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Protocol Amendment to COVID-19 Anticoagulation Domain-Specific Appendix (formerly known as the COVID-19 Therapeutic Anticoagulation Domain) Summary of changes

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

REMAP-CAP COVID-19 Anticoagulation DSA Protocol Amendment Summary Version 1 dated 03 March 2021

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1. CURRENT VERSIONS OF PROTOCOL DOCUMENTS

1.1. The current versions of pandemic specific protocol documents:

- REMAP-CAP Core Protocol Version 3, dated 10 July 2019
- Pandemic Appendix to Core Version 1.1, dated 12 February 2020
- Domain-Specific Appendices

2. CURRENT AMENDMENT

The COVID-19 Anticoagulation DSA protocol document (formerly known as the COVID-19 Therapeutic Anticoagulation Domain version 2) underwent an amendment in February 2021.

2.1. Summary of changes

Section	Original text	New Text	Reason
Front page and whole document header	REMAP-CAP COVID-19 Therapeutic Anticoagulation Domain-Specific Appendix Version 2.0 dated 24 th June 2020	REMAP-CAP COVID-19 Anticoagulation Domain-Specific Appendix Version 3.0 dated 27 th February 2021	Administrative change
Summary Page 2	<p>In this domain of the REMAP-CAP trial, participants meeting the platform entry criteria with suspected or microbiological testing-confirmed COVID-19 infection will be randomized to one of two interventions:</p> <ul style="list-style-type: none"> • Local standard venous thromboprophylaxis • Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin <p>At this participating site the following interventions have been selected within this domain:</p> <p><input type="checkbox"/> Local standard venous thromboprophylaxis</p> <p><input type="checkbox"/> Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin</p>	<p>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:</p> <ul style="list-style-type: none"> • Conventional low dose thromboprophylaxis • Intermediate dose thromboprophylaxis • Continuation of therapeutic dose anticoagulation (only in the Prior Therapeutic Anticoagulation Stratum) <p>At this participating site the following interventions have been selected within this domain for patients in the No Prior Therapeutic Anticoagulation Stratum:</p> <p><input type="checkbox"/> Conventional low dose thromboprophylaxis</p> <p><input type="checkbox"/> Intermediate dose thromboprophylaxis</p>	Updated to reflect adaptation of the domain with new interventions

		At this participating site the following interventions have been selected within this domain for patients in the Prior Therapeutic Anticoagulation Stratum: <input type="checkbox"/> Conventional low dose thromboprophylaxis <input type="checkbox"/> Intermediate dose thromboprophylaxis <input type="checkbox"/> Continuation of therapeutic dose anticoagulation					
Summary Page 3	Blank						Addition of a standard table to outline the application of the domain with respect to states and strata. This table also outlines which interventions will be submitted for ethical review in this jurisdiction; and which interventions will be offered to patients in ward and ICU settings by illness severity state.
		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	<input type="checkbox"/> Conventional low dose <input type="checkbox"/> Intermediate dose	<input type="checkbox"/> Conventional low dose <input type="checkbox"/> Intermediate dose	Not available	

					<input type="checkbox"/> Continuation of therapeutic dose anticoagulation		
		Interventions offered at this site	Ward	ICU	ICU	ICU	ICU
			Not available	Not available	<input type="checkbox"/> Conventional low dose <input type="checkbox"/> Intermediate dose	<input type="checkbox"/> Conventional low dose <input type="checkbox"/> Intermediate dose <input type="checkbox"/> Continuation of therapeutic dose anticoagulation	Not available
Summary table Heading Page 4	REMAP-CAP: COVID-19 Therapeutic Anticoagulation Domain Summary				REMAP-CAP: COVID-19 Therapeutic Anticoagulation Domain Summary		Administrative change for new domain name
Summary table Interventions Page 4	<ul style="list-style-type: none"> Local standard venous thromboprophylaxis Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin 				<ul style="list-style-type: none"> Conventional low dose thromboprophylaxis Intermediate dose thromboprophylaxis Continuation of therapeutic dose anticoagulation (Prior Therapeutic Anticoagulation Stratum only) 		Updated to reflect changed interventions
Summary table Unit of Analysis, Strata, and State Page 4	The pandemic statistical model includes only patients who are in the Pandemic Infection Suspected or Proven (PISOP) stratum. Within this stratum, the unit-of-analysis is defined by illness severity state at time of enrollment, defined as either Moderate State or Severe State. Unit-of-analysis may also be defined by SARS-CoV-2 infection or d-dimer strata or both. Borrowing is permitted between states and strata. If the SARS-CoV-2				The pandemic statistical model includes only patients who are in the Pandemic Infection Suspected or Proven (PISOP) stratum. With 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		Addition of new 'domain-specific' strata and its impact on the unit-of -analysis

	strata is applied in analysis, Response Adaptive Randomization will be applied to all PISOP patients, in each illness severity state, using probabilities derived from the SARS-CoV-2 confirmed stratum. Response Adaptive Randomization may also be applied according to D-dimer strata status.	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.	
Summary table Evaluable treatment- by-treatment Interactions Page 4	No interaction will be evaluated with any other domain.	Interactions with the Antiplatelet Domain will be modeled.	Updated to match what is already specified in the antiplatelet domain that the anticoagulation domain and the antiplatelet domain are evaluated in a factorial structure that permits platform conclusions to be reached for combinations of therapies from each domain.
Summary table Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following:	Patients will be excluded from this domain if they have any of the following:	Domain-level exclusion criteria updated to take

<p>Page 4</p>	<ul style="list-style-type: none"> • More than 48 hours has elapsed since ICU admission (noting that this may be operationalized as more than 48 hours has elapsed since commencement of organ failure support) • Clinical or laboratory bleeding risk or both that is sufficient to contraindicate therapeutic anticoagulation, including intention to continue or commence dual anti-platelet therapy • Therapeutic anticoagulation is already present due to prior administration of any anticoagulant agent that is known or likely to still be active or a clinical decision has been made to commence therapeutic anticoagulation • Enrolment in a trial evaluating anticoagulation for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial • Known or suspected previous adverse reaction to UFH or LMWH including heparin induced thrombocytopenia (HIT). • The treating clinician believes that participation in the domain would not be in the best interests of the patient 	<ul style="list-style-type: none"> • 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 <p>Additional stratum specific exclusion criteria are applied. In the Prior Therapeutic Anticoagulation Stratum patients will be excluded if they have:</p>	<p>into account the evaluation of new interventions in the domain.</p> <p>Addition of domain-specific stratum exclusion criteria to take into account the</p>
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		<ul style="list-style-type: none"> • Clinical or laboratory bleeding risk or both that is sufficient to contraindicate continuation of therapeutic dose anticoagulation <p>In the No Prior Therapeutic Anticoagulation Stratum patients will be excluded if they have any of the following:</p> <ul style="list-style-type: none"> • 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. 	domain structure is modified by this additional strata.
SECTION 1 ABBREVIATIONS	Original text	New Text	Reason
Page 9	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	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	Administrative update

DSWG	Domain-Specific Working Group	DSMB	Data Safety and Monitoring Board
HIT	Heparin Induced Thrombocytopenia	DSWG	Domain-Specific Working Group
ICU	Intensive Care Unit	HIT	Heparin Induced Thrombocytopenia
ISIG	International Statistics Interest Group	HTE	Heterogeneity of Treatment Effect
ITSC	International Trial Steering Committee	ICU	Intensive Care Unit
LMWH	Low Molecular Weight Heparin	ISIG	International Statistics Interest Group
MERS-CoV	Middle East respiratory syndrome coronavirus	ITSC	International Trial Steering Committee
PAAtC	Pandemic Appendix to the Core Protocol	LMWH	Low Molecular Weight Heparin
PE	Pulmonary Embolus	LSVT	Local Standard Venous Thromboprophylaxis
PISOP	Pandemic infection is suspected or proven	MERS-CoV	Middle East respiratory syndrome coronavirus
RCT	Randomized controlled trial	mpRCT	Multi-platform RCT
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia	PAAtC	Pandemic Appendix to the Core Protocol
RSA	Region-Specific Appendix	PE	Pulmonary Embolus
SAE	Serious Adverse Event	PISOP	Pandemic infection is suspected or proven
SARS	Serious Acute Respiratory Syndrome	RCT	Randomized controlled trial
UFH	Unfractionated heparin	REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
VTE	Venous Thromboembolism	RSA	Region-Specific Appendix
WHO	World Health Organization	SAE	Serious Adverse Event
		SARS	Serious Acute Respiratory Syndrome
		UFH	Unfractionated heparin
		VTE	Venous Thromboembolism
		WHO	World Health Organization

SECTION 3 COVID-19 ANTICOAGULATION DOMAIN-SPECIFIC APPENDIX VERSION	Original text	New Text	Reason
Page 12	The version of the COVID-19 Therapeutic Anticoagulation Domain-Specific Appendix is in this document's header and on the cover page.	The version of the COVID-19 Therapeutic Anticoagulation Domain-Specific Appendix is in this document's header and on the cover page.	Administrative update to reflect changed domain name
3.1. Version History Page 12	Version 1: Approved by the COVID-19 Therapeutic Anticoagulation Domain Specific Working Group (DSWG) on 20 th April 2020 Version 2: Approved by the COVID-19 Therapeutic Anticoagulation DSWG on 24 th June 2020	Version 1: Approved by the COVID-19 Therapeutic Anticoagulation Domain Specific Working Group (DSWG) on 20 th April 2020 Version 2: Approved by the COVID-19 Therapeutic Anticoagulation DSWG on 24 th June 2020 Version 3: Approved by the COVID-19 Anticoagulation DSWG on 27th February 2021	Administrative change
SECTION 4 COVID-19 ANTICOAGULATION DOMAIN GOVERNANCE	Original text	New Text	Reason
4.1. Domain members Page 12	Chair: Dr Ryan Zarychanski Deputy Chair: Dr Ewan Goligher Members: Prof. Derek Angus Dr. Scott Berry Dr. Shailesh Bihari Dr. Charlotte Bradbury	Chair: Dr Ryan Zarychanski Deputy Chair: Dr Ewan Goligher Dr Charlotte Bradbury (Version 3 adaptation lead) Members: Prof. Derek Angus Dr. Diptesh Aryal Dr. Scott Berry	Domain working group members updated

Prof. Marc Carrier	Dr. Shailesh Bihari	
Prof. Dean Fergusson	Prof. Marc Carrier	
Prof. Robert Fowler	Prof. Dean Fergusson	
A/Prof. Timothy Girard	Prof. Robert Fowler	
Prof. Anthony Gordon	A/Prof. Timothy Girard	
A/Prof. Ghady Haidar	Dr. Ewan Goligher	
A/Prof. Christopher Horvat	Prof. Anthony Gordon	
Prof. David Huang	A/Prof. Ghady Haidar	
Prof. Beverley Hunt	A/Prof. Christopher Horvat	
Prof. Anand Kumar	Prof. David Huang	
Prof. Mike Laffan	Prof. Beverley Hunt	
Dr. Patrick Lawler	Dr. Deva Jayakumar	
Dr. Patrick Lawless	Prof. Anand Kumar	
Dr. Sylvain Lothar	Prof. Mike Laffan	
Dr. Peter MacCallum	Dr. Patrick Lawler	
Dr. Colin McArthur	Dr. Patrick Lawless	
A/Prof. Bryan McVerry	Dr. Sylvain Lothar	
Prof. John Marshall	Dr. Peter MacCallum	
Prof. Saskia Middeldorp	Dr. Colin McArthur	
Dr. Zoe McQuilten	A/Prof. Bryan McVerry	
A/Prof. Matthew Neal	Prof. John Marshall	
Prof. Alistair Nichol	Prof. Saskia Middeldorp	
Prof. John Pasi	Dr. Zoe McQuilten	
A/Prof. Christopher Seymour	A/Prof. Matthew Neal	

	<p>Prof. Roger Schutgens</p> <p>Prof. Simon Stanworth</p> <p>Dr. Alexis Turgeon</p> <p>Prof. Steve Webb</p> <p>A/Prof. Alexandra Weissman</p>	<p>Prof. Alistair Nichol</p> <p>Prof. Sid Patanwala</p> <p>Prof. John Pasi</p> <p>A/Prof. Christopher Seymour</p> <p>Prof. Roger Schutgens</p> <p>Prof. Simon Stanworth</p> <p>Dr. Alexis Turgeon</p> <p>Prof. Steve Webb</p> <p>A/Prof. Alexandra Weissman</p>	
<p>4.3. Interaction with ATTACC and ACTIV-IV platform trials</p> <p>Page 13</p>	<p>4.3. Interaction with ATTACC</p> <p>ATTACC is a trial that also evaluates the treatment effect of therapeutic anticoagulation in patients with COVID-19. There is overlap between the leadership of the ATTACC trial and the leadership of this domain. This domain and ATTACC have been designed to be complementary with pre-specified plans in relation to methods of analysis. It is intended that data from ATTACC may be incorporated into the pandemic statistical model of REMAP-CAP. The protocol, governance, and data management of ATTACC are separate from REMAP-CAP but the REMAP-CAP DSMB will also serve the ATTACC trial.</p>	<p>4.3. Interaction with ATTACC and ACTIV-IV platform trials</p> <p>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-</p>	<p>Administrative update</p> <p>– new heading and explanation of the relationship between this domain and the ATTACC asnd ACTIV-IV trials which are recruiting in Canada and the United States.</p>

		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.	
SECTION 5 COVID-19 ANTICOAGULATION DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION	Original text	New Text	Reason
Page 14	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.	The COVID-19 Anticoagulation 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.	Administrative update to reflect changed domain name
SECTION 6 BACKGROUND AND RATIONALE	Original text	New Text	Reason
6.1. Domain definition Page 14	This is a domain within the REMAP-CAP platform to test the effectiveness of therapeutic anticoagulation versus local venous thromboprophylaxis for patients with acute illness due to suspected or proven COVID-19.	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.	Modification to the domain definition to take into account adaptation of the domain with new interventions.

<p>6.2.1. COVID-19 infection Page 15</p>	<p>The first report of infection with COVID-19 occurred in Wuhan, China, in late 2019. Since that time, and as of the time of writing of this DSA, there have been over 1 million reported cases across the world with a range of severity, approximately 60,000 deaths and sustained human-human transmission. On January 30th 2020, the World Health Organization (WHO) declared this outbreak a Public Health Emergency of International Concern (https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)). Given past history with novel coronaviruses, such as Severe Acute Respiratory Syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS-CoV), public health agencies have responded aggressively to the urgent need to acquire knowledge regarding this emerging infection. An important component of this urgently needed knowledge includes understanding the effectiveness of alternative treatment strategies in patients with suspected or proven infection. It should also be noted that clinical guidance issued by the WHO indicates that unproven therapies should be administered preferably</p>	<p>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/situation-reports/20200311-sitrep-51-covid-19.pdf).</p>	<p>Completely rewritten with up-to-date knowledge of COVID-19</p>
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	<p>only as part of a clinical trial (https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf).</p> <p>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.</p> <p>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</p>	<p>source/coronaviruse/clinical-management-of-novel-cov.pdf).</p>	
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	<p>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 (Xu et al., 2020). 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, 2020a). 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</p>		
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	<p>supportive care, has been formally evaluated in randomized controlled trials with sufficient statistical power to identify changes in patient-centered outcomes.</p> <p>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).</p>		
<p>6.2.2.1 Current clinical trials and interventions being evaluated Page 15</p>	<p>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.</p> <p>A wide range of interventions are being evaluated in trials that have been registered including arbidol, lopinavir/ritonavir, darunavir/cobicistat, remdesivir,</p>	<p>Text deleted and incorporated in revised section 6.2.2.</p>	<p>Information has been synthesized into one section</p>

	<p>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.</p> <p>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</p> <p>(https://apps.who.int/iris/bitstream/handle/10665/330694/WHO-HEO-RDBlueprintnCoV-2020.4-eng.pdf?ua=1).</p> <p>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</p>		
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	(delivered according to local practice in each region) in critically ill patients with COVID-19.		
6.2.2.2. Need for evidence in patients who are critically ill as well as hospitalized patients Page 15	<p>There is need to evaluate interventions for COVID-19 infection in patients who are critically ill or hospitalized and not critically ill, separately, because of the possibility of differential treatment effect, depending on illness severity. The number of current studies that are focused on patients who are critically ill is uncertain and, for those studies that are enrolling hospitalized patients, it is unclear if stratification by severity is a design feature.</p> <p>Among trials that evaluate interventions in patients who are critically ill it is common for the results of the trial to be different to that which was predicted based on a prior understanding of mechanism of action combined with known mechanism of disease (Landoni et al., 2015, Webb, 2015). This observation reinforces the importance of not necessarily relying on extrapolation of results (both positive and negative) from patients who are not critically ill. It is also possible different disease mechanisms apply at different levels of illness severity and that this may also influence balance between beneficial and adverse effects of a particular intervention. This reinforces the importance of</p>	Text deleted and incorporated in revised section 6.2.2.	Information has been synthesized into one section

	obtaining estimates of treatment effect dependent on the level of illness severity.		
6.2.2. Clinical trials for COVID-19 infection Page 15	Previous 6.2.2.1 and 6.2.2.2 revised and rewritten	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	Completely rewritten with up-to-date knowledge of COVID-19 trials

		<p>interventions and domains is available at www.remapcap.org.</p> <p>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.</p>	
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<p>6.2.3. Intervention strategy for this domain Page 16</p>	<p>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.</p> <p>If at, any stage, evidence of harm or definitive evidence of absence of effectiveness in critically ill or ward patients or both emerges for one or more interventions specified in this domain, the ITSC, as advised by the DSWG, may remove the intervention(s) prior to declaration of a Platform Conclusion. If this occurs, presentation and publication of results that relate to the intervention will occur, so as to contribute additional weight of evidence in the public domain. Rationale for therapeutic anticoagulation in COVID-19</p> <p>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).</p>	<p>This domain will test the potential benefits of different strategies for patients with acute illness due to suspected or proven COVID-19.</p> <p>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.</p>	<p>Minor modifications to language and deletion of redundant text</p>
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	<p>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</p>		
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	<p>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., 2020a).</p> <p>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., 2020a).</p> <p>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</p>		
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	<p>arrhythmia—both associated with poor outcome (Guo et al., 2020b).</p> <p>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.</p> <p>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</p>		
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	<p>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).</p> <p>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)</p>		
<p>6.2.4. Venous thromboprophylaxis is standard care for hospitalized patients who do not have COVID-19</p> <p>Page 16</p>	<p>Evidence of effect for anticoagulation in sepsis and COVID-19 disease.</p> <p>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).</p> <p>In a propensity matched retrospective cohort study of patients with septic shock therapeutic dose UFH was associated with reduced 28-day when administered</p>	<p>Venous thromboprophylaxis is standard care for hospitalized patients who do not have COVID-19</p> <p>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.</p> <p>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</p> <p>(https://www.nice.org.uk/guidance/ng89, https://www.sign.ac.uk/media/1060/sign122.pdf,</p>	<p>Restructured and modified background so as to incorporate rationale for domain adaptation that has arisen largely as a consequence of prior results derived from REMAP-CAP.</p>

	<p>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 (odd 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</p>	<p>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.</p>	
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	<p>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).</p> <p>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).</p> <p>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.</p>		
<p>6.2.5. Thrombotic complications are common in patients admitted to hospital with COVID-19</p> <p>Page 17</p>	Blank	<p>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., 2020b, Bilaloglu et al., 2020, Al-Samkari et al., 2020). Patients at</p>	<p>New section as part of modified rationale and background</p>

		<p>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.</p>	
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		<p>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., 2020b, 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</p>	
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		<p>(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).</p> <p>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%; $P < .001$).</p> <p>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</p>	
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		<p>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., 2020a). 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).</p> <p>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).</p>	
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<p>6.2.6. Pathogenesis of thrombotic complications in patients with COVID-19</p> <p>Page 18</p>	<p>Blank</p>	<p>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., 2020b).</p> <p>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</p>	<p>New section as part of modified rationale and background</p>
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		<p>prothrombotic state is causally related to poor outcomes.</p> <p>In multiple large case series, elevated D-dimer is consistently associated with a higher risk of developing ARDS and death (Wu and McGoogan, 2020b, 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).</p>	
<p>6.2.7. Rationale for evaluation of anticoagulation strategies in patients with COVID-19</p> <p>Page 19</p>	Blank	<p><i>6.2.7.1. Introduction</i></p> <p>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.</p> <p>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 antiplatelet agents has shown synergistic efficacy, albeit with an increased bleeding risk.</p> <p><i>6.2.7.2. Current treatment guidelines for prevention of thrombotic complications</i></p> <p>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</p>	<p>New section as part of modified rationale and background</p>

	<p>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.</p> <p><i>Table 1. Summary of published statements on thromboprophylaxis in COVID-19, available as of January 2021.</i></p> <table><tr><th>Organization</th><th>Severe COVID-19 patients (ICU)</th><th>Moderate COVID-19 patients (ward)</th></tr><tr><td></td><td></td><td></td></tr></table>	Organization	Severe COVID-19 patients (ICU)	Moderate COVID-19 patients (ward)				
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 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 Consider intermediate dose LMWH (50% of panel)	Conventional low dose thromboprophylaxis after considering the bleeding risk Consider intermediate dose LMWH (30% of panel)	
		American College of Chest Physicians 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 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 (icmanaesthesiacovid-19.org)	Intermediate or higher doses of LMWH	Conventional low dose LMWH D-dimer levels alone should not be used to guide LMWH dosing
		American society of Haematology (hematology.org/covid-19/covid-19-and-vte- anticoagulation)	Conventional low dose thromboprophylaxis	Conventional low dose thromboprophylaxis
		NICE https://www.nice.org.uk/guidance/ng186/chapter/Rationales	Consider Intermediate dose LMWH	Conventional low dose LMWH
		WHO COVID-10 Clinical management guidelines 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		

		<p>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.</p> <p>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)</p> <p>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</p>	
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		<p>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.</p> <p>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.</p> <p>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.</p>	
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		<p>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.</p> <p>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.</p> <p>The following conclusions have been made by the REMAP-CAP investigators:</p>	
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		<ul style="list-style-type: none"> • 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. <p>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.</p>	
6.2.10. Safety of unfractionated heparin and low molecular weight heparin Page 25	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	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	Revised section on safety of anticoagulant medications incorporating more recent information

	<p>data is available. Therapeutic anticoagulation is commonly used in hospitalized patients for the treatment of venous thromboembolic disease, acute coronary syndromes, and stroke prevention in patients with atrial fibrillation (Tiryaki et al., 2011). The dosing and management of both unfractionated heparin and low molecular weight heparin are very familiar to clinicians. Overall, patients receiving therapeutic anticoagulation with these agents have a 1 - 5% risk of major bleeding, depending on underlying risk and duration of exposure (Mismetti et al., 2005, Petersen et al., 2004, Crowther and Warkentin, 2008).</p> <p>Patients with an underlying systemic hypercoagulable state (such as COVID-19), in whom therapeutic anticoagulation is being given to offset this, may intuitively have a lower risk of bleeding. For example, in cancer-associated venous thromboembolisms – an underlying hypercoagulable state – the estimated rate of major bleeding was reported to be 3.2% over a 6 months period (Lee et al., 2015, Li et al., 2019).</p> <p>In the PROTECT trial, a multi-national thromboprophylaxis RCT comparing UFH to LMWH in critically ill patients (n=3764), the major bleeding rate was 5.6% (Protect Investigators for the Canadian Critical</p>	<p>data is available. Therapeutic anticoagulation is commonly used in hospitalized patients for the treatment of venous thromboembolic disease, acute coronary syndromes, and stroke prevention in patients with atrial fibrillation (Tiryaki et al., 2011). The dosing and management of both unfractionated heparin and low molecular weight heparin are very familiar to clinicians. Overall, patients receiving therapeutic anticoagulation with these agents have a 1 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).</p> <p>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</p>	<p>from patients with COVID-19 and deleting redundant text.</p>
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	<p>Care Trials Group et al., 2011b). 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).</p> <p>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).</p> <p>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.</p>	<p>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).</p>	
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	<p>Overall, the rate of bleeding may not be significantly different between unselected critically ill patients receiving low dose thromboprophylaxis and selected patients receiving therapeutic dose heparin or LMWH. The incidence of heparin-induced thrombocytopenia with LMWH and UFH when administered to general medical-surgical ICU patients is approximately 0.3 to 0.6% (Protect Investigators for the Canadian Critical Care Trials Group et al., 2011a). 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).</p>		
SECTION 7 DOMAIN OBJECTIVES	Original text	New Text	Reason
Page 26	<p>The objective of this domain is to determine the effectiveness of therapeutic anticoagulation for patients with acute illness due to suspected or proven pandemic infection.</p> <p>We hypothesize that the probability of the occurrence of the primary endpoint specified in the relevant core</p>	<p>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.</p> <p>We hypothesize that the probability of the occurrence of the primary endpoint specified in the relevant core</p>	<p>Updated with minor language changes and the amended interventions.</p>

	<p>protocol documents will differ based on allocation to different anticoagulation strategy. The following interventions will be available:</p> <ul style="list-style-type: none"> • Local standard venous thromboprophylaxis • Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin <p>We hypothesize that the treatment effect of therapeutic anticoagulation is different depending on whether SARS-CoV-2 infection is confirmed to be present or absent.</p> <p>We hypothesize that the treatment effect of therapeutic anticoagulation is different depending on the illness severity state at the time of enrollment.</p> <p>We hypothesize that the treatment effect of therapeutic anticoagulation is different depending on D-dimer strata status.</p>	<p>protocol documents will differ based on allocation to different anticoagulation strategies. The following interventions will be available:</p> <ul style="list-style-type: none"> • Conventional low dose thromboprophylaxis • Intermediate dose thromboprophylaxis • Continuation of therapeutic dose anticoagulation (only in the Prior Therapeutic Anticoagulation Stratum) <p>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.</p> <p>We hypothesize that the treatment effect of different anticoagulation strategies is different depending on whether prior therapeutic anticoagulation is present or absent.</p> <p>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.</p>	<p>New hypotheses added to take into account new interventions, the possibility of different treatment effect within the domain-specific stratum, and the interaction with the antiplatelet domain, specified previously only in the antiplatelet DSA.</p>
SECTION 8 TRIAL DESIGN	Original text	New Text	Reason

8.1.1. State Page 26	Blank	This domain is available for patients who have acute illness due to suspected or proven pandemic infection in the Severe State.	New generic section, intended to be used in all DSAs, added to identify which state or states apply to this domain
8.1.2. Domain-specific strata Page 27	Blank	<p>Domain-specific strata are applied to patients in the Severe State at the time of assessment for this domain.</p> <p><i>8.1.2.1. Prior Therapeutic Anticoagulation Stratum</i> 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.</p> <p><i>8.1.2.2. No Prior Therapeutic Anticoagulation Stratum</i> 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.</p>	New section added to identify which domain-specific strata apply to this domain
8.2. Eligibility criteria Page 27	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-	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	Administrative update to reflect changed domain name.

	<p>COVID Core Protocol. Patients eligible for the REMAP may have conditions that exclude them from this specific COVID-19 Therapeutic Anticoagulation Domain. This domain is available for patients who have acute illness due to suspected or proven pandemic infection in both the Moderate State and the Severe State.</p>	<p>Core Protocol. Patients eligible for the REMAP may have conditions that exclude them from this specific COVID-19 Therapeutic Anticoagulation Domain.</p>	<p>Some text deleted as this is included elsewhere in the Domain-specific Appendix</p>
<p>8.2.2.Domain exclusion criteria Page 27</p>	<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 (noting that this may be operationalized as more than 48 hours has elapsed since commencement of sustained organ failure support) • Clinical or laboratory bleeding risk or both that is sufficient to contraindicate therapeutic anticoagulation, including intention to continue or commence dual anti-platelet therapy • Therapeutic anticoagulation is already present due to prior administration of any anticoagulant agent that is known or likely to still be active or a clinical decision has been made to commence therapeutic anticoagulation • Enrolment in a trial evaluating anticoagulation for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial 	<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, 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 • 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 	<p>Domain-level exclusion criteria updated to take into account the evaluation of new interventions in the domain and because the protocols use US spelling <i>enrolment</i> changed to <i>enrollment</i></p>

	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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 	
<p>8.2.3. Stratum-specific domain exclusion criteria</p> <p>Page 28</p>	Blank	<p>8.2.3. Stratum-specific domain exclusion criteria</p> <p>In the Prior Therapeutic Anticoagulation Stratum, patients will be excluded from this domain if they have any of the following:</p> <ul style="list-style-type: none"> • Clinical or laboratory bleeding risk or both that is sufficient to contraindicate continuation of therapeutic dose anticoagulation with heparin <p>In the No Prior Therapeutic Anticoagulation Stratum, patients will be excluded from this domain if they have any of the following:</p> <ul style="list-style-type: none"> • 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 	<p>New section for exclusion criteria that are specific for each of the new domain-specific stratum.</p>

8.2.5. Eligibility for Antiplatelet Domain Page 28	Blank	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.	New section added to outline the eligibility elements that apply between this domain and the Antiplatelet Domain. This is adapted from the antiplatelet DSA, but is also updated to take into account new interventions specified in this amendment to the anticoagulation domain.
8.3. Interventions Page 29	8.3. Anticoagulant interventions	8.3. Anticoagulant Interventions	Administrative change to section heading
8.3.1. Anticoagulation interventions Page 29	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. <input type="checkbox"/> Local standard venous thromboprophylaxis <input type="checkbox"/> Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin	Patients will be randomly assigned to receive one of the following open-label strategies. The interventions will be commenced immediately after allocation status is revealed. <input type="checkbox"/> Conventional low dose thromboprophylaxis <input type="checkbox"/> Intermediate dose thromboprophylaxis <input type="checkbox"/> Continuation of therapeutic dose anticoagulation (only in the Prior Therapeutic Anticoagulation Stratum)	Interventions in amended domain updated in light of findings from the previous iteration of the domain

	Administration of venous thromboprophylaxis is based on local practice and is mandatory.	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 Page 29	<p>8.3.2. Local standard venous thromboprophylaxis</p> <p>Standard venous thromboprophylaxis that complies with local guidelines or usual practice will be administered for 14 days following randomization or until hospital discharge, whichever occurs first. The dose of agent that is chosen should not be sufficient to result in therapeutic anticoagulation. After 14 days decisions regarding thromboprophylaxis and anticoagulation are at the discretion of the treating clinician.</p> <p><i>8.3.2.1. Use of therapeutic anticoagulation in patients randomized to local standard venous thromboembolism</i></p> <p>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</p>	<p>8.3.2. Conventional low dose thromboprophylaxis</p> <p>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.</p> <p><i>8.3.2.1. Use of therapeutic dose anticoagulation in patients assigned to conventional low dose thromboprophylaxis</i></p>	Interventions in amended domain updated in light of findings from the previous iteration of the domain

	<p>event, intermittent hemodialysis or sustained low-efficiency daily dialysis.</p> <p>Systemic therapeutic anticoagulation for continuous renal replacement therapy is not permitted, unless there is an additional indication for anticoagulation. Regional citrate, heparin priming and low-dose heparin administration (without measurable systemic anticoagulation) are permitted for continuous renal replacement therapy. If regional low-dose heparin administration is used to facilitate continuous renal replacement therapy, the dose may be increased as necessary to prevent clotting of the filter, however the dose of heparin should be minimized as much as possible.</p>	<p>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.</p>	
<p>8.3.3. Intermediate dose thromboprophylaxis</p> <p>Page 30</p>	Blank	<p>8.3.3. Intermediate dose thromboprophylaxis</p> <p>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</p>	<p>Interventions in amended domain updated in light of findings from the previous iteration of the domain</p>

		<p>the discretion of the treating clinician. In the absence of bleeding complications, administration of conventional low dose thromboprophylaxis is considered a protocol deviation.</p> <p><i>8.3.3.1. Use of therapeutic anticoagulation in patients assigned to intermediate dose thromboprophylaxis</i></p> <p>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).</p>	
8.3.4. Continuation of therapeutic dose anticoagulation Page 30	<p>8.3.4. Continuation of Therapeutic Anticoagulation</p> <p>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. After 14 days or hospital discharge decisions</p>	<p>8.3.4. Continuation of therapeutic dose anticoagulation</p> <p>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</p>	Interventions in amended domain updated in light of findings from the previous iteration of the domain

	regarding thromboprophylaxis or anticoagulation are at the discretion of the treating clinician.	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 Page 30	Unfractionated heparin	Therapeutic dose unfractionated heparin	Administrative change to heading only
8.3.4.2. Therapeutic dose low molecular weight heparin Page 30	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.	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.	Administrative change to heading, correction of grammatical error – <i>measure changed to measured</i> and guidance provided for how to adjust dosing
8.3.4.3. Duration of therapeutic dose anticoagulation Page 31	Duration of therapeutic anticoagulation The duration of therapeutic anticoagulation is 14 days. For patients who are discharged from hospital before 14 days, therapeutic anticoagulation should be ceased prior to hospital discharge. For patients admitted to an ICU therapeutic anticoagulation may be ceased before 14 days at the discretion of the treating clinician at ICU	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	Details of interventions in amended domain updated in light of findings from the previous iteration of the domain

	<p>discharge but, during the 14 day period, all patients receiving invasive mechanical ventilation should receive therapeutic anticoagulation until at least 24 hours after cessation of mechanical ventilation.</p> <p>After 14 days decisions regarding thromboprophylaxis and anticoagulation are at the discretion of the treating clinician.</p>	<p>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.</p> <p>After 14 days decisions regarding thromboprophylaxis and anticoagulation are at the discretion of the treating clinician.</p>	
<p>8.3.5. Discontinuation of study intervention Page 31</p>	<p>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.</p> <p>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.</p> <p>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</p>	<p>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.</p> <p>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.</p> <p>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.</p>	<p>Minor refinements to the criteria for discontinuing the intervention</p>

	<p>– 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.</p> <p>Temporary or permanent cessation of the study interventions for clinically significant bleeding is not a protocol deviation.</p>	<p>Temporary or permanent cessation of the study interventions for clinically significant bleeding is not a protocol deviation.</p>	
<p>8.3.6. Anticoagulation strategy in patients negative for COVID-19 infection Page 32</p>	<p>COVID-19 anticoagulation strategy in patients negative for COVID-19 infection</p> <p>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.</p>	<p>Anticoagulation strategy in patients negative for COVID-19 infection</p> <p>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.</p>	<p>Change to strategy for managing participants who test negative for COVID-19 following allocation to an active treatment in the domain</p>
<p>8.4. Concomitant care Page 32</p>	<p>Additional agents, other than those specified in the platform, that are intended to modify the patient's coagulation function as a treatment for COVID-19 infection should not be administered. A patient who receives an agent that act to inhibit platelet function as a usual medication may have this medication continued.</p>	<p>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</p>	<p>Minor modification to language</p>

	<p>Commencement of any new agent that inhibits platelet function is not permitted unless there is an accepted clinical indication such as an acute coronary syndrome, ischemic stroke or transient ischemic event or the agent that inhibits platelet function has been specified in another domain of this platform.</p> <p>All other treatment that is not specified by assignment within the platform will be determined by the treating clinician.</p>	<p>this platform. A patient who receives an agent that acts to inhibit platelet function as a usual medication may have this medication continued.</p> <p>All other treatment that is not specified by assignment within the platform will be determined by the treating clinician.</p>	
<p>8.5.2. Secondary endpoints Page 32</p>	<p>The domain-specific secondary outcome measures (from randomization, during the index hospitalization, censored 90 days after enrollment) will be:</p> <ul style="list-style-type: none"> • Serial detection of SARS-CoV-2 in upper or lower respiratory tract specimens (using only specimens collected for routine clinically indicated testing) • Confirmed deep venous thrombosis • Confirmed pulmonary embolism • Confirmed ischemic cerebrovascular event • Total red cell blood cell units transfused between randomization and the end of study day 15 • Confirmed acute myocardial infarction • Peak troponin between randomization and the end of study day 15 • Major bleeding 	<p>The domain-specific secondary outcome measures (from randomization, during the index hospitalization, censored 90 days after enrollment) will be:</p> <ul style="list-style-type: none"> • Serial detection of SARS-CoV-2 in upper or lower respiratory tract specimens (using only specimens collected for routine clinically indicated testing) • Confirmed deep venous thrombosis • Confirmed pulmonary embolism • Confirmed ischemic cerebrovascular event • Total red cell blood cell units transfused between randomization and the end of study day 15 • Confirmed acute myocardial infarction • Peak troponin between randomization and the end of study day 15 • Major bleeding 	<p>One secondary endpoint removed as experience to date has indicated that data necessary for this secondary end-point is often not available. REMAP-CAP relies on test results collected as part of routine care and serial PCRs are often not done as part of routine clinical practice.</p>

	<ul style="list-style-type: none"> • Other confirmed thrombotic event including mesenteric ischemia and limb ischemia • SAE as defined in Core Protocol and this DSA below 	<ul style="list-style-type: none"> • Other confirmed thrombotic event including mesenteric ischemia and limb ischemia • SAE as defined in Core Protocol and this DSA below 	
SECTION 9 TRIAL CONDUCT	Original text	New Text	Reason
9.2. Domain-specific data collection Page 33	<p>Additional domain-specific data will be collected.</p> <ul style="list-style-type: none"> • Baseline measures of coagulation including d-dimer • Administration of anticoagulant agents • Administration of agents that inhibit platelet function • Transfusion of red cells • Peak troponin • Acute myocardial infarction (using fourth international definition) • Major bleeding (using the International Society on Thrombosis and Haemostasis definition) • Mesenteric Ischemia, limb ischemia, and other clotting events 	<p>Additional domain-specific data will be collected.</p> <ul style="list-style-type: none"> • 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 	The protocols use US spelling - <i>Haemostasis</i> changed to <i>Hemostasis</i> and one other language change
SECTION 10 STATISTICAL CONSIDERATIONS	Original text	New Text	Reason
10.1. Domain-specific stopping rules Page 34	<p>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</p>	<p>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</p>	Context provided from statistical perspective in relation to adaptation of the domain, in relation to interventions in the

	<p>Conclusion. This rule corresponds to the one-sided equivalency region.</p> <p>In all other respects the stopping rules for this domain are those outlined in the relevant core protocol documents.</p>	<p>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.</p> <p>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.</p> <p>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.</p>	<p>previous version of the domain. Updated set of possible platform conclusions appropriate for the redesigned domain.</p>
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		<p>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</p> <p>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</p> <ul style="list-style-type: none"> • 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. <p>The following Platform Conclusions are possible in the No Prior Therapeutic Anticoagulation stratum and in combination with the Antiplatelet Domain:</p> <ul style="list-style-type: none"> • Superiority of either intervention • Superiority of any combination of either intervention in the Anticoagulation Domain and any Antiplatelet Domain 	
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		<p>intervention compared with all possible combinations in both domains</p> <ul style="list-style-type: none"> • Futility of intermediate dose thromboprophylaxis compared to conventional low dose thromboprophylaxis • Effectiveness of: <ul style="list-style-type: none"> 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 	
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		<p>intervention in the Anticoagulation Domain and no antiplatelet intervention in the Antiplatelet Domain</p> <p>In all other respects the stopping rules for this domain are those outlined in the relevant core protocol documents.</p>	
<p>10.2. Unit-of-analysis and strata Page 36</p>	<p>This domain is analyzed only in the pandemic statistical model and includes only patients who are in the pandemic suspected or proven stratum, as specified in the REMAP-CAP Pandemic Appendix and corresponding to the eligibility criteria specified in the REMAP-COVID Core Protocol. Within this stratum, the unit-of-analysis is defined by illness severity state at time of enrollment, defined as either Moderate State or Severe State. Unit-of-analysis may also be defined by SARS-CoV-2 infection or d-dimer strata or both. The D-dimer strata will contain 3 stratum, the breakpoints of which will be determined not later than the first interim analysis using data derived from patients enrolled in REMAP-CAP as well as any other trials that may utilize the same statistical model. Borrowing is permitted between states and strata. If the SARS-CoV-2 strata is applied in analysis, Response Adaptive Randomization will be applied to all PISOP patients, in each illness severity state, using probabilities derived from the SARS-CoV-2 confirmed stratum. Response Adaptive Randomization</p>	<p>This domain is analyzed only in the pandemic statistical model and includes only patients who are in the pandemic suspected or proven stratum, as specified in the REMAP-CAP Pandemic Appendix and corresponding to the eligibility criteria specified in the REMAP-COVID Core Protocol. Within this stratum, the unit-of-analysis is defined by illness severity state at time of enrollment, defined as either Moderate State or Severe State. Unit-of-analysis 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.</p> <p>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</p>	<p>Update of unit-of-analysis appropriate for the adapted domain.</p>

	<p>may also be applied according to D-dimer strata status.</p> <p>The decision to apply the SARS-CoV-2 and D-dimer strata will be operational.</p> <p>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.</p>	<p>testing, microbiological tests do not detect or isolate COVID-19 infection, and testing is not performed.</p>	
<p>10.4. Interactions with interventions in other domains</p> <p>Page 37</p>	<p>An a priori interaction with the Antibiotic Domain is not able to be evaluated as analysis occurs in different statistical models.</p> <p>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.</p> <p>An a priori interaction with the Influenza Antiviral Domain is not able to be evaluated as analysis occurs in different statistical models.</p> <p>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.</p> <p>An a priori interaction with the COVID-19 Immune Modulation Domain is not considered possible and will</p>	<p>An a priori interaction with the following domains is considered possible and will be incorporated into the statistical model used to analyze this domain:</p> <ul style="list-style-type: none"> • 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. <p>Interactions with all other domains are either not evaluable or not considered possible and will not be</p>	<p>Addition of text to explain interaction with interventions in the Antiplatelet Domain which had not commenced at the time of the initial Anticoagulation Domain. Interactions with all other active domains have been summarized</p>

	<p>not be incorporated into the statistical models used to analyze this domain.</p> <p>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.</p> <p>An a priori interaction with the COVID-19 Statin Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.</p> <p>An a priori interaction with the Vitamin C Domain is either not considered possible and will not be incorporated into the statistical model used to evaluate this domain in the pandemic statistical model or is not able to be evaluated for PINSNP patients as analysis occurs in different statistical models.</p> <p>No interaction is evaluable between the Ventilation Domain and this domain.</p>	<p>incorporated into the statistical model or models in which this domain is evaluated.</p> <p>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.</p>	
10.5. Nesting of interventions Page 37	Nesting is not applicable to this domain.	There is no nesting in this domain.	Language updated to maintain consistency across all protocol documents
10.6. Threshold probability for superiority, effectiveness, harm and inferiority	<p>Threshold probability for superiority and inferiority</p> <p>The threshold odds ratio delta for superiority and inferiority in this domain are those specified in the</p>	Threshold probability for superiority, effectiveness, harm and inferiority	Updated to reflect available platform conclusions.

Page 37	<p>Operating Characteristics document derived from Pandemic Appendix and the REMAP-COVID Core Protocol. It is noted that the threshold for superiority and inferiority in the current model has been modified from 0.95 to 0.99 to provide adequate control of type I error, following the evaluation of simulations. It is also noted that asymmetric probabilities may be specified for harm, to allow early cessation and declaration of a Platform Conclusion for interventions that are unlikely to be effective and may be harmful. If so, this will be specified in the Operating Characteristics document which is placed in the public domain.</p>	<p>The threshold probability for statistical triggers for superiority, effectiveness, harm, and inferiority are those specified in the relevant core protocol documents</p>	
10.7. Threshold odds ratio delta for equivalence and futility Page 37	<p>Threshold odds ratio delta for equivalence</p> <p>The Platform Conclusion of equivalence will not be evaluated in this domain. The same odds ratio delta as specified in the relevant core protocol documents for equivalence will be used for futility: this will be applied in a one-sided analysis for futility of therapeutic anticoagulation.</p> <p>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.</p>	<p>Threshold odds ratio delta for equivalence and futility</p> <p>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.</p> <p>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</p>	<p>Update so that statistical triggers for adapted domain are specified and pre-specification of adaptation in event of a futility trigger.</p>

		with an analysis of secondary endpoints. This would be a decision of the ITSC, in association with the DSMB.	
10.9. Post-trial sub-groups Page 38	<p>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:</p> <ul style="list-style-type: none"> • 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 	<p>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:</p> <ul style="list-style-type: none"> • 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 	Post-hoc sub-groups have been updated in line with the protocol changes
SECTION 11 ETHICAL CONSIDERATIONS	Original text	New Text	Reason
11.3. Domain-specific consent issues Page 39	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 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	Minor modification to language consistent with new interventions

	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.	safety criteria are used to exclude patients from this domain for appropriate clinical reasons.	
11.4. Relationship to Antiplatelet Domain	11.4. Relationship to Antiplatelet Domain An Antiplatelet Domain of REMAP-CAP is being planned currently. If such a domain is implemented, it is intended that the Antiplatelet Domain and the Therapeutic Anticoagulation Domain will be analyzed as a 2 x N factorial, with N interventions being available within the Antiplatelet Domain.	Text deleted	Deleted as no longer relevant with the Antiplatelet Domain now active
SECTION 14 APPENDIX 1. ANTICOAGULATION DOSING TABLES	Original text	New Text	Reason
14. Appendix 1	14. APPENDIX 1. OVERVIEW OF DESIGN AND INITIAL RESULTS FOR THE THERAPEUTIC ANTICOAGULATION DOMAIN 14.1. Introduction This document describes the statistical design and analysis of the testing of therapeutic anticoagulation with intravenous UFH or subcutaneous LMWH compared to local standard venous thromboprophylaxis in the COVID-19 appendix as part of the REMAP-CAP trial. Our goal is to	All deleted and replaced with new section 14 tables as below	Simulations appendix removed as applied to the previous version which was a two intervention domain. Generic simulations appropriate for this

	<p>investigate whether this is independently beneficial in increasing the number of ICU- free days for patients with COVID-19.</p> <p><i>14.1.1. Treatment Arms</i></p> <p>The main effect for therapeutic anticoagulation in this domain will be modeled as specified in the PATC.</p> <p><i>14.1.2. Primary Endpoint</i></p> <p>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.</p> <p><i>14.2. Primary Analysis Model</i></p> <p>The primary analysis is based on a Bayesian cumulative logistic regression assuming proportional odds for intervention effects (reference the PATC stats document??).</p> <p><i>14.2.1. Domain Platform Conclusions.</i></p> <p>The Platform Conclusions of Superiority and Inferiority are as specified in the PATC and are unchanged.</p> <p>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.</p> <p><i>14.3. Simulation Details</i></p>		<p>domain are available on the REMAP-CAP website.</p>
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In this section, we outline the simulations conducted for understanding the performance of this domain. Simulations were conducted separately assuming only this domain, as there are no interactions with any other domains.

14.3.1. Standard-of-Care Rates and therapeutic anticoagulation effect assumptions

We created possible standard-of-care rates across the 23 levels of the outcome. We worked within a few clinically guided expected parameters: 20% mortality rate, 10% of patients are in the ICU 21 days, and median number of days in the ICU is 7 amongst those that did not die. Figure 1 shows the assumed rates for the ICU-free day endpoint in the left panel.

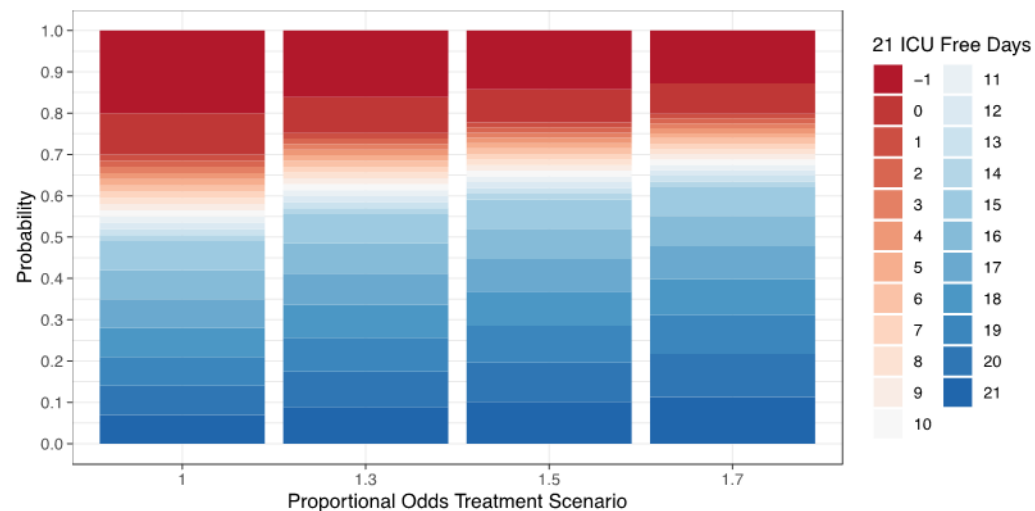


Figure 1. control outcome probabilities for the icu-free day end point (left panel) and then the probabilities for treatment effects of odds ratios of 1.3, 1.5, and 1.7.

For the simulations in this section interim analyses are assumed to occur at 200, 400, 600, 800, 1000, 1500, 2000, 2500, and 3000 patients enrolled in this domain.

14.4. Operating characteristics

Figure 2 presents the cumulative power to determine that therapeutic anticoagulation is superior to the standard-of-care intervention as a function of the total number of patients enrolled (x-axis) and the assumed effect sizes (1.3, 1.5, and 1.7).

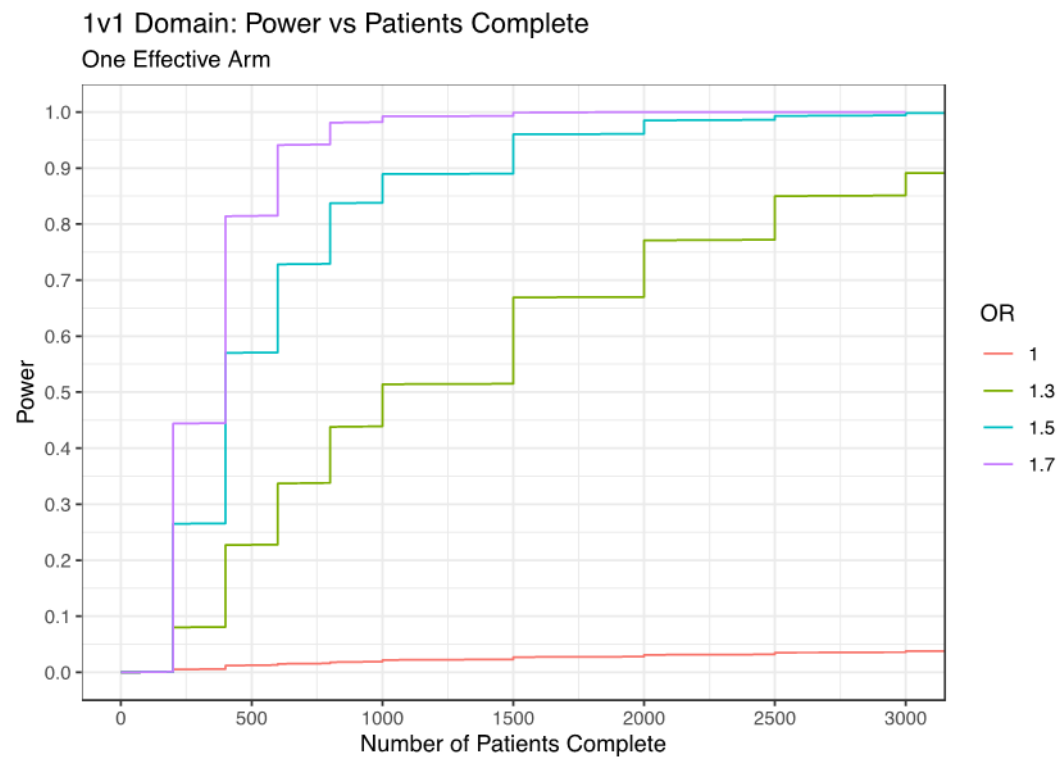


Figure 2: the cumulative power for each of the explored treatment effects (odds ratios of 1.3, 1.5, and 1.7). the cumulative type I error is shown as the red line (effect size of 1).

	<div>14.5. Summary</div> <div>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%.</div>																														
14.1. Enoxaparin Page 47	Text deleted	<div>14.1. Enoxaparin</div> <table><tr><th>Weight</th><th>Renal function (consider UFH or antiXa monitoring if CrCl<20ml/min)[¶]</th><th>Enoxaparin sc Conventional low dose thromboprophylaxis</th><th>Enoxaparin sc Intermediate dose thromboprophylaxis</th><th>Enoxaparin sc therapeutic dose (local protocols for acute VTE dosing can be followed including dose rounding)</th></tr><tr><td><50kg</td><td>CrCl <30ml/min</td><td>0.25mg/kg once daily</td><td>0.5mg/kg once daily</td><td>1mg/kg once daily</td></tr><tr><td><50kg</td><td>CrCl ≥30ml/min</td><td>20mg once daily</td><td>40mg once daily</td><td>1mg/kg twice daily OR 1.5mg/kg once daily</td></tr><tr><td>50-100kg</td><td>CrCl <30ml/min</td><td>20mg once daily</td><td>0.5mg/kg once daily</td><td>1mg/kg once daily</td></tr><tr><td>50-100kg</td><td>CrCl ≥30ml/min</td><td>40mg once daily</td><td>40mg twice daily</td><td>1mg/kg twice daily OR 1.5mg/kg once daily</td></tr></table>				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	Addition of table outlining enoxaparin dosing adjustment in participants with renal function impairment
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)																											
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50-100kg	CrCl ≥30ml/min	40mg once daily	40mg twice daily	1mg/kg twice daily OR 1.5mg/kg once daily																											

		<table><tr><td>101-150kg</td><td>CrCl <30ml/min</td><td>40mg once daily</td><td>0.5mg/kg once daily</td><td>1mg/kg once daily</td></tr><tr><td>101-150kg</td><td>CrCl ≥30ml/min</td><td>40mg twice daily</td><td>60mg twice daily</td><td>1mg/kg twice daily OR 1.5mg/kg once daily</td></tr><tr><td>>150 kg</td><td>CrCl <30ml/min</td><td>60mg once daily</td><td>0.5mg/kg once daily</td><td>1mg/kg once daily</td></tr><tr><td>>150 kg</td><td>CrCl ≥30ml/min</td><td>60mg twice daily</td><td>80mg twice daily</td><td>1mg/kg twice daily OR 1.5mg/kg once daily</td></tr></table> <p>¶ If antiXa levels are checked in renal failure or obesity and suggest heparin accumulation, dose reduction is permitted.</p>	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	
101-150kg	CrCl <30ml/min	40mg once daily	0.5mg/kg once daily	1mg/kg once daily																			
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>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																			
14.2 Dalteparin Page 48	Text deleted	<table><tr><td colspan="5">14.2. Dalteparin</td></tr><tr><td>Weight</td><td>Renal function (consider UFH or antiXa monitoring if CrCl<20ml/min) ¶</td><td>Dalteparin sc Conventional low dose thromboprophylaxis</td><td>Dalteparin sc Intermediate dose thromboprophylaxis</td><td>Dalteparin therapeutic dose (local protocols for acute VTE dosing can be followed including dose rounding)</td></tr><tr><td><50kg</td><td>CrCl <30ml/min</td><td>1250 units once daily</td><td>2500 units once daily</td><td>100 units/kg once daily</td></tr></table>	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	Addition of table outlining dalteparin dosing adjustment in participants with renal function impairment					
14.2. Dalteparin																							
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<50kg	CrCl <30ml/min	1250 units once daily	2500 units once daily	100 units/kg once daily																			

		<table><tr><td><50kg</td><td>CrCl ≥30ml/min</td><td>2500 units once daily</td><td>2500 units twice daily</td><td>Either 100 units/kg twice daily or 200 units/kg once daily</td></tr><tr><td>50-120kg</td><td>CrCl <30ml/min</td><td>2500units once daily</td><td>5000 units once daily</td><td>100 units/kg once daily</td></tr><tr><td>50-120kg</td><td>CrCl ≥30ml/min</td><td>5000units once daily</td><td>5000 units twice daily</td><td>Either 100 units/kg twice daily or 200 units/kg once daily</td></tr><tr><td>121-150kg</td><td>CrCl <30ml/min</td><td>5000 units once daily</td><td>7500 units once daily</td><td>100 units/kg once daily</td></tr><tr><td>121-150kg</td><td>CrCl ≥30ml/min</td><td>7500 units once daily</td><td>7500 units twice daily</td><td>Either 100 units/kg twice daily or 200 units/kg once daily</td></tr><tr><td>>150 kg</td><td>CrCl <30ml/mi</td><td>7500 units once daily</td><td>5000 units twice daily</td><td>100 units/kg once daily</td></tr><tr><td>>150 kg</td><td>CrCl ≥30ml/min</td><td>5000 units twice daily</td><td>10,000 units twice daily</td><td>Either 100 units/kg twice daily or 200 units/kg once daily</td></tr></table> <p>¶ If antiXa levels are checked in renal failure or obesity and suggest heparin accumulation, dose reduction is permitted.</p>	<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	
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>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																																		
14.3 Tinzaparin Page 49	Text deleted	14.3. Tinzaparin			Addition of table outlining tinzaparin dosing adjustment in																																	

			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)	participants with renal function impairment
		<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 Page 50	Text deleted	<div>14.4. Unfractionated Heparin</div> <div>If estimated CrCl is greater than 30 ml/min, LMWH is preferred.</div> <table><tr><th>Weight</th><th>Unfractionated Heparin sc Conventional low dose thromboprophylaxis</th><th>Unfractionated Heparin sc Intermediate dose thromboprophylaxis</th></tr><tr><td><50kg</td><td>2500 units twice daily</td><td>5000 units twice daily</td></tr><tr><td>50-120kg</td><td>5000 units twice daily</td><td>7500 units twice daily*</td></tr><tr><td>121-150kg</td><td>7500 units twice daily</td><td>10,000 units twice daily</td></tr><tr><td>>150 kg</td><td>10,000 units twice daily</td><td>15,000 units twice daily</td></tr></table> <div>*7500 units three times daily is an acceptable alternative</div> <div>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.</div>	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	Addition of table outlining unfractionated heparin dosing adjustment in participants with renal function impairment
Weight	Unfractionated Heparin sc Conventional low dose thromboprophylaxis	Unfractionated Heparin sc Intermediate dose thromboprophylaxis																
<50kg	2500 units twice daily	5000 units twice daily																
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