

- Antiplatelet Domain. The expectation and possibility of a meaningful interaction between the antiplatelet domain and the Anticoagulation Domain is high. Hence the interaction priors between these domains is based on a prior with wider support, with larger standard

deviations. A prior with a mean of 0 and a standard deviation of 0.33 is selected for each interaction between the Anticoagulation Domain and the Antiplatelet Domain.

Interactions with all other domains are either not evaluable or not considered possible and will not be incorporated into the statistical model or models in which this domain is evaluated.

If an interaction is specified with a future domain, it is sufficient for the interaction to be specified only in the DSA of such a future domain.

### 10.5. Nesting of interventions

There is no nesting in this domain.

### 10.6. Threshold probability for superiority, effectiveness, harm and inferiority

The threshold probability for statistical triggers for superiority, effectiveness, harm, and inferiority are those specified in the relevant core protocol documents.

### 10.7. Threshold odds ratio delta for equivalence and futility

The Platform Conclusion of equivalence will not be evaluated initially 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 continuation therapeutic dose anticoagulation and intermediate dose thromboprophylaxis compared to conventional low dose thromboprophylaxis.

In the event of a futility trigger with a mean odds ratio near or above 1, the domain may continue recruitment with introduction of an equivalence threshold combined with an analysis of secondary endpoints. This would be a decision of the ITSC, in association with the DSMB.

### 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:

- Shock strata

- Receiving invasive mechanical ventilation at baseline

- Baseline troponin

- Concomitant administration of an antiplatelet at baseline

- 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

Both conventional low dose and intermediate dose are being used in routine clinical practice 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 the 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.

# 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.

## 13.REFERENCES

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## 14.APPENDIX 1. ANTICOAGULANT DOSING TABLES

### 14.1. Enoxaparin

| Weight | Renal function (consider UFH or antiXa monitoring if CrCl<20ml/min)¶ | Enoxaparin sc Conventional low dose thromboprophylaxis | Enoxaparin sc Intermediate dose thromboprophylaxis | Enoxaparin sc therapeutic dose (local protocols for acute VTE dosing can be followed including dose rounding) |
|---|---|---|---|---|
| <50kg | CrCl <30ml/min | 0.25mg/kg once daily | 0.5mg/kg once daily | 1mg/kg once daily |
| <50kg | CrCl ≥30ml/min | 20mg once daily | 40mg once daily | 1mg/kg twice daily OR 1.5mg/kg once daily |
| 50-100kg | CrCl <30ml/min | 20mg once daily | 0.5mg/kg once daily | 1mg/kg once daily |
| 50-100kg | CrCl ≥30ml/min | 40mg once daily | 40mg twice daily | 1mg/kg twice daily OR 1.5mg/kg once daily |
| 101-150kg | CrCl <30ml/min | 40mg once daily | 0.5mg/kg once daily | 1mg/kg once daily |
| 101-150kg | CrCl ≥30ml/min | 40mg twice daily | 60mg twice daily | 1mg/kg twice daily OR 1.5mg/kg once daily |
| >150 kg | CrCl <30ml/min | 60mg once daily | 0.5mg/kg once daily | 1mg/kg once daily |
| >150 kg | CrCl ≥30ml/min | 60mg twice daily | 80mg twice daily | 1mg/kg twice daily OR 1.5mg/kg once daily |

¶ If antiXa levels are checked in renal failure or obesity and suggest heparin accumulation, dose reduction is permitted.

## 14.2. Dalteparin

| Weight | Renal function (consider UFH or antiXa monitoring if CrCl<20ml/min) ¶ | Dalteparin sc Conventional low dose thromboprophylaxis | Dalteparin sc Intermediate dose thromboprophylaxis | Dalteparin therapeutic dose (local protocols for acute VTE dosing can be followed including dose rounding) |
|---|---|---|---|---|
| <50kg | CrCl <30ml/min | 1250 units once daily | 2500 units once daily | 100 units/kg once daily |
| <50kg | CrCl ≥30ml/min | 2500 units once daily | 2500 units twice daily | Either 100 units/kg twice daily or 200 units/kg once daily |
| 50-120kg | CrCl <30ml/min | 2500units once daily | 5000 units once daily | 100 units/kg once daily |
| 50-120kg | CrCl ≥30ml/min | 5000units once daily | 5000 units twice daily | Either 100 units/kg twice daily or 200 units/kg once daily |
| 121-150kg | CrCl <30ml/min | 5000 units once daily | 7500 units once daily | 100 units/kg once daily |
| 121-150kg | CrCl ≥30ml/min | 7500 units once daily | 7500 units twice daily | Either 100 units/kg twice daily or 200 units/kg once daily |
| >150 kg | CrCl <30ml/mi | 7500 units once daily | 5000 units twice daily | 100 units/kg once daily |
| >150 kg | CrCl ≥30ml/min | 5000 units twice daily | 10,000 units twice daily | Either 100 units/kg twice daily or 200 units/kg once daily |

¶ If antiXa levels are checked in renal failure or obesity and suggest heparin accumulation, dose reduction is permitted.

### 14.3. Tinzaparin

| Weight | Renal function (consider antiXa monitoring if CrCl<30ml/min. Consider UFH if CrCl <20ml/min) | Tinzaparin sc Conventional low dose thromboprophylaxis | Tinzaparin sc Intermediate dose thromboprophylaxis | Tinzaparin therapeutic dose (local protocols for acute VTE dosing can be followed including dose rounding) |
|---|---|---|---|---|
| <50kg | CrCl ≥20ml/min | 2500 units once daily | 2500 units twice daily | 175 units/kg once daily |
| 50-90kg | CrCl ≥20ml/min | 3500 units once daily | 3500 units twice daily | 175 units/kg once daily |
| 90-120kg | CrCl ≥20ml/min | 4500 units once daily | 4500 units twice daily | 175 units/kg once daily |
| 121-150kg | CrCl ≥20ml/min | 7000* units once daily | 7000* units twice daily | 175 units/kg once daily |
| >150 kg | CrCl ≥20ml/min | 9,000^ units once daily | 9,000^ units twice daily | 175 units/kg once daily |

¶ If antiXa levels are checked in renal failure or obesity and suggest heparin accumulation, dose reduction is permitted

*8000 units is an acceptable alternative

^10,000units is an acceptable alternative

## 14.4.    Unfractionated Heparin

If estimated CrCl is greater than 30 ml/min, LMWH is preferred.

| Weight | Unfractionated Heparin sc Conventional low dose thromboprophylaxis | Unfractionated Heparin sc Intermediate dose thromboprophylaxis |
|---|---|---|
| <50kg | 2500 units twice daily | 5000 units twice daily |
| 50-120kg | 5000 units twice daily | 7500 units twice daily* |
| 121-150kg | 7500 units twice daily | 10,000 units twice daily |
| >150 kg | 10,000 units twice daily | 15,000 units twice daily |

*7500 units three times daily is an acceptable alternative

If unfractionated heparin is used for therapeutic dose anticoagulation then this should be administered as an intravenous infusion with dose adjustment according to aPTT or anti Xa monitoring as per local protocols for acute VTE treatment.