Domain-Specific Appendix: Endothelial Modulation Domain

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

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Endothelial Domain-Specific Appendix Version 1.0 dated 27th May, 2022

In this domain of the REMAP-CAP trial, participants meeting the platform entry criteria will be randomized to one of two interventions:

- No Endothelial modulator
- Enteral imatinib

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

☐ No Endothelial modulator

☐ Enteral imatinib

This DSA applies to the following states and stratum:

<table>
<tr><td>Stratum</td><td colspan="2">Pandemic infection suspected or proven (PISOP)</td><td>Pandemic infection neither suspected nor proven (PINSNP)</td></tr>
<tr><td>Core protocol documents</td><td colspan="2">REMAP-CAP Core Protocol + Pandemic Appendix, or REMAP-COVID Core Protocol</td><td>REMAP-CAP Core Protocol</td></tr>
<tr><td>Illness Severity State</td><td>Moderate State</td><td>Severe State</td><td>Severe State</td></tr>
<tr><td>Interventions specified in this DSA</td><td>Not available</td><td>No Endothelial modulator
Enteral imatinib</td><td>No Endothelial modulator
Enteral imatinib</td></tr>
<tr><td>Interventions submitted for approval in this jurisdiction</td><td>Not available</td><td>☐ No Endothelial modulator
☐ Enteral imatinib</td><td>☐ No Endothelial modulator
☐ Enteral imatinib</td></tr>
<tr><td rowspan="2">Interventions offered at this site</td><td>Ward</td><td>ICU</td><td>ICU</td><td>ICU</td></tr>
<tr><td>Not available</td><td>Not available</td><td>☐ No Endothelial modulator
☐ Enteral imatinib</td><td>☐ No Endothelial modulator
☐ Enteral imatinib</td></tr>
</table>

REMAP-CAP: Endothelial Domain Summary	
Interventions	• No Endothelial modulator • Enteral imatinib
Unit of Analysis, Strata, and State	This domain is analyzed in two different statistical models. The interpandemic model includes patients corresponding to the Pandemic Infection neither Suspected nor Proven (PINSNP) stratum. Within the PINSNP stratum there are two units of analysis. Analysis also occurs in the pandemic statistical model, corresponding to the Pandemic Infection Suspected or Proven (PISOP) stratum. In the pandemic statistical model unit-of-analysis is defined by illness severity at time of enrollment, defined as Severe state. Unit-of-analysis may also be defined by SARS-CoV-2 infection. 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.
Evaluable treatment-by-treatment Interactions	No interactions will be evaluated with any other domain.
Nesting	None.
Timing of Reveal	Randomization with immediate Reveal and Initiation, or Randomization with Deferred reveal if prospective agreement to participate is required.
Inclusions	None.
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • More than 48 hours has elapsed since ICU admission, 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. • Patient is already receiving or a clinical decision has been made to commence imatinib or another tyrosine kinase inhibitor targeting the same pathway as imatinib (i.e. dasatinib, nilotinib, ponatinib) • Patient was receiving imatinib or another tyrosine kinase inhibitor targeting the same pathway as imatinib (i.e. dasatinib, nilotinib, ponatinib) prior to this hospital admission • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	Criteria that exclude a patient from a one or more interventions are: • Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent. • Known or suspected pregnancy or breast-feeding will exclude a patient from receiving enteral imatinib. It is normal practice that women admitted who are in an age group in which pregnancy is considered possible will have a pregnancy test conducted. The results of such tests will be used to determine interpretation of this exclusion criteria • Known viral hepatitis B or hepatitis C will exclude a patient from receiving imatinib • Known severe liver disease or an alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) that is more than five times the upper limit of normal or bilirubin more than three times the upper limit of normal will exclude a patient from receiving enteral imatinib • A baseline platelet count <50 $x10^9$/L will exclude a patient from receiving enteral imatinib

	• A baseline neutrophil count <1.0 x 10^9/L will exclude a patient from receiving enteral imatinib • Receiving strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, erythromycin) or inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) will exclude a patient receiving enteral imatinib • Receiving immune suppressive therapy with a calcineurin inhibitor (e.g. cyclosporine, tacrolimus), everolimus or sirolimus will exclude a patient from receiving enteral imatinib
Outcome measures	Primary REMAP endpoint: refer to REMAP-CAP Core Protocol + Pandemic Appendix and REMAP-COVID Core Protocol Secondary REMAP endpoints: refer to REMAP-CAP Core Protocol + Pandemic Appendix and REMAP-COVID Core Protocol Secondary domain-specific endpoints: From randomization in this domain, during the index hospitalization until the end of study day 15: • Severe thrombocytopenia (defined as <50 x 109/L) • Severe neutropenia (defined as <1.0 x 109/L) • Major bleeding (as defined by the ISTH criteria) • Increase in AST or ALT to 5 x ULN or bilirubin 3 x ULN From randomization in this domain, during the index hospitalization unless otherwise specified, censored 90 days after enrollment: • Confirmed proximal deep venous thrombosis • Confirmed pulmonary embolism • Acute myocardial infarction • Confirmed ischemic cerebrovascular event • Other thrombotic events • Serious adverse events as defined in relevant core protocol documents and this DSA

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1. ABBREVIATIONS

ALT	Alanine aminotransferase
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate transaminase
CML	Chronic Myeloid Leukemia
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
GIST	Gastrointestinal Stromal Tumor
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
NFKB	Nuclear Factor KB
NT-proBNP	N terminal pro-brain natriuretic peptide level
PAtC	Pandemic Appendix to the Core Protocol
PDGF-R	Platelet-Derived Growth Factor Receptor
Ph+	Philadelphia Chromosome positive
PISOP	Pandemic infection is suspected or proven
RCT	Randomized controlled trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
ROS	Reactive Oxygen Species
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome

TKI	Tyrosine Kinase Inhibitor
ULN	Upper Limit of Normal

2. PROTOCOL APPENDIX STRUCTURE

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

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

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

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

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

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

The current version of the relevant Core Protocol (either REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol), DSAs, RSAs, and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org).

3. ENDOTHELIAL MODULATION DOMAIN-SPECIFIC APPENDIX VERSION

The version of the Endothelial Modulation Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the Endothelial Modulation Domain-Specific Working Group (DSWG) on 27th May, 2022

4. ENDOTHELIAL MODULATION DOMAIN GOVERNANCE

4.1. Domain members

Co-chairs: Prof. Frank L. van de Veerdonk
A/Prof. Zoe McQuilten

Members:

Prof. Derek Angus
Prof. Djillali Annane
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5. ENDOTHELIAL MODULATION DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The Endothelial Modulation Domain-Specific Working Group have read this appendix and authorize it as the official Endothelial Modulation Domain-Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee

Co-chair
Prof. Frank L. van de Veerdonk

Date 27th May 2022

Co-chair
A/Prof. Zoe McQuilten

Date 27th May 2022

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP platform to test the effectiveness of endothelial modulators for patients with severe CAP, including patients with suspected or proven influenza or COVID-19 infection or both.

6.2. Domain-specific background

6.2.1. Influenza and bacterial CAP

The background that is relevant to Influenza and bacterial CAP is located in the REMAP-CAP Core Protocol.

6.2.2. COVID-19 infection

6.2.2.1. *Introduction*

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

6.2.2.2. *Clinical trials for COVID-19 infection*

Observational data cannot determine treatment effects reliably due to the risk of systematic bias (Califf et al., 2020). Clinical trials to identify effective COVID-19 treatments are needed and a large number of trials are underway. Early in the pandemic, the WHO provided guidance regarding both trial design and prioritization of candidate therapies. With regards to trial design, the WHO noted that initially there were no treatments with proven efficacy in patients with COVID-19. Therefore, the recommended 'standard of care' comparator was a control group that did not receive an agent intended to be active against COVID-19 infection, its associated immune response, or other complications (https://apps.who.int/iris/bitstream/handle/10665/330694/WHO-HEO-RDBlueprintnCoV-2020.4-eng.pdf?ua=1). As effective COVID-19 treatments are identified, it is anticipated that 'standard of care', both inside and outside of a clinical trial, will continue to change to incorporate the use of agents with proven efficacy. REMAP-CAP randomizes COVID-19 patients to a range of therapeutic interventions across different domains. Up to date information regarding active and inactive interventions and domains is available at www.remapcap.org.

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

therapies should be evaluated independently in pre-defined patient groups e.g. those who are critically ill, those who are admitted to hospital but are not critically ill, and those who have COVID-19 but have not been admitted to hospital. Among trials that evaluate interventions in patients who are critically ill, it is common for the results of the trial to be different to that which was predicted based on a prior understanding of mechanism of action combined with known mechanism of disease (Landoni et al., 2015, Webb, 2015). This observation reinforces the importance of not necessarily relying on extrapolation of results (both positive and negative) from patients who are not critically ill. It is also possible different disease mechanisms apply at different levels of illness severity and that this may influence the balance between beneficial and adverse effects of a particular intervention, reinforcing the importance of obtaining estimates of treatment effect dependent on the level of illness severity.

6.2.3. Rationale for Endothelial Modulation Domain

6.2.3.1. *The role of endothelium in acute respiratory distress syndrome*

Acute respiratory distress syndrome (ARDS) represents a life-threatening complication of many systemic inflammatory and primary pulmonary disorders, including sepsis, trauma, pancreatitis, and infectious or aspiration pneumonia. ARDS accounts for a substantial proportion of all intensive care unit (ICU) admission, and leads to death in approximately 35% of patients (Bellani et al., 2016). Clinical investigations have demonstrated improved mortality when ARDS patients are ventilated with strategies designed to limit cyclic stretch and alveolar over-distension (Acute Respiratory Distress Syndrome Network et al., 2000), but effective adjunctive therapies, targeting the pathogenesis of ARDS are limited. Additionally, ARDS is increasingly recognized as a heterogeneous syndrome with various subphenotypes demonstrating differential response to therapeutic interventions (Famous et al., 2017, Calfee et al., 2018). Pathophysiologically, in ARDS, inflammation and mechanical injury lead to increased vascular permeability, allowing leakage of intravascular fluid and protein into the interstitial space and subsequently the alveoli. In response to local alveolar hypoxemia, small muscular pulmonary arteries constrict to redirect blood flow to better-ventilated lung regions in order to optimize ventilation/perfusion (V/Q) matching and limit systemic hypoxemia. Infection, inflammation, and lung injury are known to inhibit homeostatic hypoxic pulmonary vasoconstriction (Brimioulle et al., 2002, Hill et al., 2004) thus worsening shunt and systemic hypoxemia.

The pulmonary vascular endothelium is central to the development of ARDS, as it plays a key role in regulating inflammatory cell recruitment, maintaining alveolar barrier integrity, modulating the

coagulation cascade, and regulating regional blood flow to match alveolar ventilation. Thus, pulmonary vascular dysfunction is manifest in ARDS as permeability, vasomotor dysfunction, and increased microvascular thrombosis. Indeed, pulmonary vasomotor dysfunction has been associated with poor outcomes from critical illness and specifically ARDS (Bull et al., 2010, Stamm et al., 2011), and promotion of pulmonary capillary endothelial barrier integrity reduces regional edema accumulation and improves gas exchange in animal models of ARDS (McVerry et al., 2004, Szczepaniak et al., 2008, Peng et al., 2004). The mechanisms underlying pulmonary endothelial barrier dysfunction and the development of novel therapeutics targeting the endothelium have been active areas of investigation for years, although this has not yet led to an impact on treatment or outcomes.

The clinical presentation of severe COVID-19 highlights the critical role of the endothelium in the pathogenesis of ARDS with thrombo-embolic events, microvascular thrombosis, vascular permeability, and hyperinflammation with massive immune cell influx in the lung being hallmark features. COVID-19 also provides a unique insight into endothelial function in ARDS in that SARS-CoV-2 can directly infect blood vessels of organoids and pulmonary endothelial cells in vivo (Varga et al., 2020, Monteil et al., 2020). Postmortem studies confirmed that widespread vascular damage is key to COVID-19-related pulmonary pathophysiology, with disruption of the endothelial barrier and widespread endothelial apoptosis (Varga et al., 2020, Delorey et al., 2021). Similar to non-COVID ARDS (van der Heijden et al., 2008), plasma studies of circulating markers of vascular injury like angiopoietin-2, von Willebrand Factor (vWF) and E-selectin have linked vascular injury to clinical severity in COVID-19 (Vassiliou et al., 2021, Villa et al., 2021). Levels of circulating angiopoietin-2 and E-selectin were found to be higher in patients requiring ICU admission, while high levels at presentation or increasing levels during admission predicted mortality (Smadja et al., 2020).

Given the important pathophysiological role of pulmonary endothelial dysregulation in ARDS and severe COVID-19, it may be a valuable treatment target to prevent lung injury and disease progression due to the cytokine storm, vascular leakage, and the associated coagulopathy. Targeting the endothelium in this domain will be categorized in three key areas: 1) endothelial barrier regulation, 2) inflammatory cell trafficking, and 3) modulation of coagulation.

1) Endothelial Barrier regulation

The endothelial barrier is a dynamic structure that is able to regulate exchange of fluids, plasma proteins, and cells such as leukocytes. Several endothelial signaling pathways and vascular mediators control the integrity of the vascular barrier, including barrier enhancing molecules, such as

angiopeitin-1 and Tie2, and permeability enhancing molecules, such as bradykinin and vascular endothelial growth factor (VEGF). Maintaining this integrity is crucial for prevention of fluid overload in the interstitium causing edema. These are all an active process that involves endothelial signaling induced by shear stress or vascular mediators. These signaling cascades can thus be an attractive target for modulating endothelial function. In addition, permeability enhancing factors can act on actomyosin-based contractility or inhibition of the adhesive function of VE-cadherin. These signaling pathways induced by factors (VEGF and bradykinin) that increase permeability of the endothelium are another potential target for modulation.

2) Inflammatory cell trafficking

Leukocyte migration into the tissue is critical for host containment of infection. It involves priming the endothelium, the processes of capturing, rolling, activation of integrins, arrest, crawling and finally passage of the leukocytes across the endothelium (Kolaczkowska and Kubes, 2013). Activation of complement, an essential part of the innate immune system, leads to recruitment and priming of neutrophils and other leucocytes to the site of endothelial activation (Jin et al., 2020, Keragala et al., 2018). However, these processes require tight control in order to prevent an overwhelming influx of immune cells that can lead to a detrimental inflammatory reaction and resultant vascular leakage. The inflammatory reaction during infection may impact vascular integrity such as modulation of VE-cadherin and tight junctions via cytokines interleukin (IL)-1 and tumor necrosis factor (TNF), and pathogen-associated molecular patterns (PAMPs) from microorganisms, such as lipopolysaccharides (LPS) via Toll-like receptor (TLR) 4 (Jin et al., 2020). This interaction results in activation of endothelial cells, inducing expression of receptors and proteins that can further interact with the coagulation system and the immune system.

3) Modulation of coagulation

At the luminal surface, the endothelium can also directly interact with the coagulation system. Loss of endothelial integrity and endothelial cell death leads to exposure of the basal membrane to the plasma and activating the coagulation system (Schouten et al., 2008, van Hinsbergh, 2012, Wang et al., 2018, Hoepel et al., 2021). Inflammatory responses induce expression of von Willebrand factor (vWF), fibrinogen and P-selectin, that bind and activate platelets (Hoepel et al., 2021) and subsequent release of VEGF, resulting in expression of tissue factor on endothelial cells and activation of the coagulation system (Wang et al., 2018). Endothelial cells are covered with a thick layer of negatively charged glycosaminoglycans (GAGs), termed the glycocalyx (Yang and Schmidt,

2013). Heparan sulfate (HS) is the predominant sulfated GAG in the glycocalyx. Degradation of HS by heparanase, the only known mammalian HS-degrading enzyme, disrupts the endothelial glycocalyx and leads to endothelial barrier dysfunction and microthrombus formation, as observed in ARDS (Schmidt et al., 2012). Microthrombosis and loss of glycocalyx integrity or endothelial cell death leads to differences in flow, and subsequently disturbed flow can also modulate the activation status of the endothelium highlighting the complex interaction of many pathways and mechanism at the level of the endothelium.

This domain within the REMAP-CAP platform will test the effectiveness of strategies to restore or protect the endothelial function and ameliorate its maladaptive secondary effects that might contribute to inflammation and thrombosis in patients with acute illness due to severe pneumonia including that due to suspected or proven COVID-19. Specifically, this domain will evaluate interventions that target the following:

1. Mechanisms for maintaining endothelial integrity and regulating permeability
2. Interaction between the endothelium and the immune system
3. Interaction between the endothelium and the coagulation system

6.2.4. Intervention strategy for this domain

This domain will test the potential benefits of interventions that modulate endothelial function, and will commence evaluating enteral imatinib compared to no endothelial modulator.

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

6.2.5. Imatinib

6.2.5.1. *Pre-clinical evidence for the use of imatinib in acute lung injury*

Imatinib mesylate is a small molecule tyrosine kinase inhibitor (TKI) known to inhibit tyrosine kinases Abl-1 (c-Abl), Abl-2 (Abl-related gene, ARG), the gene fusion product BcrAbl, Platelet-Derived Growth Factor Receptor (PDGF-R)-α and -β, c-KIT and Discoid Domain Receptor-1 (DDR-1).

In vitro studies using endothelial cells of various origins have shown that imatinib dose-dependently protects against endothelial barrier disruption, irrespective of the agent used to induce barrier disruption (Table 1). The Abelson (ABL) family of nonreceptor tyrosine kinases (ABL1 and ABL2) likely mediate vascular barrier function through a number of mechanisms (Aman et al., 2012, Chislock and Pendergast, 2013, Stephens et al., 2014, Amado-Azevedo et al., 2021):

- phosphorylation of several cytoskeletal effectors that have established roles in vascular permeability
- regulation of actin cytoskeleton
- response to barrier-altering agonists
- regulation of cell-cell and cell-matrix junction dynamics
- activation of nuclear factor KB (NFKB) and production of proinflammatory cytokines
- regulation of reactive oxidative species (ROS) signaling pathways

Evidence to support the potential therapeutic benefit of imatinib in ARDS include several pre-clinical animal models of lung injury. Imatinib was shown to reduce LPS-induced lung oxidant injury, lung apoptosis and pulmonary edema as well as to attenuate systemic cytokine expression and mortality in a mouse model (Pappas et al., 2005). In a "two-hit" model of acute lung injury (ALI) caused by LPS and ventilator-induced lung injury, imatinib significantly decreased bronchioalveolar lavage protein, total cells, neutrophils and TNF-alpha levels. Furthermore, when given 4h after LPS, imatinib attenuated acute lung injury, suggestive of a therapeutic benefit after the onset of injury (Rizzo et al., 2015). In another mouse model, imatinib (and nilotinib) attenuated LPS-induced ALI during neutropenia recovery, with evidence of significant downregulation of several inflammatory and chemotactic cytokines. This study reported imatinib resulted in inhibition of infiltration of inflammatory cells into the lung and reduction in the cytokines TNF-a, IL-6 and IL-1b compared to untreated mice. Early release of cytokines such as TNF-a, IL-6 and IL-1b are thought to contribute to inflammatory responses in acute lung injury.

The protective effect of imatinib on the endothelial barrier is mediated by direct inhibition of the ABL tyrosine kinase Arg/Abl2 (Aman et al., 2012, Amado-Azevedo et al., 2021). Although there is evidence that imatinib improves vascular via inhibition of PDGF-R (Su et al., 2008), this effect mainly results from PDGF-R inhibition on pericytes, the relevance of which is unclear for the alveolocapillary membrane. Experimentally, prevention of vascular barrier disruption by imatinib protects against sepsis- and LPS-induced lung injury (Aman et al., 2012, Letsiou et al., 2015). The preclinical data that

provide evidence for a beneficial effect of imatinib mesylate on vascular leak are further summarized in Table 1.

These *in vitro* and *in vivo* studies revealed that imatinib protects the endothelial barrier under inflammatory conditions, and falls in the area of targeting mechanisms that protect vascular integrity.

Table 1. Preclinical data on the efficacy of imatinib mesylate in reversing vascular leak

In vitro model				
Model	**Application of imatinib before/ after inflammatory stimulus**	**Concentration/ dose of imatinib used**	**Effect of imatinib**	**Reference**
Rat aortic endothelial cells	2 hours before	10^{-6}M	Protects endothelial barrier	Kurimoto, *Am J Physiol Heart Circ Physiol* 2004
Human umbilical vein endothelial cells	1 hour before	10 x10^{-6}M	Protects endothelial barrier	Aman, *Circulation* 2012
	1 hour before	10 x10^{-6}M	Improves cell-matrix adhesion	
Human lung microvascular endothelial cells	1 hour before	10 x10^{-6}M	Protects endothelial barrier	Aman, *Circulation* 2012
Immortalized endothelial cells	1 hour before	10 x10^{-6}M	Protects endothelial barrier	Chislock, *PLoS One* 2013
Human umbilical vein endothelial cells	30 min before	10 x10^{-6}M	Protects endothelial barrier	Kim, *ATVB* 2014
Mouse lung microvascular endothelial cells	4 hours before	20 x10^{-6}M	Protects endothelial barrier	Stephens, *Am J Physiol Cell Physiol* 2014
In vivo model			**Effect of imatinib**	**Reference**
Isolated perfused lung model (mouse)	30 min before	100mg/kg	Inhibits lung vascular leak	Aman, *Circulation* 2012
Miles assay (mouse)	30 min before	20mg/kg	Attenuates vascular leak in skin	Aman, *Circulation* 2012
Cecal Ligation & Puncture (Sepsis) (mouse)	6 hours after	50mg/kg	Attenuates vascular leak in lungs, kidneys	Aman, *Circulation* 2012
Intratracheal LPS (mouse)	2 days before	100mg/kg once daily	Attenuates pulmonary edema in mice recovering from neutropenia	Kim, *Crit Care* 2013
Intravenous LPS (mouse)	1 day before	200mg/kg	Attenuates lung vascular leak	Stephens, ATS abstract 2014
			Improves survival	
Intratracheal LPS (mouse)	Immediately prior to	75mg/kg	Attenuates lung vascular leak	Rizzo, ATS abstract 2014

	4 hours after	75mg/kg	Attenuates lung vascular leak	
Miles assay (mouse)	30 min before	20mg/kg	Attenuates vascular leak in skin	Kim, *ATVB* 2014
Miles assay (mouse)	Co-injection	15 x10^{-6}M	Attenuates vascular leak in skin	Chislock, *PLoS One* 2013
Bleomycin-induced lung injury (mouse).	Co-administration (same day)	100mg/kg	Reduces Lung Injury Score and reduces inflammatory cytokines in broncho-alveolar lavage fluid	Rhee, *Respir* 2011

6.2.5.2. *Evidence for efficacy of imatinib in treatment of acute lung injury/ARDS*

The first case report of a role for imatinib in pulmonary vascular leak was published in 2008, where Overbeek et al. showed reversal of lung edema with imatinib in clinical pulmonary veno-occlusive disease (Overbeek et al., 2008). Subsequently, imatinib (300mg/day) treatment was shown to result in clinical improvement in a patient with acute respiratory failure due to chemotherapeutic toxicity (Carnevale-Schianca et al., 2011). Imatinib was used on a compassionate basis in two additional patients – in both cases initiation of imatinib therapy (200-400mg/day) was followed by reversal of idiopathic vascular leak and/or respiratory failure (Aman et al., 2013).

6.2.5.3. *Evidence for efficacy of imatinib in COVID-19*

Several case reports of use of imatinib for COVID-19 have been published. One of the earlier reports was of a 38-year-old woman who was treated with imatinib 400mg daily, commencing on day 12 of symptoms when she developed worsening radiological changes suggestive of a hyperinflammatory state. Three days following treatment, she experienced resolution of fever, stability of radiology changes and no longer required supplemental oxygen (Morales-Ortega et al., 2020). Subsequently, a case series detailed 20 consecutive COVID-19 patients who received imatinib as part of their treatment between 2-13 days after onset of symptoms. All except one had pneumonia and were PCR positive for SARS-CoV-2. Assessment of therapeutic efficacy was limited by the study design, and the main side effects reported were mild gastrointestinal symptoms. Three patients died of COVID-19, and the remaining recovered. There was no evidence that timing of treatment was associated with outcomes (Morales-Ortega et al., 2021).

There are no published, completed clinical trials of imatinib for COVID-19, although a number are underway (see Table 2 below). Based on the aforementioned experimental and early clinical findings, a randomized, double-blind, placebo-controlled trial in hospitalized Covid-19 patients requiring supplemental oxygen was conducted: the CounterCOVID study (EUdraCT 2020-001236-10,

(Aman et al., 2021)). Patients were randomly (1:1) assigned to oral imatinib (800mg loading dose, followed by 400mg daily for 9 days) or placebo. Primary outcome of the study was time to liberation from ventilation and supplemental oxygen for more than 48 hours while being alive during a 28-day period. Secondary outcomes included 28-day mortality and need for invasive mechanical ventilation. Four hundred patients were randomized in 13 hospitals. 385 patients (median age 64 (range 28-93) years) received at least 1 dose of study medication and were included in the analysis. While no difference was found in time to liberation from ventilation and supplemental oxygen between the two groups (hazard ratio [HR] 0.95; 95% confidence interval [CI] 0.76-1.20), we observed significant reductions in mortality (8% in the imatinib group, compared to 14% in the placebo group (HR 0.51; 95% CI 0.27-0.95) and median duration of invasive mechanical ventilation (7 days in the imatinib group, compared to 12 days in the placebo group (P=0.008).

Table 2. Current registered trials of imatinib for COVID-19

Trial identifier	Population	Intervention/Comparator	Primary outcome	Number patients
NCT04346147	Adult (>18y) Confirmed COVID	Imatinib 400mg daily vs Baricitinib 4mg daily Vs SOC	Time to clinical improvement (2 points on 7 category ordinal scale)	165
NCT04357613 IMAGE-19	Age 70y+ Confirmed COVID ≤7 days of COVID Non-severe	Imatinib 800mg/d vs SOC	Severe COVID-19 30-day mortality	99
NCT04794088 INVENT COVID	Age ≥18y Moderate-severe ARDS Confirmed COVID	Imatinib 200mg IV vs placebo	Change in extravascular lung water index day 1-7	90
NCT04422678	PCR positive Hospitalized with moderate to severe respiratory symptoms	400mg imatinib daily for 21d vs imatinib 200mg daily for 21d vs SOC	Disease progression (need for MV)	30
NCT04394416	PCR positive >18y	400mg imatinib daily for 14d vs. placebo	Proportion of patients with 2-point change in 8-category ordinal scale	204
NCT04953052 (IMPRESS COVID)	Age >18y PCR positive, Moderate-severe ARDS	Imatinib 200mg IV twice daily vs placebo	Change from baseline in oxygen saturation index	84
ISRCTN18066414 (Solidarity trial plus)	Age >18y, Confirmed COVID, hospitalized	Imatinib 400mg daily for 14d vs. standard of care/infliximab/artesunate	In hospital mortality	Not stated

6.2.5.4. *Safety of enteral imatinib*

Imatinib has a well-characterized safety profile, including for long-term therapy, through its extensive use as a treatment for the following indications:

- Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, accelerated phase or blast crisis
- Ph+ acute lymphoblastic leukemia (Ph+ ALL) integrated with chemotherapy or as monotherapy in relapsed/refractory disease
- myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR gene re-arrangements.
- advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFRα rearrangement.
- c-Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).
- unresectable dermatofibrosarcoma protuberans (DFSP).

The most frequently reported adverse drug reactions during clinical development (>10%) were neutropenia, thrombocytopenia, anemia, headache, dyspepsia, edema, weight increase, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, and abdominal pain. Events were of mild to moderate grade, and only 2 to 5 % of patients permanently discontinued therapy due to a drug-related event (https://www.medicines.org.uk/emc/product/2297/smpc#UNDESIRABLE_EFFECTS). Superficial edemas were a common finding in all studies and were described primarily as periorbital or lower limb edemas. However, these edemas were rarely severe, and may be managed with diuretics, other supportive measures, or by reducing the dose of imatinib (https://www.medicines.org.uk/emc/product/2297/smpc#UNDESIRABLE_EFFECTS). They were also more likely to occur with extended use (unlike the short duration proposed in this study).

Other common side effects (>1/100 to <1/10) included fever, abdominal distension, dry mouth, constipation, hyperbilirubinemia, taste disturbance, dizziness and insomnia. Uncommon (>1/1000 to <100) and rare (<1/1000) adverse events include congestive cardiac failure, pulmonary edema, pericardial effusion, gastrointestinal hemorrhage (particularly GIST patients), mouth ulceration, gastric ulceration, hepatitis and hepatic failure, electrolyte disturbance, pulmonary fibrosis/hypertension and thrombosis.

Adverse events were similar for all indications, with the exception of more myelosuppression observed in patients with CML (particularly later stage disease), and more serious GI bleeds (including intra-tumoral bleeds) in GIST patients. These differences are likely due to the underlying condition being treated.

In the CounterCOVID study (Aman et al., 2021), where treatment was given for a much shorter duration than what is routinely done in CML and GIST, no new safety signals emerged. The total number of adverse events grade 3 or larger (according to the CTCAE v5.0) was significantly lower as compared to placebo. However, 15% of patients treated with imatinib requested early discontinuation of treatment as compared to 6.4% in the placebo group. Reasons for treatment discontinuation were symptoms of nausea, vomiting and diarrhea. These side-effects were much more common in patients concomitantly using chloroquine or hydroxychloroquine. In the CounterCOVID study, blood biochemistry was closely monitored and repeated ECG measurements were performed to assess possible prolongation of QTc time. No differences were observed in liver enzymes, cytopenia, NT-proBNP or QTc interval between groups and there were no specific adverse events attributed to the use of imatinib.

Imatinib is not safe in pregnancy or during breastfeeding. Imatinib is classified as a Category D medication in pregnancy (https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-04296-3&d=202104151016933). In animal studies, Imatinib had clear embryo-fetal toxic and teratogenic effects. There have been post-marketing reports of spontaneous abortions and infant congenital abnormalities from women who have taken imatinib during pregnancy. Both imatinib and its active metabolite can be found in human milk, with a milk plasma ratio of 0.5 for imatinib and 0.9 for its active metabolite. The effects of low-dose exposure to imatinib in infants are not known. As such, women who are pregnant, or who are of child-bearing age with unknown pregnancy status, or who are breastfeeding, will not be eligible for imatinib intervention within this domain.

Reactivation of hepatitis B can occur in patients who are chronic carriers receiving imatinib. As such, patients with known active hepatitis B will not be eligible for the imatinib interventions within this domain.

The domain-specific entry criteria, reportable SAEs, and safety secondary end-points have been chosen taking the known possible adverse events into account.

6.2.5.5. *Dosing of enteral imatinib*

6.2.5.5.1. Enteral imatinib

The dose of enteral imatinib for approved indications ranges from 400mg to 800mg (given as a divided dose) daily. The only concentration effect study in the *in vitro* endothelial model showed that optimal inhibition of vascular leak was reached at a total concentration of 2-10uM (Aman et al., 2012), which is double the C_{trough} reached at a dose of 400mg once daily (most commonly used in CML), but in the same range as the C_{max} at steady state. Imatinib is used in doses of up to 800 mg per day in the maintenance phase of germatofibrosarcoma protuberans or GIST with c-KIT exon-9 mutations. In addition, a recent publication of Reardon et al showed that doses up to 1000mg daily were considered safe in glioblastoma multiforme (Reardon et al., 2008). However, concentration-toxicity studies demonstrated optimum concentrations corresponding to a 400mg once daily dose (Widmer et al., 2006). In addition, the only experience in patients in the ICU is with doses up to 400mg daily. The CounterCOVID study administered a loading dose of 800mg, to ensure optimal inhibition of vascular leakage upon treatment initiation, followed by a maintenance dose of 400mg daily. We have access to a limited set of pharmacokinetic results from the CounterCOVID study. This shows that while total imatinib concentrations were higher than what is usually seen in CML/GIST, the free fraction C_{max} at steady state was near the expected and targeted level. Toxicity with the 400mg once daily dosing scheme was minimal, but low-grade gastrointestinal side effects were more common in imatinib patients, leading to a higher spontaneous rate of study drug discontinuation. Higher free concentrations could result in more side effects. Therefore, in this domain we propose to stay with an 800mg loading dose, followed by a dose of 400mg enteral imatinib once daily for 13 days (total of 14 days therapy). Patients not able to swallow can receive imatinib as a suspension via a nasogastric tube if one has been placed as part of routine care.

Renal impairment: Imatinib and its metabolites are not excreted by the kidney to a significant extent (https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-04296-3&d=202104151016933, https://www.medicines.org.uk/emc/medicine/15014#gref). In patients with mild to moderate renal impairment, no dose adjustment of imatinib is required. Patients with severe renal impairment should be treated with caution and the dose can be reduced/withheld if not tolerated. There are reports of use of imatinib of up to 600mg daily without evidence of increased plasma levels in patients with end stage renal failure (Pappas et al., 2005).

Liver impairment (https://www.medicines.org.uk/emc/medicine/15014#gref): Metabolism of imatinib is mainly hepatic, and only 13% of excretion is through the kidneys. No dose adjustment is

required for patients with mild or moderate hepatic dysfunction, however peripheral blood counts and liver enzymes should be carefully monitored. In this trial, patients with severe liver dysfunction at baseline are excluded and development of significant impairment of liver function will result in cessation of administration of imatinib.

6.2.5.6. *Known drug interactions*

Caution should be used when taking imatinib with strong CYP3A4 inducers, strong CYP3A4 inhibitors, CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporin or pimozide) or CYP2C9 substrates with a narrow therapeutic window (e.g. warfarin and other coumarin derivatives) (https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-04296-3&d=202104151016933).

CYP3A4 inducers that may reduce imatinib levels: rifampicin, phenytoin, carbamazepine, dexamethasone (see below).

CYP3A4 inhibitors that may increase imatinib levels: ketoconazole, erythromycin, itraconazole.

Drugs that may have their plasma concentration increased by imatinib: cyclosporin, pimozide, statins, triazole-benzodiazepines, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel, quinidine, warfarin.

6.2.5.6.1. Specific interactions relevant in COVID-19 and critically ill

- Dexamethasone may reduce drug levels of imatinib potentially increasing the risk of therapeutic failure of Imatinib (Recoche et al., 2016). However, there are no published papers on drug-drug interactions with imatinib and dexamethasone, and so no dose adjustments are required if dexamethasone is co-administered with imatinib in this domain.
- In vitro, remdesivir is a minor substrate and inhibitor of CYP3A4. Remdesivir is extensively metabolized by multiple pathways including activation by hydrolyses in vivo, therefore it is unlikely to have relevant interactions with imatinib. Moreover, since remdesivir is metabolized quickly and therefore cleared rapidly after IV administration, remdesivir is unlikely to have a relevant effect on imatinib exposure (Gandhi et al., 2020).
- Imatinib may reduce exposure to levothyroxine.
- Imatinib may reduce the metabolism of acetaminophen.
- Imatinib may prolong the activity of Vitamin K antagonist (warfarin), leading to possible bleeding during coadministration, and more frequent monitoring.

- Imatinib may increase concentration of fentanyl. If fentanyl is co-administered with imatinib, patients should be monitored for respiratory depression and sedation at frequent intervals, as occurs routinely in patients admitted to an ICU, with consideration of fentanyl dose adjustments until stable drug effects are achieved.

6.2.5.6.2. Specific interactions with REMAP-CAP domains

Macrolide Domain Specific Appendix: Although clarithromycin may increase the AUC of imatinib, the likely increase is within normal dosing range of imatinib, and so co-administration will be allowed. Potential adverse effects due to imatinib which are dose-dependent, including cytopenias and abnormal liver function, are monitored within this domain.

Simvastatin Domain Specific Appendix: Imatinib may increase the AUC of simvastatin, with potential to increase risk of adverse side effects from simvastatin. This will be monitored within the Simvastatin DSA, which specifies monitoring of liver function tests, serum creatinine kinase, and renal function at least once during the first 7 to 14 days after randomization and repeated between study day 21 and 28 if the patient is still receiving simvastatin.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of interventions that modulate endothelial function for patients with severe CAP, including proven or suspected COVID-19 or influenza or both.

We hypothesize that the probability of the occurrence of the primary endpoint specified in the relevant core protocol documents will differ based on allocation to Endothelial Modulation Domain therapy. The following interventions will be available:

- No Endothelial modulator (no placebo)
- Enteral imatinib

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

We hypothesize that the treatment effect of Endothelial Modulation Domain therapy is different depending on whether influenza infection is confirmed to be present or absent.

We hypothesize that the treatment effect of Endothelial Modulation Domain therapy is different depending on whether neither SARS-CoV-2 nor influenza infection is confirmed to be present or absent.

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial. Treatment allocation will be based on response adaptive randomization, as described in the core protocol documents.

8.1. Population

The REMAP enrolls patients with severe CAP, including patients with suspected or proven influenza and/or COVID-19.

8.1.1. State

This domain is available for patients who have suspected or proven pandemic infection and patients who are pandemic infection neither suspected nor proven in the Severe State.

8.1.2. Domain-specific strata

Domain-specific strata are not applied to patients at the time of assessment for this domain.

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in either the REMAP-CAP Core Protocol + Pandemic Appendix or the REMAP-COVID Core Protocol. It is noted that during the COVID-19 pandemic, that platform-level inclusion criteria are different for patients with pandemic infection suspected or proven (PISOP stratum) and for patients in whom pandemic infection is neither suspected nor proven (PINSNP). Patients in either stratum are eligible for this domain. Patients eligible for the REMAP may have conditions that exclude them from this Domain.

8.2.1. Domain inclusion criteria

Nil.

8.2.2. Domain exclusion criteria

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

- More than 48 hours has elapsed since ICU admission, unless the patient has already been assigned a treatment in another domain in the Moderate State in which case exclusion will occur if more than 48 hours has elapsed since commencement of sustained organ failure support in an ICU.
- Patient is already receiving or a clinical decision has been made to commence imatinib or another tyrosine kinase inhibitor targeting the same pathway as imatinib (i.e. dasatinib, nilotinib, ponatinib)
- Patient was receiving imatinib or another tyrosine kinase inhibitor targeting the same pathway as imatinib (i.e. dasatinib, nilotinib, ponatinib) prior to this hospital admission
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

8.2.3. Stratum-specific domain exclusion criteria

Nil.

8.2.4. Intervention exclusion criteria

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons. In such cases, patients will be randomly allocated to a remaining intervention from among those available at that site.

Patients who are eligible for only a single intervention at a site (i.e. all other interventions are contraindicated) are not eligible for this domain. Patients in whom all interventions are contraindicated will be treated according to the current standard of care at the clinician's discretion.

Criteria that exclude a patient from one or more interventions are:

- Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent.
- Known or suspected pregnancy or breast-feeding will exclude a patient from receiving enteral imatinib. It is normal practice that women admitted who are in an age group in which pregnancy is considered possible will have a pregnancy test conducted. The results of such tests will be used to determine interpretation of this exclusion criteria
- Known viral hepatitis B or hepatitis C will exclude a patient from receiving imatinib
- Known severe liver disease or an alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) that is more than five times the upper limit of normal or bilirubin

more than three times the upper limit of normal will exclude a patient from receiving enteral imatinib

- A baseline platelet count <50 x10^9/L will exclude a patient from receiving enteral imatinib
- A baseline neutrophil count <1.0 x 10^9/L will exclude a patient from receiving enteral imatinib
- Receiving strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, erythromycin) or inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) will exclude a patient receiving enteral imatinib
- Receiving immune suppressive therapy with a calcineurin inhibitor (e.g. cyclosporine, tacrolimus), everolimus or sirolimus will exclude a patient from receiving enteral imatinib

8.3. Interventions

8.3.1. Endothelial Modulation Domain Interventions

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

☐ No Endothelial modulator therapy

☐ Enteral imatinib

8.3.2. No Endothelial modulator therapy

Patients assigned to this intervention are not to receive imatinib or another tyrosine kinase inhibitor targeting the same pathway as imatinib (i.e. dasatinib, nilotinib) unless for an accepted clinical indication (e.g. new diagnosis of chronic myeloid leukemia) until the end of study day 14 or until intensive care unit discharge, whichever occurs first.

8.3.3. Enteral imatinib

Enteral imatinib will be administered as a 800mg loading dose (study day 1) followed by 400mg once daily (study day 2-14).

8.3.4. Duration of Endothelial modulator therapy

Enteral imatinib will be administered for a total of 14 days or until intensive care unit discharge, whichever occurs first.

8.3.5. Monitoring for cytopenias and liver function

A full blood count (to monitor for cytopenias) and liver function tests (bilirubin, ALT +/- AST) should be performed, as part of usual care, at least twice weekly whilst receiving enteral imatinib.

8.3.6. Discontinuation of study intervention

The following reasons should prompt discontinuation of imatinib therapy:

- If a patient develops neutropenia (neutrophil count <1.0 x 10^9/L) and/or thrombocytopenia (platelet count <50 x 10^9/L), stop imatinib and do not restart
- If a patient develops elevation in bilirubin 3 times the upper limit of normal or ALT/AST 5 times the upper limit of normal, imatinib should be discontinued and not restarted
- If a patient develops a severe adverse reaction, imatinib should be discontinued and not restarted

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.

8.3.7. Strategy in patients negative for COVID-19 or influenza infection

In patients with suspected COVID-19 or influenza infection who receive an allocation status to receive an active intervention in this domain who subsequently test negative for COVID-19 infection or influenza should continue treatment according to their allocated intervention.

8.4. Concomitant care

Additional agents, other than those specified in the platform, that are intended to modulate endothelial function, are not permitted. Specifically, administration of imatinib (or other tyrosine kinase inhibitor targeting the same pathway as imatinib such as nilotinib or dasatinib) to a patient assigned to the 'No Endothelial modulator therapy' intervention, unless for an accepted clinical indication (e.g. new diagnosis of CML), until the end of study day 14 is a protocol deviation.

Imatinib may increase the concentration of fentanyl. If fentanyl is co-administered with imatinib, patients should be monitored at frequent intervals and consider fentanyl dose adjustments until stable drug effects are achieved.

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

8.5. Endpoints

8.5.1. Primary endpoint

The primary endpoint for this domain is the primary outcome specified in the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol.

8.5.2. Secondary endpoints

All secondary endpoints as specified in the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol

The domain-specific secondary outcome measures will be:

From randomization in this domain, during the index hospitalization until the end of study day 15:

- Severe thrombocytopenia (defined as platelet count <50 x 10^9/L)
- Severe neutropenia (defined as neutrophil count <1.0 x 10^9/L)
- Major bleeding (as defined by the ISTH criteria)
- Increase in AST or ALT to 5 x ULN or bilirubin 3 x ULN

From randomization in this domain, during the index hospitalization unless otherwise specified, censored 90 days after enrollment:

- Confirmed proximal deep venous thrombosis
- Confirmed pulmonary embolism
- Acute myocardial infarction
- Confirmed ischemic cerebrovascular event
- Other thrombotic events
- Serious adverse events as defined in relevant core protocol documents and this DSA

9. TRIAL CONDUCT

9.1. Microbiology

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

9.2. Domain-specific data collection

Additional domain-specific data will be collected.

- Baseline and nadir platelet and neutrophil counts (between randomization and day 15) and date of nadir result
- Baseline and peak AST, ALT and bilirubin (between randomization and day 15)
- Administration of imatinib
- Administration of immune modulatory agents intended to influence host response to infection
- Administration of anticoagulation or antiplatelet therapy

9.3. Criteria for discontinuation

Refer to relevant core protocol documents for criteria for discontinuation of participation in the REMAP-CAP trial.

9.4. Blinding

9.4.1. Blinding

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

9.4.2. Unblinding

Not relevant.

10.STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

The following Platform Conclusions are possible in this domain:

- Inferiority for all interventions in the domain
- Superiority for an active endothelial modulator intervention compared with all other interventions in the domain
- Effectiveness for one or more active endothelial modulator intervention(s) compared with no endothelial modulator intervention

- Futility for one or more active endothelial modulator intervention(s) compared with no endothelial modulator intervention
- Non-inferiority among a pair of active endothelial modulator interventions, if additional endothelial modulator interventions are integrated into a future version of the domain. This will only be applied if the No Endothelial Modulator arm is closed following a Platform Conclusion. The comparator for non-inferiority will be the active endothelial modulator that showed superiority over No Endothelial Modulator.

In all other respects the stopping rules for this domain are those outlined in the relevant core protocol documents.

10.2. Unit-of-analysis and strata

With respect to strata, there are two units-of-analysis for this domain specified by the presence or absence of suspected or proven pandemic infection. As these strata are analyzed in different statistical models, no borrowing is permitted, unless the pandemic and interpandemic statistical models are merged. For patients with suspected or proven pandemic infection, units-of-analysis, as determined by the ITSC and based on an understanding of the sensitivity and availability of testing for COVID-19 infection, may be modified to allow separate analysis of the COVID-19 infection confirmed and not confirmed stratum. This will be an operational decision. For patients in the pandemic infection neither suspected nor proven stratum, unit-of-analysis will be defined by influenza present or absent stratum. At the time of a Platform Conclusion derived from the pandemic model, 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.

It is anticipated that during the life-time of this domain a revision of the core protocol will occur that results in the merging of the current pandemic and interpandemic statistical models. If the pandemic and interpandemic statistical models are merged the combination of pathogen stratum (from among COVID-19, influenza, and bacterial CAP) that will be applied to specify the unit-of-analysis will be determined as an operational decision that is specified in the Current State document. Borrowing will be permitted between specified pathogen-specific stratum.

Response Adaptive Randomization may be applied. If RAR is applied, the cap on the maximum or minimum proportion of patients assigned to an intervention that is specified in core protocol documents may be modified by the Statistical Analysis Committee (SAC) if needed to reduce the

likelihood of sites being unblinded or to improve power. If required, any such modifications will be an operational decision of the Design Team specified in the Current State document and applied by the SAC.

The shock strata will not contribute to unit-of-analysis for this domain.

10.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal if prospective agreement to participate is required for this domain (see relevant core protocol documents).

10.4. Interactions with interventions in other domains

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

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

10.5. Nesting of interventions

There is no nesting of interventions in this domain.

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

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

10.7. Threshold odds ratio delta for equivalence and futility

The threshold odds ratio delta for equivalence in this domain is that specified in the relevant core protocol documents. 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 for active interventions specified in this domain.

10.8. Informative priors

This domain will launch with priors that are not informative for main effects.

10.9. Post-trial sub-groups

Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The *a priori* patient sub-groups of interest are:

- Shock strata
- Receiving invasive mechanical ventilation at baseline vs. not receiving invasive mechanical ventilation at baseline
- Age <65 years vs. ≥ 65 years
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

11.ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, efficacy, inferiority, or futility of different interventions with respect to the primary endpoints are possible.

The DSMB should take into account the public health, as well as clinical significance, of the analyses of this domain and are empowered to discuss results with relevant international and national public health authorities, with rapid dissemination of results to the larger community being the goal.

Safety secondary outcomes will be reported to the DSMB who are empowered to require additional analyses regarding these outcomes as required.

11.2. Potential domain-specific adverse events

Unexpected respiratory depression (including if due to suspected drug interaction between fentanyl and imatinib) should be reported as an SAE.

Other SAEs should be reported only where, in the opinion of the site-investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see relevant core protocol documents).

11.3. Risks and benefits of participation

Potential benefits of participation in this domain include access to novel treatments for severe CAP that are not standard of care. Potential risks of participation are outlined above in the background on evidence for safety for each intervention. Adverse events related to the trial interventions are being collected as secondary outcomes and will be made available to and monitored by the DSMB. Domain 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.

11.4. Domain-specific consent issues

As noted in the background, and endorsed by the WHO (with respect to COVID), in the absence of evidence of effectiveness of any interventions specified in this DSA or alternative intervention that lies within this domain, the use of a usual care control is both appropriate and ethical.

Interventions in this domain are in "off-label" clinical use in patients who meet entry criteria, and typically without consent, for patients who meet the entry criteria for this domain. Clinicians may choose not to enroll individual patients if they feel that participation is not in the patient's best interests, and safety criteria are used to exclude patients from this domain for appropriate clinical reasons.

Where all interventions that are available at a participating site and are regarded as being part of the acceptable spectrum of standard care and given the time imperative necessary to evaluate these interventions, entry to the study, for participants who are not competent to consent, is preferred to be via waiver-of-consent or some form of delayed consent.

During a pandemic, visiting by relatives of affected patients may not be possible. In such situations, alternative methods for confirming consent including electronic and telephone communication, as permitted by an appropriate ethical review body, may be acceptable methods for confirming agreement to participate in this (and other) domains of the platform.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. This domain has not received any additional domain-specific funding but such funding, from any source, may be obtained during the life-time of the domain.

12.2. Funding of domain interventions and outcome measures

All Endothelial Modulation Domain agents will be provided by participating hospitals.

12.3. Domain-specific declarations of interest

All investigators involved in REMAP-CAP maintain a registry of interests on the REMAP-CAP website. These are updated periodically and publicly accessible on the study website.

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