This supplement contains the following items:

1. The original protocol documents, the final protocol documents and summary of changes
2. The original / final statistical analysis plans for this specific analysis and the core protocol.

Due to the modular nature of this ongoing platform trial there is also an introduction to explain the protocol structure.

1.1. Introduction

As an international multi-factorial adaptive platform trial, designed to run in both interpandemic and pandemic periods, the REMAP-CAP protocol is modular and was updated as the COVID-19 pandemic developed. This supplement provides an introductory summary of the various protocol documents relevant to the convalescent plasma analysis in the Immunoglobulin Domain for patients with proven Covid-19 presented in this manuscript, as well as including the relevant full protocol documents for reference. The original versions all predate the first screening of inclusion of Covid-19 patients.

1.2. Protocol structure

The key central features of the platform, focusing mainly on community acquired pneumonia (CAP)in the inter-pandemic period, are described in the REMAP-CAP Core protocol and the details of thespecific interventions evaluated are contained in Domain Specific Appendices (DSA). For this manuscript that is the COVID-19 Immunoglobulin Therapy DSA.

As the threat of the Covid-19 pandemic developed in early 2020, the REMAP-CAP Core protocol was updated to be more applicable to this new disease. These adaptations aredefined in the Pandemic Appendix to Core (PAtC) protocol.
In some countries, REMAP-CAP was not running prior to the pandemic. Therefore, a simplified combined version of the REMAP-CAP Core protocol and Pandemic Appendix toCore was produced to focus only on those details relevant for patients with Covid-19 (REMAP-COVID Core protocol).

Relevant protocol documents included in this supplement are:

All additional protocol documents can be found at www.remapcap.org/protocol-documents

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

PANDEMIC APPENDIX TO THE CORE PROTOCOL (REMAP-COVID)

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

Summary

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

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

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

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

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

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

Methods: The methods that will be utilized during a pandemic are those in the Core Protocol but with potential for changes to the primary end-point, frequency and process for adaptive analyses, and determination of which domains will be analyzed using a statistical model that includes data from patients with proven or suspected pandemic infection. During a pandemic, patients who are

neither suspected nor proven to have pandemic infection and for certain pre-existing domains, will continue to be analyzed using the statistical model that is outlined in the Core Protocol that was operating during the pre-pandemic period. Depending on the characteristics of a pandemic, one or more interpandemic domains may be analyzed within the pandemic statistical model and one or more pandemic-specific domains may be commenced for patients with suspected or proven pandemic infection.

Lay description

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

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1. ABBREVIATIONS

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

2. PROTOCOL APPENDIX STRUCTURE

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

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

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

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

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

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

3. PANDEMIC APPENDIX TO THE CORE PROTOCOL VERSION

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

3.1. Version History

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

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

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

4. PANDEMIC APPENDIX TO THE CORE PROTOCOL GOVERNANCE

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

4.1. Pandemic Working Group

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

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

Members: Prof. Derek Angus

Prof. Yaseen Arabi

Prof. Richard Beasley

A/Prof. Scott Berry

Prof. Frank Brunkhorst

Dr. Lennie Derde

Dr. Robert Fowler

Prof. Anthony Gordon

Mr. Cameron Green

Dr. Ed Litton

Prof. John Marshall

Dr. Colin McArthur

A/Prof Bryan McVerry

Dr. Srinivas Murthy

Prof. Alistair Nichol

Ms. Jane Parker

Prof. Kathy Rowan

Prof. Tim Uyeki

Prof. Steve Webb

4.2. Contact Details

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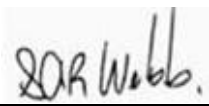
5. PANDEMIC WORKING GROUP AUTHORISATION

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

Chair  Date 18th May, 2020

Steve Webb

6. BACKGROUND AND RATIONALE

6.1. Introduction

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

Previous pandemics and outbreaks of emerging infectious diseases have outlined the urgent need for evidence, preferably from Randomized Controlled Trials (RCTs), to guide best treatment. However, there are substantial challenges associated with being able to organize such trials when

the time of onset of a pandemic and its exact nature are unpredictable[4-6]. As an adaptive platform trial that enrolls patients during the interpandemic period, REMAP-CAP is ideally positioned to adapt, in the event of a respiratory pandemic, to evaluate existing treatments as well as novel approaches.

One of the challenges associated with planning clinical trials during a pandemic is that the precise nature of the infecting organism, clinical consequences, and suitable interventions (particularly those that are pathogen-specific) cannot be reliably known in advance. The speed of clinical progression, from initial infection to life-threatening severe respiratory infection is another feature that cannot be reliably known in advance. It is likely that a proportion of patients will present with severe CAP but other patients may present to medical attention with illness that is less severe, but remain at risk of progression to severe illness. Patients who require hospital admission, but have less severe illness are a particularly important group, because early intervention at this stage of illness may prevent progression to life-threatening illness. It is also possible that proposed treatment interventions may have differential treatment effect depending on the level of illness severity at the time that treatment is commenced, including treatment effects that are divergent. Nevertheless, a range of scenarios can be anticipated and used to provide direction and guidance regarding the most appropriate research response.

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

6.2. Pandemic research preparedness

6.2.1. Introduction

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

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

6.2.2. Pre-planned

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

6.2.3. Pre-approved

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

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

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

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

6.2.4. Practiced

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

6.2.5. Implications of REMAP design during a pandemic

6.2.5.1 *Time-critical generation of evidence*

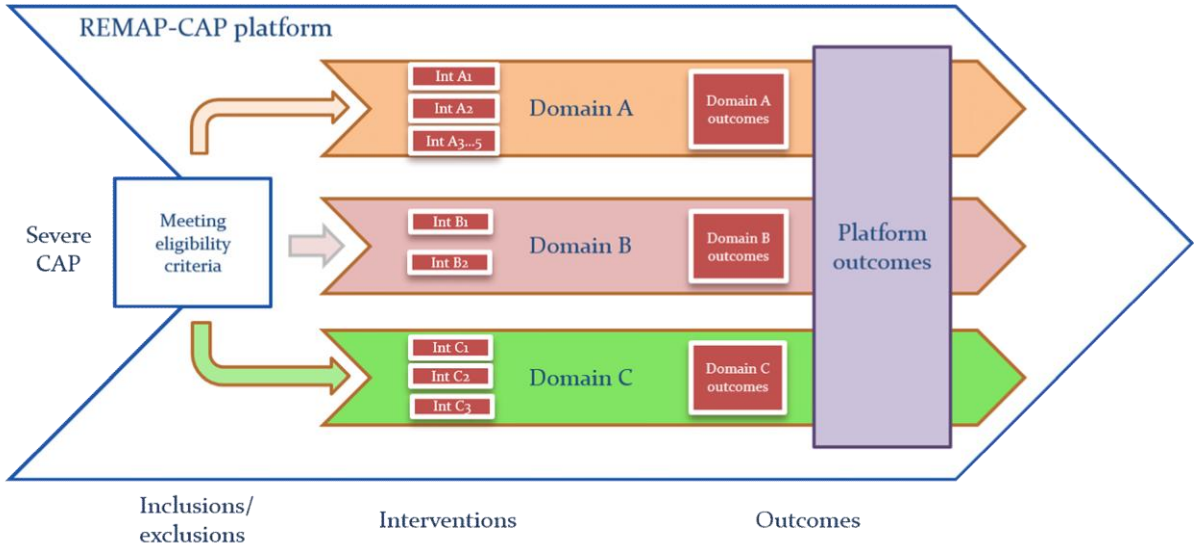
A pandemic will likely result in a large number of affected persons with cases occurring over a short period of time, perhaps as short as a few months. Conventional clinical trials that utilize frequentist statistical techniques require a fixed sample size with limited capacity to analyze the results of the trial until recruitment is completed. The setting of the sample size requires an estimate of the size of the treatment effect and it is known that the assumptions that are made in setting the size of the treatment effect are often incorrect[13,14]. A frequentist trial that over-estimates the size of the treatment effect may conclude without reaching a valid conclusion, whereas one that under-estimates the size of the treatment effect is delayed in providing time-critical information that the treatment is even more effective than estimated.

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

6.2.5.2 *Multifactorial design and evaluation of interactions*

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

Figure 1: The multifactorial structure of REMAP-CAP



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

6.2.6. Setting of research priorities

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

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

REMAP-CAP is not able to meet all of these requirements but is well suited to evaluate the effectiveness of antiviral therapies active against influenza, immune modulatory strategies and

different aspects of supportive care[15]. Identical or similar research questions would exist for any pandemic caused by an organism that was not influenza and REMAP-CAP has also similar capabilities in this scenario.

6.3. WHO endorsement

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

7. ADAPTATION OF REMAP-CAP DURING A PANDEMIC

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

7.1. Objectives

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

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

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

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

such as access to single rooms to achieve objectives related to infection control and prevention. This can influence both admission as well as discharge practices. Thirdly, the threshold at which support for failed organs is provided may be influenced by infection control practices. For example, some forms of respiratory support may be withheld because of concerns related to the risk that staff who are caring for patients may acquire the infection.

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

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

7.3. Eligibility criteria

Platform-level eligibility criteria may be modified if necessary to accommodate a published case definition, to align with criteria specified in guidelines, such as the ATS/IDSA guidelines on CAP[16], or to accommodate necessary modifications to the online eligibility system used for enrollment. In previous epidemics of community-based infection, nosocomial acquisition has been well described. Relaxation of the requirement for community acquisition or organ failure criteria or both may be appropriate. In this regard, Version 2.0 of this Appendix modifies the organ failure support criteria so that these no longer apply as a platform-level inclusion criteria, permitting the enrollment of patients into the platform who are admitted to hospital or an ICU, either with or without organ failure support criteria. In association with the removal of the organ failure requirement, the requirement for a patient to meet criteria for pneumonia may be replaced with a requirement for acute illness due to suspected or proven pandemic infection. All changes to eligibility criteria would apply only to patients in the pandemic stratum (see section 7.4).

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

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

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

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

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

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

7.4. Pandemic stratum

7.4.1. Introduction

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

7.4.2. Activation and deactivation of the PAtC and PISOP stratum

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

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

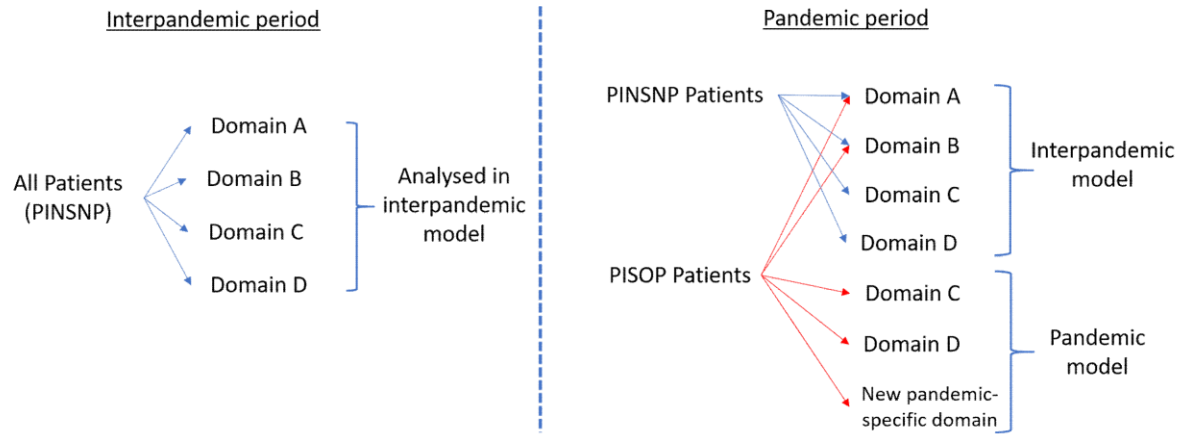
The PAtC is activated and deactivated for a site at the same time as the PISOP stratum is opened and closed. If a pandemic commences prior to ethical and governance approval of the PAtC, the PISOP stratum can be activated using approvals for the Core Protocol, and the PAtC would be activated as soon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

7.5. The pandemic statistical model

7.5.1. Introduction

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

Figure 2: Diagram of the interpandemic and pandemic models



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

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

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

- only those domains that are relevant to the pandemic are included within the pandemic model.

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

7.5.2. Pre-specification of trial parameter options

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

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

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

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

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

7.5.4. Strata within the PISOP stratum

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

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

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

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

7.5.5. States within the PISOP stratum

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

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

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

- Provision of invasive mechanical ventilation

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

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

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

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

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

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

weighting of priors will be done by statisticians who are separate to the SAC and blind to results from adaptive analyses. With regard to selection of domains and the use of informative priors, the following principles will be applied.

7.5.6.1 *Non-influenza pandemic organism*

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

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

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

7.5.6.2 *Influenza pandemic*

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

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

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

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

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

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

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

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

7.6. Endpoints

7.6.1. Pandemic primary endpoint

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

If appropriate, based on an understanding of clinical and biological factors, as well as operational factors, an alternative pandemic primary end-point may be specified at the time of activation of the PAtC or at any time prior to the first interim analysis using the pandemic statistical model. Other possible primary end-points include days alive and outside the ICU with alternative durations of follow up or the use of an alternative composite based on admission to ICU. The pandemic primary endpoint will be used for the adaptive analyses that inform the RAR and for Statistical Triggers.

If the primary end-point includes a time-based outcome measure, assignment to one or more domains will occur at different time-points if the patient receives assignments in one or more domains while in the Moderate State and one or more domains in the Severe State. The commencement of the period of observation commences at the time of assignment, which can lead to the same patient having different values for different domains, as determined by the state in which enrollment occurred. This can be accommodated because there are separate statistical models for each state. Where a patient is eligible for two or more domains in a state, assignment

can only occur at a single time-point, i.e. it is not possible to have more than one time of assignment for different domains in the same state.

7.6.2. Secondary endpoints

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

7.7. Principles of the statistical analysis

7.7.1. Adaptive analyses

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

7.7.2. Response adaptive randomization

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

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

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

7.7.3. Unit-of-analysis

7.7.3.1 *Application of additional strata*

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

7.7.3.2 *Application of state*

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

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

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

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

7.7.3.3 *Analyses for combinations of therapies*

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

7.7.4. Thresholds for statistical triggers

7.7.4.1 *Introduction*

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

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

The default thresholds are outlined in the following sections.

7.7.4.2 *Intervention Superiority Statistical Trigger*

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

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

7.7.4.3 *Intervention Efficacy Statistical Trigger*

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

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

7.7.4.4 *Intervention Inferiority Statistical Trigger*

At any adaptive analysis, if a single intervention has less than a 0.01 posterior probability of being a member of the optimal regimen, for a unit-of-analysis, then that intervention will be deemed as

being inferior to other interventions in the domain for that target population. The 0.01 threshold is reduced as a function of how many units-of-analysis are available for the inferiority calculation (divided by the number of units minus 1). An asymmetrical inferiority statistical trigger may be set, particularly if an active intervention was being evaluated against an intervention that specifies no active treatment in that domain.

7.7.4.5 *Equivalence and futility*

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

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

7.7.4.6 *Statistical thresholds for early phase interventions*

During the pandemic there may be need to test multiple candidate interventions that are at an early phase of development, identifying those interventions that are most promising to be retained within the platform. Such interventions may be evaluated after a fixed recruitment against a 'stop-go' criteria for retention, and expansion, within the platform. The default threshold for retention and expansion of an intervention will be a posterior probability of 0.5 or more that there is at least a 30% benefit in odds ratio.

7.7.5. Actions when a Statistical Trigger is achieved

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

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

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

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

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

7.7.8. Domains with their own statistical model

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

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

8.1. Decision to activate pandemic stratum

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

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

8.2. Safety Monitoring and Reporting

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

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

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

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

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

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

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

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

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

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

- The relevant competent authorities and ethics committees should be notified of the SUSAR by the Sponsor or designee in each region.
- A SUSAR that results in death or is life-threatening, should be reported to the aforementioned bodies within 7 days of the Sponsor (or designee) becoming aware of the event. Further relevant information should be sought and a follow-up report completed as soon as possible and submitted within 8 additional days.

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

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

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

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

8.3. Data collection and management

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

8.4. Role of the DSMB

In a pandemic the role of the DSMB is modified, taking into account the public health importance of clinical evidence during a pandemic. In meeting the requirements of their Charter during a pandemic the DSMB should consider issues of public health in addition to the well-being of participants and the scientific integrity of the platform. The in-principle views of the DSMB may be obtained by the ITSC with regard to the setting of modified thresholds for statistical triggers.

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

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

8.5. Communication of trial results

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

8.6. Funding of the trial

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

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

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

8.7. Monitoring

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

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

PANDEMIC APPENDIX TO THE CORE PROTOCOL

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

Summary

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

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

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

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

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

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

Lay description

REMAP-CAP is a global trial examining the best treatments for community-acquired pneumonia. In the setting of a pandemic that causes pneumonia, some key aspects of the study will be changed to

integrate new interventions into the trial, evaluate existing interventions within the trial specifically in patients with pandemic infection, alter trial governance, and provide time-critical data for public health. This will allow the platform to identify which treatments work best for patients during a pandemic.

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1. ABBREVIATIONS

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

2. PROTOCOL APPENDIX STRUCTURE

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

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

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

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

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

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

3. PANDEMIC APPENDIX TO THE CORE PROTOCOL VERSION

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

3.1. Version History

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

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

4. PANDEMIC APPENDIX TO THE CORE PROTOCOL GOVERNANCE

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

4.1. Pandemic Working Group

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

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

Members: Prof. Derek Angus

Prof. Yaseen Arabi

Prof. Richard Beasley

A/Prof. Scott Berry

Prof. Frank Brunkhorst

Dr. Lennie Derde

Dr. Robert Fowler

Prof. Anthony Gordon

Mr. Cameron Green

Dr. Ed Litton

Prof. John Marshall

Dr. Colin McArthur

Dr. Srinivas Murthy

Prof. Alistair Nichol

Ms. Jane Parker

Prof. Kathy Rowan

Prof. Tim Uyeki

Prof. Steve Webb

4.2. Contact Details

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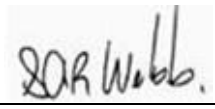
5. PANDEMIC WORKING GROUP AUTHORISATION

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

Chair  Date 12th February, 2020

Steve Webb

6. BACKGROUND AND RATIONALE

6.1. Introduction

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

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

One of the challenges associated with planning clinical trials during a pandemic is that the precise nature of the infecting organism, clinical consequences, and suitable interventions (particularly those that are pathogen-specific) cannot be reliably known in advance. Nevertheless, a range of scenarios can be anticipated and used to provide direction and guidance regarding the most appropriate research response.

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

6.2. Pandemic research preparedness

6.2.1. Introduction

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

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

6.2.2. Pre-planned

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

6.2.3. Pre-approved

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

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

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

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

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

6.2.4. Practiced

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

6.2.5. Implications of REMAP design during a pandemic

6.2.5.1. *Time-critical generation of evidence*

A pandemic will likely result in a large number of affected persons with cases occurring over a short period of time, perhaps as short as a few months. Conventional clinical trials that utilize frequentist statistical techniques require a fixed sample size with limited capacity to analyze the results of the trial until recruitment is completed. The setting of the sample size requires an estimate of the size of the treatment effect and it is known that the assumptions that are made in setting the size of the treatment effect are often incorrect[13,14]. A frequentist trial that over-estimates the size of the treatment effect may conclude without reaching a valid conclusion, whereas one that under-estimates the size of the treatment effect is delayed in providing time-critical information that the treatment is even more effective than estimated.

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

6.2.5.2. *Multifactorial design and evaluation of interactions*

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

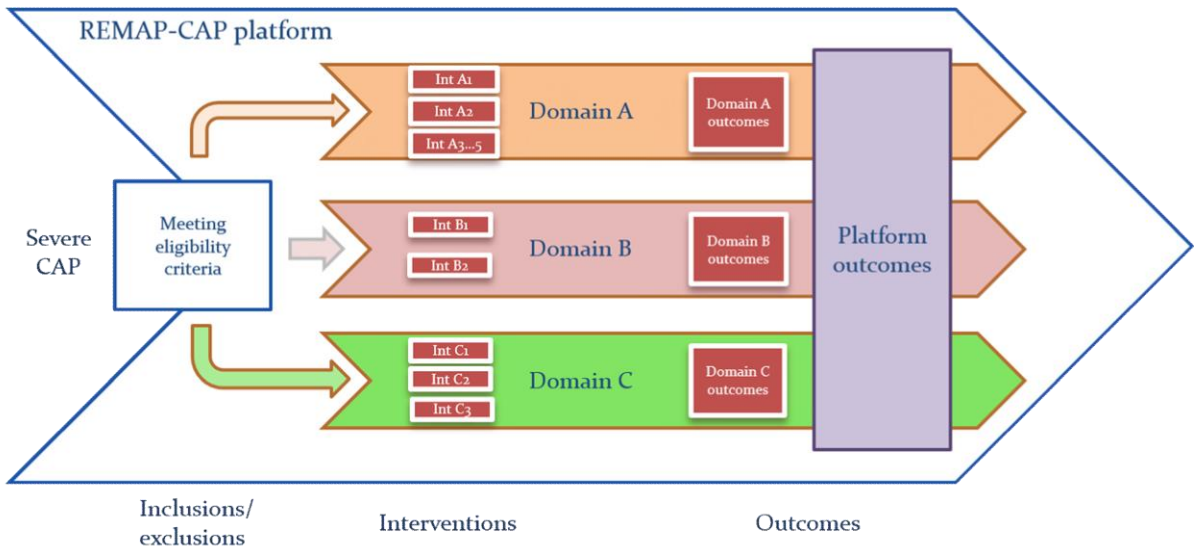


Figure 1. The multifactorial structure of REMAP-CAP

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

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

6.2.6. Setting of research priorities

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

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

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

6.3. WHO endorsement

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

7. ADAPTATION OF REMAP-CAP DURING A PANDEMIC

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

Core Protocol remain active. Activation of the PAtC will be advised to the DSMB with specification of the selected operational characteristics.

7.1. Study setting: definition of an ICU

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

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

7.2. Eligibility criteria

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

7.3. Pandemic stratum

7.3.1. Introduction

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

7.3.2. Activation and deactivation of the PAtC and PISOP stratum

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

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

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

7.4. The pandemic statistical model

7.4.1. Introduction

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

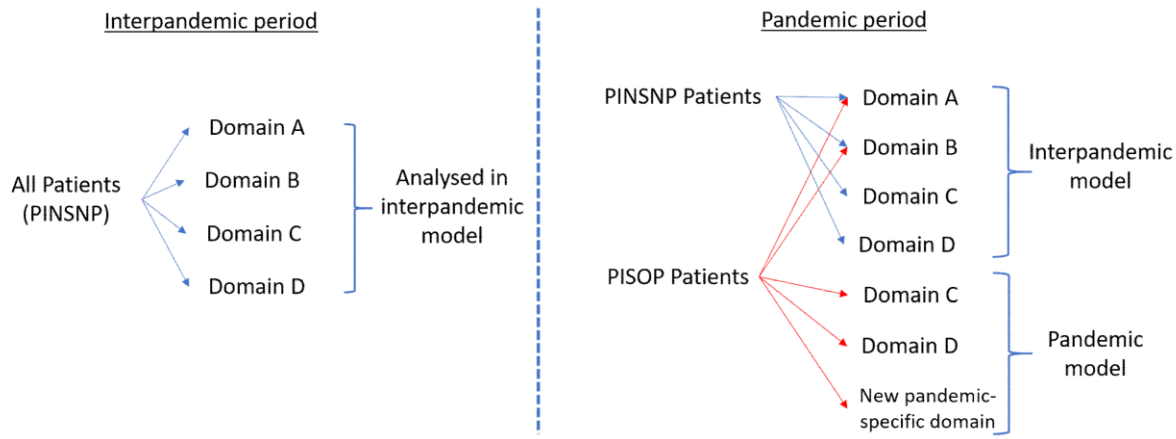


Figure 2. Diagram of the interpandemic and pandemic models

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

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

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

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

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

7.4.2. Pre-specification of trial parameter options

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

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

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

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

baseline. Patients in whom influenza was suspected, but the results of strain-specific diagnostic tests were not available at the time of assessment of eligibility, will be allocated to the PISOP stratum at sites where the stratum is active.

7.4.4. Strata within the PISOP stratum

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

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

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

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

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

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

7.4.5.1. *Non-influenza pandemic organism*

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

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

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

7.4.5.2. *Influenza pandemic*

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

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

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

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

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

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

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

7.5. Endpoints

7.5.1. Pandemic primary endpoint

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

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

7.5.2. Secondary endpoints

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

7.6. Principles of the statistical analysis

7.6.1. Adaptive analyses

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

7.6.2. Response adaptive randomization

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

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

7.6.3. Thresholds for statistical triggers

7.6.3.1. *Introduction*

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

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

The default thresholds are outlined in the following sections.

7.6.3.2. *Intervention Superiority Statistical Trigger*

At any adaptive analysis, if a single intervention has at least a 0.95 posterior probability of being a member of the optimal regimen, for that unit-of-analysis, then that intervention will be deemed as being superior to all other interventions in that domain in that target population.

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

7.6.3.3. *Intervention Inferiority Statistical Trigger*

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

7.6.3.4. *Equivalence*

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

7.6.4. Actions when a Statistical Trigger is achieved

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

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

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

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

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

7.6.7. Domains with their own statistical model

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

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

8.1. Decision to activate pandemic stratum

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

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

8.2. Data collection and management

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

8.3. Role of the DSMB

In a pandemic the role of the DSMB is modified, taking into account the public health importance of clinical evidence during a pandemic. In meeting the requirements of their Charter during a pandemic the DSMB should consider issues of public health in addition to the well-being of participants and the scientific integrity of the platform. The in-principle views of the DSMB may be obtained by the ITSC with regard to the setting of modified thresholds for statistical triggers.

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

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

8.4. Communication of trial results

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

8.5. Funding of the trial

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

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

8.6. Monitoring

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

monitored as per the non-pandemic monitoring plan will be acknowledged in the public reporting of Platform Conclusions.

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

REMAP-CAP Core Protocol Version 3 dated 10 July 2019

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1. ABBREVIATIONS AND GLOSSARY

1.1. Abbreviations

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

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

1.2. Glossary

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

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

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

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

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

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

Intervention is a treatment option that is subject to variation in clinical practice (comparative effectiveness intervention) or has been proposed for introduction into clinical practice (experimental intervention) and also is being subjected to experimental manipulation within the design of a REMAP. For the purposes of the REMAP an intervention can include an option in which no treatment is provided.

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

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

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

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

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

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

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

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

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

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

State a state is a set of mutually exclusive and exhaustive categories, defined by characteristics of a patient within the REMAP, that are capable of changing over time for a single patient at different time-points during the patient's participation in the REMAP (i.e. they can be dynamic). States are

used to define eligibility for domains and this can include defining eligibility that occurs after the time of enrollment. State is used as an additive covariate within the Bayesian statistical model.

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

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

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

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

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

2. INTRODUCTION

2.1. Synopsis

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

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

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

In a conventional trial, enrollment continues until a pre-specified sample size is obtained, at which time enrollment ceases, and the trial data are analyzed to obtain a result. The possible results are that a difference is detected or no that no difference is detected. However, when the conclusion of the statistical test is “no difference”, this could be that there truly is no meaningful difference, or that the result is indeterminate (i.e. it is possible that if more patients had been enrolled a clinically relevant difference may have been detected).

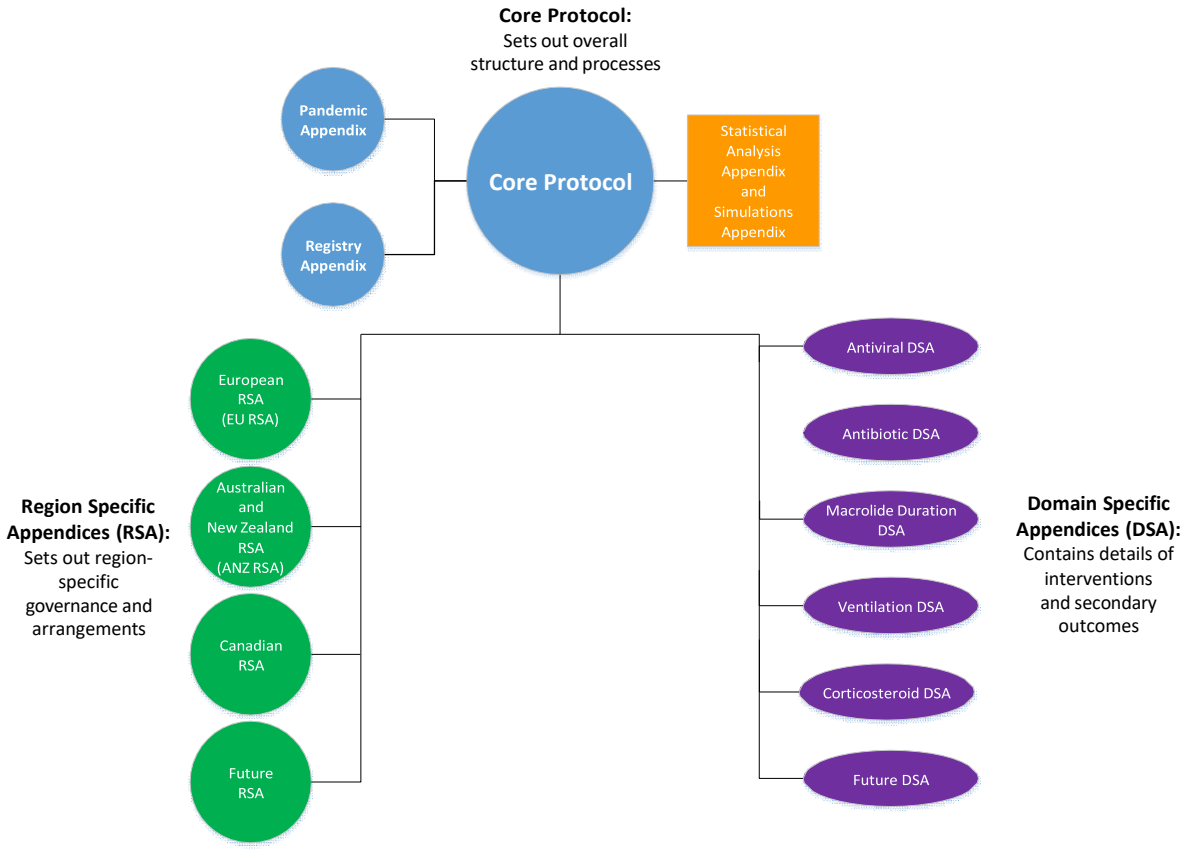
In comparison to a conventional trial, this REMAP uses an adaptive design, relying on pre-specified criteria for adaptation, that: avoids indeterminate results; concludes an answer to a question when sufficient data have accrued (not when a pre-specified sample is reached); evaluates the effect of treatment options in pre-defined subgroups of patients (termed strata); utilizes already accrued data to increase the likelihood that patients within the trial are randomized to treatments that are more likely to be beneficial; is multifactorial, evaluating multiple questions simultaneously; is intended to be perpetual (or at least open-ended), substituting new questions in series as initial questions are answered; and can evaluate the interaction between interventions in different domains. Bayesian

statistical methods will be used to establish the superiority, inferiority, or equivalence of interventions within a domain. Interventions determined to be superior will be incorporated into standard care within the ongoing REMAP. Interventions determined to be inferior will be discontinued. While a limited number of initial treatments and treatment domains have been specified at initiation, it is planned that this REMAP will continue to evaluate other treatments in the future. Furthermore, in the event of a future epidemic of a novel or re-emerging respiratory pathogen (which typically present as severe CAP), this REMAP would be adapted to evaluate the most relevant treatment options. Each new treatment that is proposed to be evaluated within the REMAP will be submitted for prospective ethical review.

2.2. Protocol Structure

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

Figure 1: Protocol Structure



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

2.2.1. Core Protocol

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

- The background and rationale for studying severe CAP
- The background and rationale for the research approach
- The trial design including study setting, the criteria that define eligibility for the REMAP, treatment allocation, strata (see glossary for a definition of this term), principles of application of trial interventions, trial endpoints, methods to control bias, principles of statistical analysis, and criteria for termination of the trial
- The trial conduct including recruitment methods, time-lines for sites, delivery of trial interventions, data collection, data management, and management of participant safety
- The overall / international trial governance structures and ethical considerations

2.2.2. Domain-Specific Appendices

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

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

2.2.3. Region-Specific Appendices

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

- the definition of the region
- the organization of trial management and administration within the region
- information about availability of domains and interventions
- data management and randomization procedures
- ethical issues that are specific to a region.

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

2.2.4. Statistical Analysis Appendix and Simulations Appendix

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

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

2.2.5. Pandemic Appendix

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

- The background and rationale for studying severe CAP caused by a pandemic
- The procedure that will determine activation of the Pandemic Appendix

- How the trial design adapts during a pandemic, including changes to one or more of study setting, treatment allocation, strata, trial endpoints, and principles of statistical analysis that will operate during a pandemic, as well as how the platform resets following a resolution of a pandemic

2.2.6. Version History

Version 1: Approved by the ITSC on 20 November 2016

Version 1.1: Approved by the ITSC on 10 April 2017

Version 2: Approved by the ITSC on 12 December 2017

Version 2.1: Approved by the ITSC on 26 March 2019

Version 3: Approved by the ITSC on 10 July 2019

2.3. Lay Description

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

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

In a conventional clinical trial, selected patients are allocated to receive one treatment from a short list of alternatives, typically one or two. This trial differs from conventional clinical trials by being randomized, embedded, multifactorial, adaptive, and a platform (a “REMAP”). (Angus, 2015) In this type of trial, we will test many alternative treatments (“multifactorial”) by replacing *ad hoc* treatment decisions with “randomized” treatment allocation (“embedded”). Although treatments will be allocated randomly, patients will preferentially be allocated to treatments that statistical models derived from trial data indicate are more likely to be the most effective treatments. The trial will “adapt” in multiple ways including answering questions as soon as sufficient data have accrued to answer the question of the effectiveness of each treatment and by changing the treatments that are being tested over-time so as to progressively determine the best package of treatments for pre-defined categories of patients with severe pneumonia. Once a treatment is identified as being optimal it is subsequently routinely provided to all eligible patients within the REMAP. The REMAP is also designed to adapt to test relevant interventions during a pandemic caused by lung infection that results in severe pneumonia.

2.4. Trial registration

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

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

2.5. Funding of the trial

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

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

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

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

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

Funding is being sought for other regions and countries.

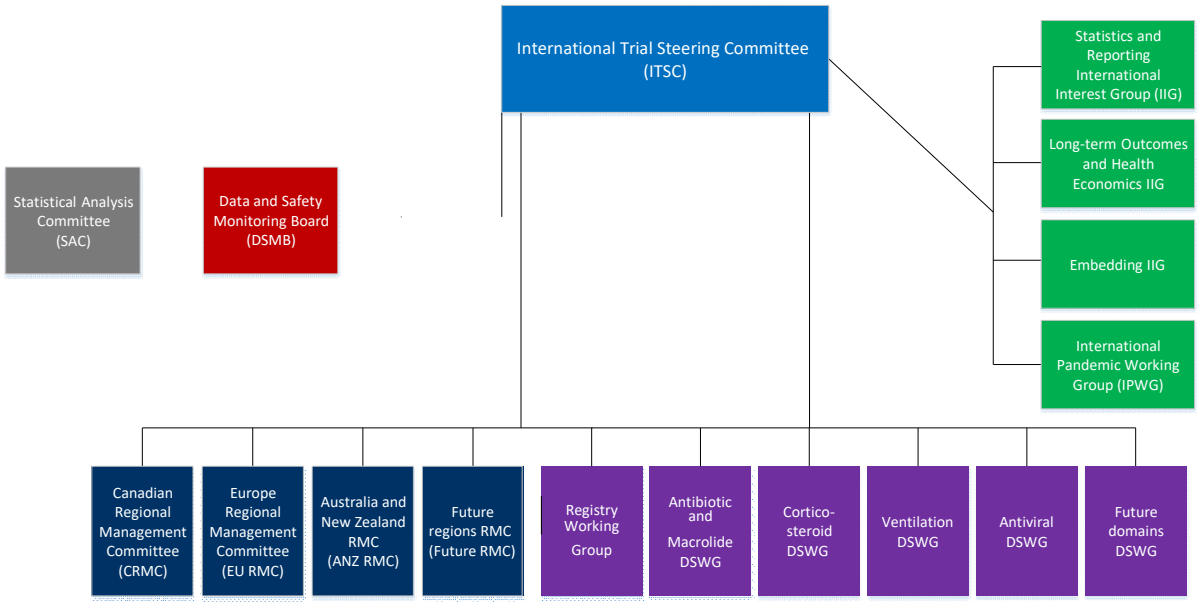
3. STUDY ADMINISTRATION STRUCTURE

The study administration structure is designed to provide appropriate management of all aspects of the study, taking into account multiple factors including representation from regions that are participating in the trial, availability of skills and expertise related to trial conduct and statistical analysis, and content knowledge regarding pneumonia and the interventions that are being evaluated. The administration model is designed to provide effective operational and strategic management of the REMAP that operates in multiple regions, is supported by multiple funding bodies and sponsors, and will evolve with addition of further regions and funding bodies as well as changes in the domains and interventions that are being evaluated.

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

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

Figure 2: REMAP-CAP Organization Chart



3.1. International Trial Steering Committee

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

3.1.1. Responsibilities

The responsibilities of the ITSC are:

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

- obtaining funding for the REMAP
- determine the strategic direction of the REMAP

3.1.2. Members

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

Professor Derek Angus, Chair Corticosteroid DSWG and Foundation member

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

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

Ms. Zahra Bhimani, Canadian Project Manager

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

Professor Frank Brunkhorst, member EU RMC

Professor Allen Cheng, Chair Antibiotic Domain and Macrolide Duration DSWG

Professor Menno De Jong, member Antiviral DSWG

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

Professor Herman Goossens, Principal Investigator for PREPARE

Professor Anthony Gordon, member EU RMC

Mr. Cameron Green, Global Project Manager

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

Dr. Ed Litton, member Australian and New Zealand (ANZ) RMC

Professor John Marshall, Canadian Executive Director

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

Dr. Shay McGuinness, Chair ANZ RMC

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

Professor Alistair Nichol, Chair Ventilation DSWG

Associate Professor Rachael Parke, member ANZ RMC

Ms. Jane Parker, Australian Project Manager

Professor Kathy Rowan, member EU RMC

Ms. Anne Turner, New Zealand Project Manager

Professor Steve Webb, ANZ Executive Director and Foundation member

3.1.3. Contact Details

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

3.2. Regional Management Committees

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

3.2.1. Responsibilities

The responsibilities of each RMC are:

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

3.3. Domain-Specific Working Groups

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

3.3.1. Responsibilities

The responsibilities of each DSWG are:

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

3.3.2. Members

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

3.4. International Interest Groups

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

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

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

3.4.1. Role

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

3.5. Sponsors

In relation to recruitment that occurs in:

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

3.5.1. Role of sponsor

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

3.5.2. Insurance

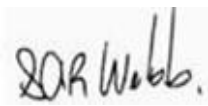
The provision of insurance is specified in each RSA.

4. INTERNATIONAL TRIAL STEERING COMMITTEE AUTHORIZATION

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

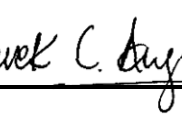
EU Executive Director
Marc Bonten

ANZ Executive Director
Steve Webb



ANZ Deputy Director
Colin McArthur

ITSC Member
Derek Angus



ITSC Member
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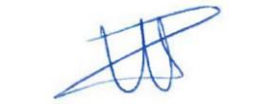

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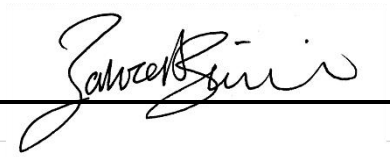

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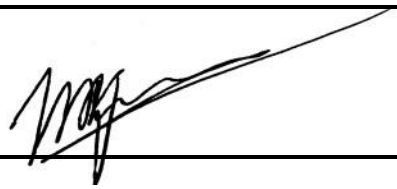
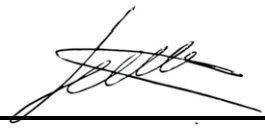
ITSC Member
Frank Brunkhorst

ITSC Member
Allen Cheng



ITSC Member
Menno De Jong



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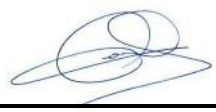

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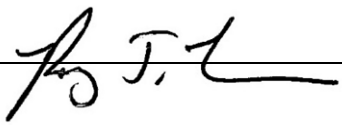

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ITSC Member
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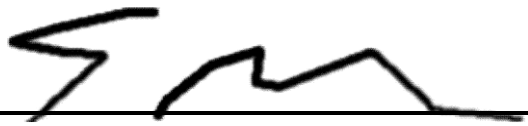
John Marshall

ITSC Member
Shay McGuinness



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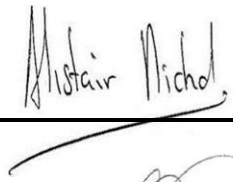

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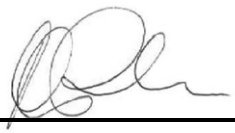
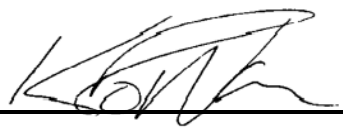


ITSC Member
Rachael Parke

ITSC Member
Jane Parker



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ITSC Member
Anne Turner

5. BACKGROUND & RATIONALE

5.1. Severe Community-Acquired Pneumonia

5.1.1. Introduction

This section, within the Core Protocol, provides background on the epidemiology, causes, treatment categories, and evidence base for the management of patients with severe community pneumonia.

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

5.1.2. Epidemiology

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

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

5.1.3. Standard care for patients with severe CAP

All patients admitted to an ICU with severe CAP will receive multiple different component therapies and many of these therapies will be administered concurrently. These therapies can be grouped into the following categories: treatment of the underlying infection (including antibacterial and antiviral agents); the optional use of agents, such as corticosteroids, that modulate the host immune response to infection; and multiple supportive therapies that are used to manage organ systems that have failed or prevent complications of critical illness and its treatment (Table 1).

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

Examples of commonly used therapies that support failed organ systems or prevent the complications of critical illness and its treatment include oxygen therapy, invasive and non-invasive

mechanical ventilation, intravenous fluid resuscitation, vasoactive drugs, dialysis, provision of nutrition, sedation, physiotherapy including mobilization, diuretic medications, suppression of gastric acid production, and mechanical or pharmacological interventions to prevent venous thromboembolism. The exact combination of supportive therapies is influenced by the spectrum of organ failures that occurs in any individual patient. (Dellinger et al., 2013)

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

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

5.1.4. Treatment guidelines

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

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

5.1.5. Variation in care and compliance with guidelines

Several observational studies report substantial variation in care with, for example, compliance with administration of antibiotics recommended by guidelines occurring in between 40% and 75% of

patients. (Bodi et al., 2005, Frei et al., 2010, Lee et al., 2014, Shorr et al., 2006) These and other studies also report better clinical outcomes for patients who received antibiotics that were recommended by guidelines. (McCabe et al., 2009, Mortensen et al., 2004, Mortensen et al., 2005) However, it remains unclear if adherence to guideline recommendations is due to a direct causal link, or whether it is a surrogate for better quality care generally. There is also widely reported variation in compliance with many supportive therapies for patients with severe CAP, such as use of low tidal volume ventilation, type of resuscitation fluid, and thresholds for the administration of transfusion for anemia. (Bellani et al., 2016, Finfer et al., 2010, Blood Observational Study Investigators of Anzics-Clinical Trials Group et al., 2010, Cecconi et al., 2015)

5.1.6. An unmet need for better evidence

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

5.2. Influenza pandemics and emerging pathogens

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

5.3. Randomized Embedded Multifactorial Adaptive Platform Trials

5.3.1. Generating clinical evidence

Angus has noted several problems encountered when generating robust clinical evidence, including barriers to conducting clinical trials, the generalizability of data from populations that are too broad or too narrow, the issue of equipoise especially when comparing different types of existing care, and the delay in translating results into clinical practice. (Angus, 2015) A REMAP provides a strategy to address many of these problems by gaining economies of scale from a common platform, which allows for broad enrollment but retaining the ability to examine for heterogeneity of treatment effects between defined subgroups. A REMAP focuses predominantly on the evaluation of treatment options for the disease of interest that are variations within the spectrum of standard care (although testing of novel or experimental therapies is not precluded) and does so by embedding the trial

within routine healthcare delivery. In this regard the REMAP seeks to replace random variation in treatment with randomized variation in treatment allowing causal inference to be generated about the comparative effectiveness of different existing treatment options. The use of RAR, which allows the allocation ratios to change over time based on accruing outcomes data, maximizes the chance of good outcomes for trial participants. The embedding of such a platform within the day-to-day activities of ICUs facilitates the translation of outcomes to clinical practice as a "self-learning" system. As such, it also functions as an embedded and automated continuous quality-improvement program. A final advantage of a REMAP for pneumonia is the ability to rapidly adapt to generate evidence if new respiratory pathogens emerge, avoiding the inevitable delays associated with conventional trials in an outbreak of a new infectious diseases. (Burns et al., 2011)

5.3.2. Underlying Principles of the Study Design

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

A conventional RCT (i.e. a non-platform trial) makes a wide range of assumptions at the time of design. These assumptions include the plausible size of the treatment effect, the incidence of the primary outcome, the planned sample size, the (typically, small number of) treatments to be tested, and that treatment effects are not influenced by concomitant treatment options. These assumptions are held constant until the trial completes recruitment and is analyzed. (Barker et al., 2009, Berry, 2012, Connor et al., 2013) Participants who are enrolled in a conventional RCT are not able to benefit from knowledge accrued by the trial because no results are made available until the trial completes. A REMAP uses five approaches to minimize the impact of assumptions on trial efficiency and also maximizes the benefit of participation for individuals who are enrolled in the trial. (Angus, 2015, Berry et al., 2015, Aikman et al., 2013, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016)

These design features are:

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

This creates a 'perpetual trial' with no pre-defined sample size, the objective of which is to define and continuously update best treatment over the life-time of the REMAP. The design aspects, including the risk of type I and type II error, are optimized prior to the commencement of the trial by

the conduct of extensive pre-trial Monte Carlo simulations, modification of the trial design, and re-simulation in an iterative manner. The methods related to the application of the design features and the statistical analysis of this trial are outlined in the methods section of the protocol (Section 7). The following sections describe the background, rationale, and potential advantages of each of the design features of a REMAP (Section 5.3.4).

5.3.3. Nomenclature

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

5.3.4. Randomization and Response Adaptive Randomization

The study will randomly allocate participants to one or more interventions, with each intervention nested within a domain. In this regard, a platform trial is no different to other forms of RCT in that randomization provides the basis for causal inference. However, unlike a conventional RCT, the proportion of participants who are randomized to each available intervention within a domain will not be fixed. Rather, the trial will incorporate RAR. RAR utilizes random allocation with a weighted probability for each intervention, with the weighted probability being proportional to the extent to which similar participants recruited earlier in the trial benefited or not from each particular intervention. (Angus, 2015, Berry, 2012, Connor et al., 2013, Aikman et al., 2013, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016) RAR will result in participants in each particular stratum being randomized with greater probability to interventions that are performing better within that stratum. At the initiation of a new domain or when a new intervention is added to a domain the randomization proportion of all new interventions is balanced and only changes, with the application of RAR, that takes into account uncertainty about treatment effect so as to avoid excessive variability in proportions generated by RAR until sufficient sample size has accrued.

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

There are potential disadvantages associated with RAR. It is intended that participating sites and trial investigators will be blind to the RAR proportions. One disadvantage is that, for interventions that

are provided without blinding, the treating clinicians may be able to draw inference about the RAR proportions and, as a consequence, draw inference about the interim standing of interventions that are being tested in the REMAP. This could have adverse consequences including that clinicians are influenced to not enroll participants within a domain but rather directly prescribe the treatment that they believe to be doing better outside the trial. However, a number of factors mitigate this potential concern. First, it can be difficult to distinguish between patterns of sequential allocation status that are derived from fixed versus RAR. Second, extreme proportions will not be used (except where a Statistical Trigger but not a Platform Conclusion has been reached, see later). Finally, for many conditions, team-based management means that an individual clinician will directly observe only a small proportion of all participants enrolled within the trial at each participating site. Another disadvantage of RAR is that, under certain allocation rules, statistical power can be reduced. This concern is mitigated via pre-trial simulation to test the effects of different allocation rules. Furthermore, a REMAP that comprises multiple domains with multiple interventions within each domain will generally have higher, rather than lower, power as a consequence of the use of RAR. Finally, by deploying RAR rules to minimize the odds of exposure to inferior interventions, the design is intended to motivate embedding in clinical practice, thereby resulting in more rapid recruitment.

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

5.3.5. Embedding

A trial is most efficient when all eligible participants are recognized and enrolled. Achieving universal enrollment of eligible participants increases the speed with which new knowledge is generated, maximizes internal and external validity, and minimizes operational complexity at the bedside (there is no need to distinguish between trial and non-trial patients, because all patients are trial patients). A number of strategies will be utilized to very tightly “nest” or embed trial processes in daily clinical care operations. The effectiveness of strategies to achieve embedding will be evaluated, updated, and shared with sites, taking into account different clinical processes at different sites. Wherever possible trial treatment allocations will be integrated with electronic customized order sets, produced at the point of delivery of care that also includes each site’s local care standards for concomitant therapies. This allows clinical staff to follow their typical workflow using protocolized order sheets to govern many aspects of patient care and serves to enhance compliance with the interventions allocated by the trial. The intention of embedding is that recruitment occurs 24/7 and is dependent on the usual medical staff who are responsible for patient care. Where possible electronic health records will be utilized to enhance screening and recruitment and specify the ‘order set’ for participants, including those orders that are determined by allocation status within the REMAP. While screening and recruitment for a REMAP can be conducted by research staff, it is not intended that recruitment should be dependent on research staff, particularly as such staff are typically only present during office hours. In addition to the facilitation of recruitment and high-fidelity delivery of the intervention, a further advantage is that the results of the trial can be translated rapidly within the ongoing REMAP so that all appropriate participants receive a treatment declared to be superior with continued allocation to that treatment option within the REMAP used to ensure implementation.

5.3.6. Multifactorial

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

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

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

5.3.7. Adaptive

5.3.7.1. *Frequent adaptive analyses*

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

5.3.7.2. *Analysis of data to reach conclusions*

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

The occurrence of a Statistical Trigger is communicated immediately to the trial DSMB by the SAC. The DSMB has primary responsibility for determining if a Statistical Trigger should lead to a Platform Conclusion. The declaration of a Platform Conclusion results in the removal of inferior intervention

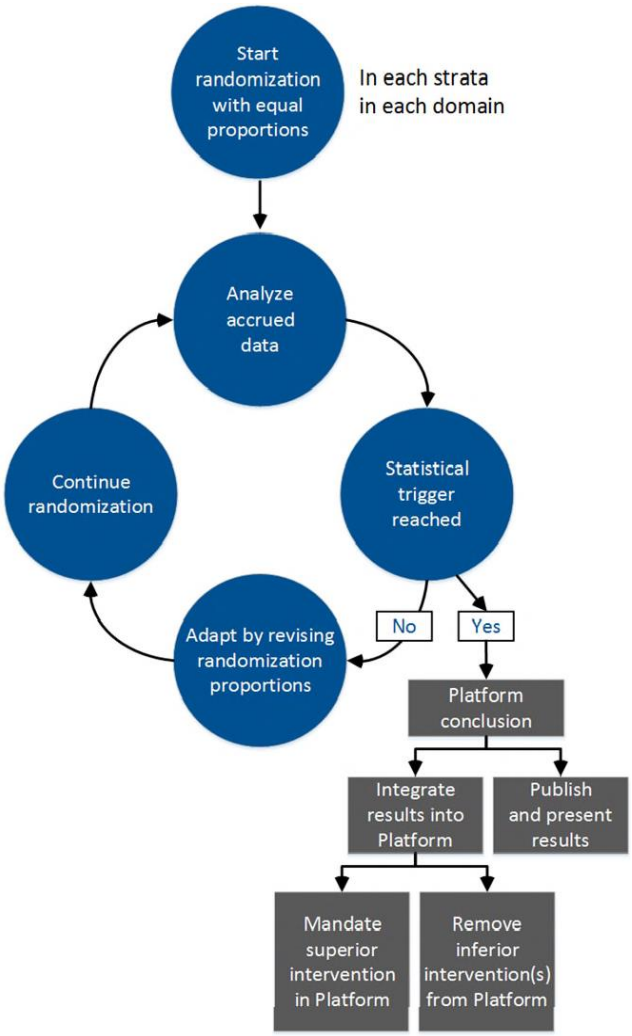
from randomization options or removal of all other interventions if an intervention is declared as superior. A Platform Conclusion will be communicated to the ITSC who have responsibility for immediate dissemination of the result by presentation and publication of the result.

The algorithm by which a Platform Conclusion is reached is different for Statistical Triggers of superiority or inferiority, compared to those triggers that arise because of equivalence. Where the Statistical Trigger is for superiority or inferiority, so long as the DSMB is satisfied that the Statistical Trigger has been met validly, the default position is that the DSMB will declare this result as a Platform Conclusion. The only exception to this situation is if there is a need to evaluate potential interactions between treatments in different domains. In this circumstance the randomization schedule will be adapted (all participants receive the superior intervention or randomization to one or more inferior interventions is removed) but Public Disclosure may be delayed until evaluation of the interaction is completed.

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

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

Figure 3: Adaptive Analyses



5.3.7.3. *Probability thresholds*

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

5.3.7.4. *Analysis within and between strata*

The frequent adaptive analyses will evaluate the primary endpoint, *within one or more stratum*. Where specified, the statistical models for each strata will be able to 'borrow' information from adjacent strata leading to the declaration of a Statistical Trigger in one, more, or all strata. The extent to which borrowing occurs is dependent on the pre-specified structure of the model and the degree of statistical congruence of treatment effect between stratum. Where treatment effects are divergent between stratum there is less 'borrowing'. The capacity to evaluate strata is particularly important for interventions that might plausibly have differential, including opposite, treatment effects in different strata. (Dellinger et al., 2013, Finfer et al., 2004, The Acute Respiratory Distress

Syndrome Network, 2000) In traditional trial designs, divergent treatment effects among sub-groups may cancel each other out and this is one plausible explanation for the trials that report no overall difference in outcome. It should be noted that strata can be different for different domains and that strata can be changed over time (in conjunction with amendment of the protocol).

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

5.3.7.5. *Frequency of adaptive analyses*

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

5.3.7.6. *Advantages of adaptive analysis*

The major advantage of this type of analysis approach is that a conclusion is reached when there is sufficient information to support the conclusion, rather than when enrollment reaches a predetermined sample size. This approach allows a result to be obtained as quickly as possible with appropriate sample size. It also avoids indeterminate results by continuing randomization until either superiority, inferiority, or equivalence is concluded. (Barker et al., 2009, Berry, 2012, Connor et al., 2013, Meurer et al., 2012, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016) An additional advantage is that dissemination of such results does not interrupt the conduct of the platform. In a single REMAP, there is no need for the "start-and-stop" periods that would typically occur under the alternative approach of multiple separate trials. These "downtime" periods can be quite extensive and carry a number of disadvantages. First, there is a lot of duplicative effort every time a near-identical treatment protocol goes through the appropriate development and approval processes. Second, clinical investigation units must maintain a certain infrastructure, and that infrastructure can be expensive to maintain during periods when participants are not being enrolled or expensive to recreate if the infrastructure degrades. Third, downtime is simply one more contributor to delay in the production of scientific knowledge. Participants at large benefit from earlier production of knowledge regardless of whether new information demonstrates a therapy is effective or ineffective. Finally, the inevitable start up delay before a trial can "go live" can wipe out any possibility of conducting effective research during time-critical situations such as a pandemic.

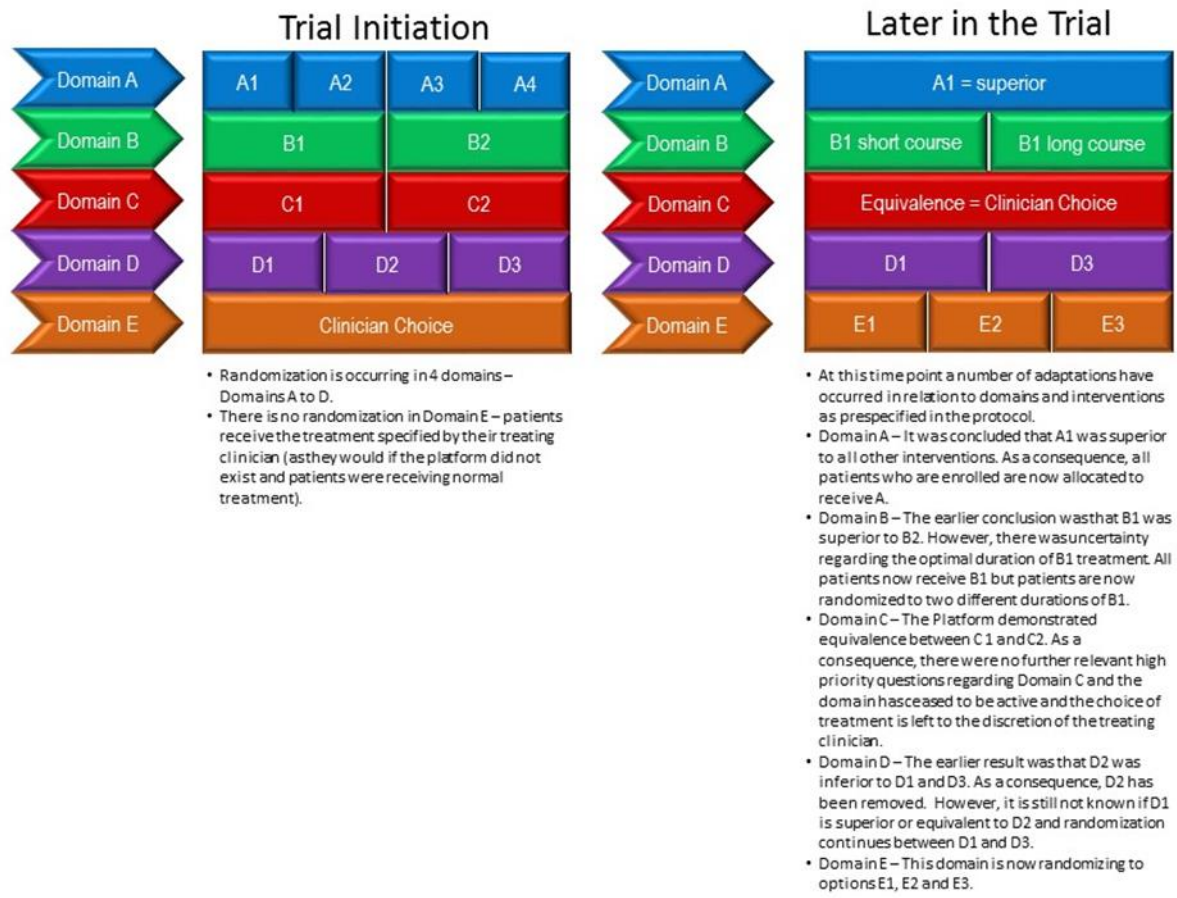
5.3.7.7. *Substitution of new domains and interventions within the REMAP*

It is intended that the REMAP will be 'perpetual'. In conjunction with a Platform Conclusion being reached, the ITSC takes responsibility for determining what new questions will be introduced to the

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

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

Figure 4: REMAP Evolution Over Time



- Randomization is occurring in 4 domains – Domains A to D.
- There is no randomization in Domain E – patients receive the treatment specified by their treating clinician (as they would if the platform did not exist and patients were receiving normal treatment).

- At this time point a number of adaptations have occurred in relation to domains and interventions as prespecified in the protocol.
- Domain A – It was concluded that A1 was superior to all other interventions. As a consequence, all patients who are enrolled are now allocated to receive A.
- Domain B – The earlier conclusion was that B1 was superior to B2. However, there was uncertainty regarding the optimal duration of B1 treatment. All patients now receive B1 but patients are now randomized to two different durations of B1.
- Domain C – The Platform demonstrated equivalence between C1 and C2. As a consequence, there were no further relevant high priority questions regarding Domain C and the domain has ceased to be active and the choice of treatment is left to the discretion of the treating clinician.
- Domain D – The earlier result was that D2 was inferior to D1 and D3. As a consequence, D2 has been removed. However, it is still not known if D1 is superior or equivalent to D2 and randomization continues between D1 and D3.
- Domain E – This domain is now randomizing to options E1, E2 and E3.

5.3.8. Nesting of the REMAP within a Registry

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

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

5.3.9. Platform

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

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

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

6. OBJECTIVES

6.1. Primary objective

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

6.2. Secondary objectives

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

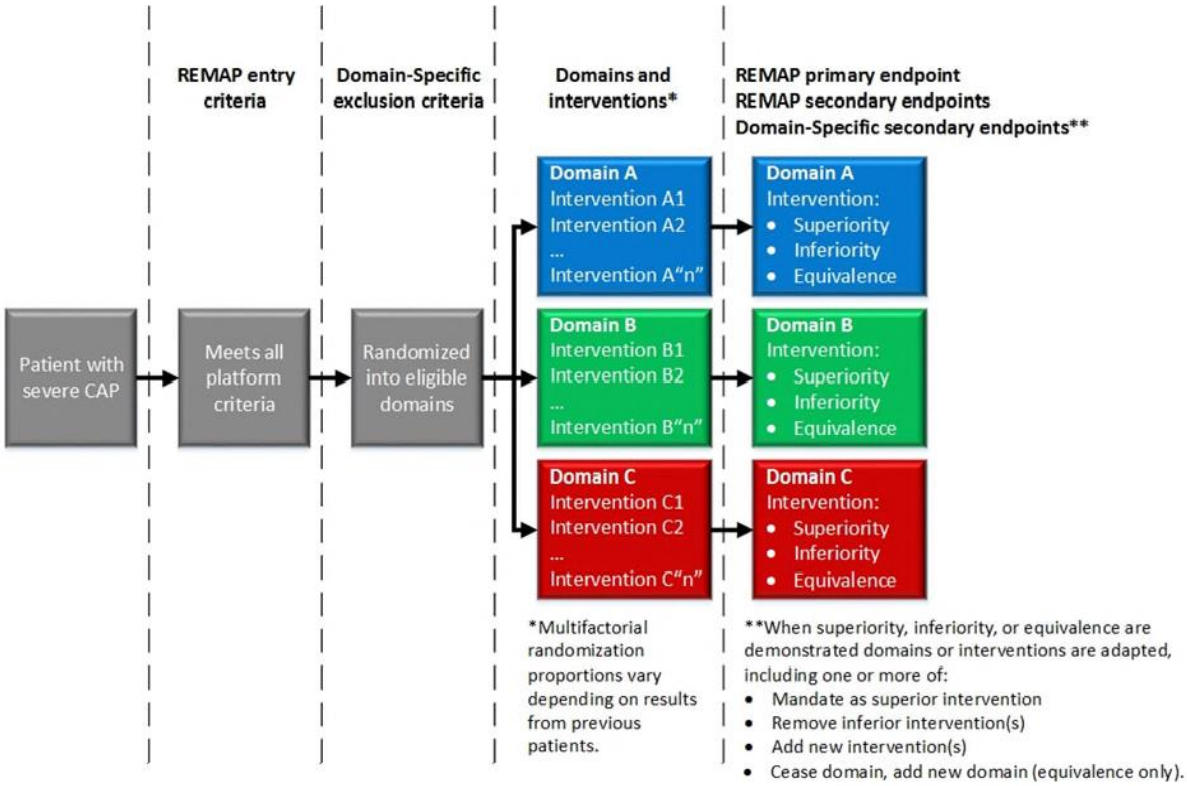
7. SUMMARY OF TRIAL DESIGN

7.1. Introduction

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

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

Figure 5: REMAP Structure



7.2. Nomenclature

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

7.3. Study setting and participating regions

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

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

The current regions are:

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

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

7.4. Eligibility criteria

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

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

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

7.4.1. REMAP Inclusion Criteria

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

1. Adult patient admitted to an ICU for acute severe CAP within 48 hours of hospital admission with
    a. symptoms or signs or both that are consistent with lower respiratory tract infection (for example, acute onset of dyspnea, cough, pleuritic chest pain) AND
    b. Radiological evidence of new onset infiltrate of infective origin (in patients with pre-existing radiological changes, evidence of new infiltrate)

2. Up to 48 hours after ICU admission, receiving organ support with one or more of:
    a. Non-invasive or invasive ventilatory support;
    b. Receiving infusion of vasopressor or inotropes or both

7.4.2. REMAP Exclusion Criteria

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

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

7.4.3. Domain-Specific Entry criteria

Each domain may have additional, domain-specific eligibility criteria, typically just exclusion criteria, although a combination of inclusion and exclusion criteria can be specified. Patients who fulfill the Overall REMAP Eligibility Criteria will be assessed for enrollment into all domains that are active at a site. A participant enrolled in the trial will receive the number of REMAP-specific interventions equivalent to the number of Domains to which they are enrolled. The additional eligibility criteria that are specific to a domain are provided in each DSA.

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

7.5. Interventions

7.5.1. Domain-Specific Information

All information related to the background, rationale, and specification of interventions that will be administered within the trial are located in the DSAs. The minimum number of interventions within a domain is two and the maximum number is limited only by statistical power. Each RMC will select the interventions that will be available within a domain that will be offered to participating sites in that region but the default position is that all interventions that are available and feasible in that region or country should be offered to sites. Individual participating sites will select the interventions within a domain that will be available at their site with the default position being all available interventions. The randomization program will only provide treatment allocations that are permitted at each participating site. This allows interventions that are not necessarily available in all regions, for example because of licensing reasons, to be included within the REMAP. Within the context of comparative effectiveness research, this also allows sites to determine the interventions that are

within their usual or reasonable spectrum of care. However, the viability of a domain is dependent on at least one intervention being available in all regions and being available at a substantial majority of participating sites. This level of 'connectedness' is necessary for the validity of the statistical models that are used to analyze trial results.

7.5.2. Treatment allocation and Response Adaptive Randomization

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

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

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

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

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

the remaining RAR proportions will be divided by one minus the sum of the unavailable proportions and applied to the available interventions.

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

7.5.3. Adaptation of Domains and Interventions

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

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

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

7.6. Endpoints

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

7.6.1. Primary Endpoint

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

7.6.2. Secondary Endpoints

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

The generic secondary endpoints for the trial are:

ICU outcomes:

- ICU mortality censored at 90 days;

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

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

Hospital outcomes:

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

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

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

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

7.7. Bias Control

7.7.1. Randomization

Randomization will be conducted through a password-protected, secure website using a central, computer-based randomization program. Randomization will be at the patient level and occur after data necessary to implement the inclusion and exclusion criteria have been entered into the secure randomization website. The RAR will occur centrally as part of the computerized randomization process. Sites will receive the allocation status and will not be informed of the randomization

proportions. Each region will maintain its own computer-based randomization program that is accessed by sites in that region but the RAR proportions will be determined by a SAC and provided monthly to the administrator of each region's randomization program who will update the RAR proportions.

7.7.2. Allocation concealment

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

7.7.3. Blinding of treatment allocation

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

7.7.4. Blinding of outcome adjudication

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

7.7.5. Follow up and missing data

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

7.8. Principles of Statistical Analysis

7.8.1. Preface

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

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

7.8.2. Introduction

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

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

Whenever a model hits a predefined threshold for any of superiority, inferiority, or equivalence for an intervention with respect to the primary endpoint, this is termed a Statistical Trigger. At any given adaptive analysis, a Statistical Trigger may be reached for all participants or for one or more stratum and will be reviewed immediately by the DSMB. When a Statistical Trigger is confirmed by the DSMB, based on a thorough review of the data including an evaluation of the proportion of patients for whom monitoring of variables that contribute to the model has been completed, and totality of evidence, and where no compelling reason exists not to reach a conclusion (see Section 7.8.9) regarding that question the result that has led to a Statistical Trigger will be specified to be a Platform Conclusion. The declaration of a Platform Conclusion will lead to appropriate modification of the interventions available within that domain and a Public Disclosure of the result. A Statistical Trigger can be considered as a mathematical threshold, whereas a Platform Conclusion is a decision regarding one or more interventions within a domain.

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

7.8.3.1. *Introduction*

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

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

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

The appropriate statistical handling of the analysis of patients who become eligible for a domain as a consequence of entering a state, after the time of enrollment, requires the use of models that take into account that the likelihood of entering the state after enrollment may have been influenced by the allocation status for other domains that specified the initiation of interventions that commenced at the time prior to entry into the state.

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

7.8.3.2. *Stratum*

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

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

The number of strata variables and the number of strata within the REMAP may be varied, depending on the impact of such decisions on statistical power, as determined by simulations. The modeling of strata may assume no differential effect for some domains. This may occur in two ways.

Firstly, when the strata structure defines the entry criteria for a domain. Secondly, when two or more stratum are combined within a single unit-of-analysis (i.e. the unit-of-analysis comprises two or more stratum). If the unit-of-analysis comprises less than all available strata the analysis that is performed assumes that treatment effect does not vary between stratum combined within a common unit-of-analysis. The RAR is applied according to the model. So, the RAR applies to the patients that comprise the unit-of-analysis, irrespective of whether the unit-of-analysis comprises a single stratum or two or more stratum.

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

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

7.8.3.3. *Treatment-by-strata interactions: borrowing between strata*

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

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

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

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

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

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

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

7.8.3.5. *State*

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

The number of state variables and the number of states within the REMAP may be varied, depending on the impact of such decisions on statistical power, as determined by simulations. The same state may be shared by one or more domains but may be different in different domains. The *a priori* defined states that are used for determination of results and for RAR may be changed during the life of the REMAP as knowledge is accumulated or as domains change and, if this occurs, will result in amendment of one or both of the Core Protocol or DSAs. Data from patients enrolled before the change in the state can be used to determine priors that are incorporated into the model at the outset of the incorporation of the new state into the model.

7.8.3.6. *Timing of randomization and revealing of allocation status*

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

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

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

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

Another situation applies when eligibility is determined by information that relates to the condition of the patient at the time of initial assessment of eligibility and is relevant to determination of eligibility but is not known until later. In this circumstance, the participant's allocation status can be revealed when the additional information becomes available. Examples of this type of information include the results of microbiological tests and the outcome of a request for consent. Information related to the safety of an intervention in individuals that may change between the time of initial assessment of eligibility and initiation of an intervention may also be reassessed and be used to determine if an allocation status will be revealed. Where initiation of the intervention is deferred pending availability of this additional information, this is referred to as **Randomization with Deferred Reveal.** It is noted that submission of information regarding microbiological results, consent, or safety information occurs without knowledge of allocation status.

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

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

7.8.3.7. *Treatment-by-treatment interactions*

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

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

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

7.8.3.8. *Nested analysis of interventions within a domain*

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

In situations in which interventions may be more similar than others, the model may nest the more similar interventions within a higher-level intervention category that comprises all the interventions deemed similar. In this situation, and to evaluate the occurrence of a Statistical Trigger, there are two models for analysis. Firstly, all patients receiving the nested interventions, treated as a single combined intervention, are compared with all other interventions in the domain. Secondly, all interventions are modeled individually. In this analysis, the interventions within a nest are modeled using a BHM incorporating the nesting structure. The BHM has a hyperprior specified for the shrinkage across interventions within the nest. This analysis will compare all interventions within a domain to all other interventions. This BHM analysis is used for the RAR assignments.

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

7.8.3.9. *Current strata and states*

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

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

The default states are defined by the occurrence of:

- Hypoxemia, defined in 3 categories, comprising participants who are not receiving invasive mechanical ventilation; participants who are receiving invasive mechanical ventilation and have a ratio of arterial partial pressure of oxygen to fractional inspired concentration of oxygen (P:F ratio) of ≥ 200 mmHg or are receiving invasive mechanical ventilation with the Positive End-Expiratory Pressure (PEEP) set to less than 5 cm of water (irrespective of the P:F ratio); and participants who are receiving invasive mechanical ventilation with a PEEP of 5 cm of water or more and have a P:F ratio of <200 mmHg.

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

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

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

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

7.8.4. Bayesian Statistical modeling

Inferences in this trial are based on a Bayesian statistical model, that will calculate the probability of superiority, inferiority, and equivalence of the interventions (known as a posterior probability distribution) within a unit-of-analysis that is defined by one or more stratum, taking into account the evidence accumulated during the trial (based on data on the outcomes of participants) and on assumed prior knowledge (known as a prior distribution). For the evaluation of the main effects of interventions within a domain (and evaluation of regimens) the default design assumes that parameters in the model have uninformative prior distributions at the first adaptive analysis. This means that any subsequent Platform Conclusion is not capable of being influenced by any discretionary choice regarding the pre-trial choice of prior distribution (i.e. it is the most conservative approach, making no assumptions regarding the prior distribution). At each subsequent adaptive analysis, the prior distribution is determined by all accumulated data available at the time of the adaptive analysis. The Bayesian approach is seen as continually updating the distribution of the model parameters.

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

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

This method of statistical analysis differs from conventional (frequentist) trials. Frequentist statistics calculate the probability of seeing patterns in the data from a trial if a hypothesis is true (including patterns not observed). This approach relies on assumptions about frequency distributions of trial results that would arise if the same trial were repeated *ad infinitum*. Thus, it requires specific sample sizes, which in turn requires pre-experiment assumptions regarding plausible effect sizes and outcome rates. Although many clinicians are comfortable with this approach, the pre-trial assumptions are frequently incorrect, and the design lacks the flexibility either to easily address the

complex questions more reflective of clinical practice or to make mid-trial corrections when the pre-trial assumptions are wrong without concern that the integrity of the final analysis is violated. To allow increased flexibility and yet still generate robust statistical inferences, REMAP relies on an overarching Bayesian, rather than frequentist, framework for statistical inference.

A Bayesian approach calculates the probability a hypothesis is true, given the observed data and, optionally, prior information and beliefs. The advantage of this approach is that, as more data are accrued, the probability can be continually updated (the updated probability is called the posterior probability). In this trial, frequent adaptive analyses will be performed, creating a very complicated sample space, and hence the Bayesian approach is a very natural one for these adaptive designs. The characterization of the risk of false positive error, or power, are done through Monte Carlo trial simulation. In contrast to frequentist confidence intervals which have awkward direct interpretation, Bayesian analyses return probability estimates that are directly interpretable as probabilities that statements are true (like the probability that one intervention is superior to another).

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

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

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

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

7.8.5. Statistical Handling of Ineligible Participants

The goal of this REMAP is to enroll as wide a participant population as possible. Because of this and the desire to explore multifactorial regimens it will not be uncommon that a participant will be ineligible for single interventions or entire domains, or interventions may be temporarily unavailable

for use. In this section we present the details for how this REMAP deals with these possible circumstances.

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

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

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

7.8.6. Intervention Superiority Statistical Trigger

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

7.8.7. Intervention Inferiority Statistical Trigger

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

7.8.8. Intervention Equivalence Statistical Trigger

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

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

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

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

7.8.9. Action when a Statistical Trigger is achieved

7.8.9.1. *Introduction*

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

7.8.9.2. *Actions following Statistical Trigger for superiority*

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

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

subject to further evaluation, by randomization, to refine the optimal characteristics of the superior intervention (for example duration of therapy or optimal dose).

7.8.9.3. *Actions following Statistical Trigger for inferiority*

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

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

7.8.9.4. *Actions following Statistical Trigger for equivalence*

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

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

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

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

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

The options following a Statistical Trigger for a pair of Interventions in a Domain with three or more Interventions are more complex. Within a domain with three or more interventions the information provided by the DSMB to the ITSC may include specification of the ordinal rank of the equivalent

interventions within the domain. With respect to reporting of Platform Conclusions and adaptations of the domain the following actions are possible:

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

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

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

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

7.8.10. Analysis set for reporting

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

7.8.11. Simulations and statistical power

The design of the trial, at initiation, and in conjunction with the planning of the introduction of new interventions within a domain or of new domains, will be informed by the conduct of extensive simulations using standard Monte Carlo methods. Simulations will be updated whenever a new intervention is added within a domain or whenever a new domain is added to the REMAP. However, simulations will not be updated when an intervention is removed from a domain because of the declaration of a Platform Conclusion that the intervention is inferior. These simulations will evaluate the impact of a range of plausible scenarios on the statistical properties of the trial.

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

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

7.8.12. Updating model after monitoring

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

7.9. Co-enrollment with other trials

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

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

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

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

7.11. Registry of non-randomized patients

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

7.12. Criteria for termination of the trial

This trial is designed as a platform, allowing for continued research in patients with CAP admitted to an ICU. The platform allows for the study to be perpetual, with multiple different domains that can be evaluated at any one time, and over time. Frequent adaptive analyses are performed to

determine whether the interventions under evaluation are still eligible for further testing or randomization should be stopped due to demonstrated inferiority, superiority or equivalence.

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

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

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

8. TRIAL CONDUCT

8.1. Site time-lines

8.1.1. Initiation of participation at a site

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

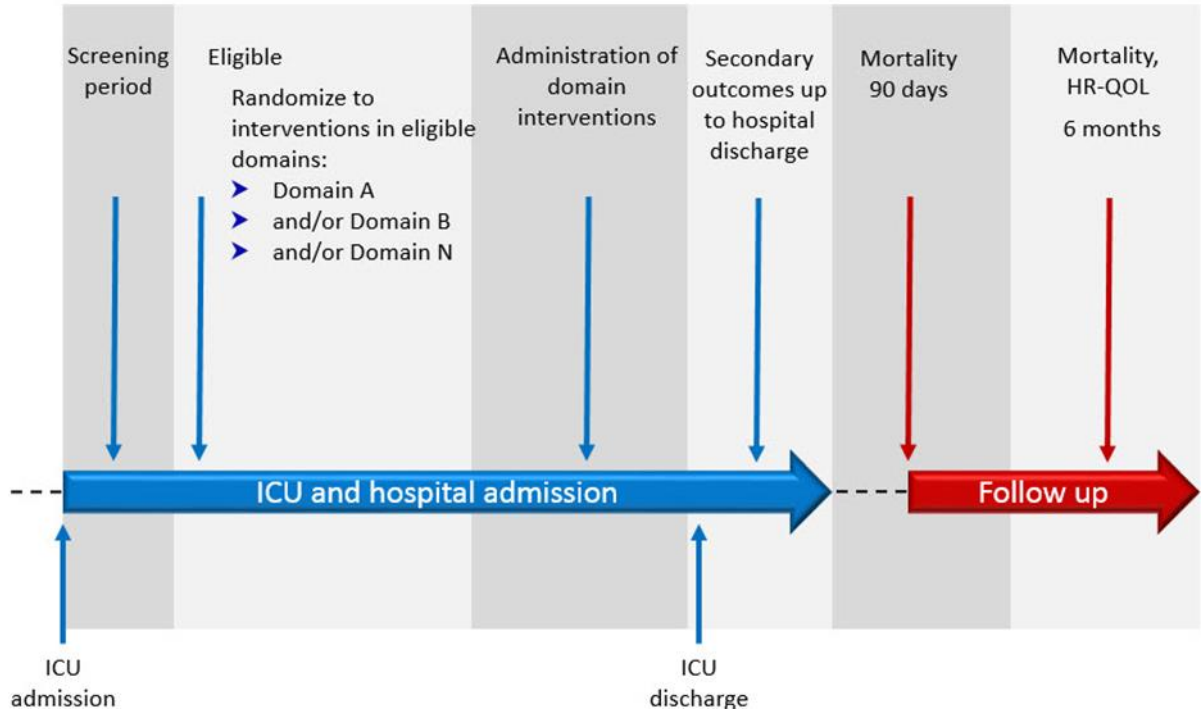
8.1.2. Vanguard sites

In each region or at the initiation of a new domain or both, the trial may consider commencing with only a small number of vanguard sites. The purpose of commencing the trial at vanguard sites is to learn about the effectiveness of different options for trial processes so that this information about the most effective trial processes can be shared with subsequent non-vanguard sites. If a site is acting as a vanguard site this will be specified in any application for ethical approval at that site.

8.2. Summary of time-lines for recruited participants

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

Figure 6: Study Procedures



8.3. Recruitment of participants including embedding

8.3.1. Embedding

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

The success of embedding can be evaluated by the proportion of eligible participants who are recruited and randomized, that recruitment and randomization occurs as soon as possible after eligibility occurs, and that there is compliance with the allocated intervention. Successful embedding will enhance the internal and external validity of the results generated by the trial.

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

8.3.2. Participant recruitment procedures at participating units

Once screened and identified as eligible the clinical staff (medical or nursing) or research staff will randomize the participant. Standard Operating Procedures (SOPs) will be developed to guide staff

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

8.4. Treatment allocation

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

8.5. Delivery of interventions

8.5.1. Treatment allocation and protocol adherence at participating units

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

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

8.6. Unblinding of allocation status

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

8.7. Criteria for discontinuation of a participant in the trial

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

Criteria for discontinuation from the REMAP interventions entirely include:

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

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

8.8. Concomitant care and co-interventions

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

8.9. Data collection

8.9.1. Principles of data collection

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

8.9.2. Variables to be collected

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

8.9.2.1. *Baseline and required for randomization*

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

8.9.2.2 *Baseline but not required for randomization*

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

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

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

8.9.2.4. *ICU Outcome data*

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

8.9.2.5. *Hospital outcome data*

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

- Discharge destination
- Results of microbiological testing

8.9.2.6. *Antimicrobial Administration*

- Administration of antibiotic medications
- Administration of antiviral medications

8.9.2.7. *Outcome data*

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

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

8.9.2.8. *Process-related outcomes*

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

8.9.3. Data required to inform Response Adaptive Randomization

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

1. Baseline and allocation status
    a. Unique trial-specific number
    b. Location (Country and Site code)
    c. Date and time of randomization
    d. Eligibility for each domain
    e. Intervention allocation for each domain
    f. Reveal status for each intervention allocation for each domain
    g. Age category
    h. Strata
        i. Shock or no shock

ii. Influenza status

iii. Pandemic strata

i. State

i. Hypoxemia

2. Outcome

a. All-cause mortality at 90 days

b. Date of hospital discharge

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

8.9.4. Blinding of outcome assessment

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

8.10. Data management

8.10.1. Source Data

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

8.10.2. Confidentiality

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

8.11. Quality assurance and monitoring

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

8.11.1. Plans for improving protocol adherence and complete data

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

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

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

8.11.2. Data Monitoring

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

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

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

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

8.12. Data safety and monitoring board

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

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

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

8.13. Safety monitoring and reporting

8.13.1. Principles

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

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

8.13.2. Definition

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

8.13.3. Reporting Procedures for Serious Adverse Events

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

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

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

8.13.4. Attribution of serious events to study interventions

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

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

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

9. GOVERNANCE AND ETHICAL CONSIDERATIONS

9.1. Management of participating sites and trial coordination

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

9.2. Ethics and regulatory issues

9.2.1. Guiding principles

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

9.2.2. Ethical issues relevant to this study

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

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

- Patients who, in the opinion of the treating clinician, are competent to consent will be provided with information about the trial and invited to participate
- The vast majority of patients who are eligible for the REMAP will not be competent to consent. For such patients, and as permitted by local laws and requirements for ethical approval:
    - For domains in which all interventions available at the participating site are regarded as being part of the spectrum of acceptable standard care by the clinicians at that site, entry to the study is preferred to be via waiver-of-consent or some form of delayed consent. If required by local laws or ethical requirements and alternative to this pathway will be participation in conjunction with the agreement of an authorized representative of the participant.
    - For domains in which at least one intervention available at the participating site is regarded as experimental or not part of the spectrum of acceptable standard care then prospective agreement by an authorized representative will be required. An exception to this principle is recognized when there is a time-imperative to commence the intervention which would routinely preclude obtaining the prospective agreement by an authorized representative.

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

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

9.2.3. Approvals

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

9.3. Protocol modifications

9.3.1. Amendments

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

- the safety or physical or mental integrity of the subjects of the trial;

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

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

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

9.4. Confidentiality

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

9.5. Declarations of interest

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

9.6. Post-trial care

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

9.7. Communication

9.7.1. Reporting

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

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

9.7.2. Communication of trial results

Trial results will be communicated by presentation and publication.

9.8. Publication policy

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

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

9.9. Data access and ownership

9.9.1. Data ownership

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

9.9.2. Access to Data

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

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

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

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

9.10. Consent form

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

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Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-acquired (REMAP-CAP)

Core protocol* for COVID-19 patients (REMAP-CAP:covid, or REMAP-COVID)

* The REMAP-COVID core protocol is a sub-core of the REMAP-CAP core protocol

REMAP-COVID Core Protocol Version 1 dated 27 March 2020

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1. ABBREVIATIONS AND GLOSSARY

1.1. Abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	Acute Respiratory Distress Syndrome
BHM	Bayesian Hierarchical Model
CAP	Community-Acquired Pneumonia
CRF	Case Report Form
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
eCIS	Electronic Clinical Information System
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
HRQoL	Health Related Quality of Life
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IIG	International Interest Group
ITT	Intention-To-Treat
LOS	Length of Stay
OFFD	Organ Failure Free Days
P:F Ratio	Ratio of Partial Pressure of Oxygen in Arterial Blood and Fraction of Inspired Oxygen Concentration
PEEP	Positive End-Expiratory Pressure
RAR	Response Adaptive Randomization
REMAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RCT	Randomized Controlled Trial
SAC	Statistical Analysis Committee
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SOPs	Standard Operating Procedures
TSC	Trial Steering Committee
WG	Working Group

1.2. Glossary

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

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

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

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

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

Intervention is a treatment option that is subject to variation in clinical practice (comparative effectiveness intervention) or has been proposed for introduction into clinical practice (experimental intervention) and also is being subjected to experimental manipulation within the design of a REMAP. For the purposes of the REMAP an intervention can include an option in which no treatment is provided.

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

Platform Conclusion describes when a Statistical Trigger has been reached and, following evaluation by the Data Safety and Monitoring Board (DSMB) +/- the Trial Steering Committee (TSC), there is a *decision* to conclude that superiority, inferiority or equivalence has been demonstrated. Under all circumstances a Platform Conclusion leads to implementation of the result within the REMAP and under almost all circumstances a Platform Conclusion leads, immediately, to Public Disclosure of the result by presentation and publication. Where the Statistical Trigger is for superiority or inferiority, so long as the DSMB is satisfied that the Statistical Trigger has truly been met a Platform Conclusion

will be automatic in almost all circumstances. Where the Statistical Trigger is for equivalence the DSMB, in conjunction with the TSC, may decide to not reach a Platform Conclusion at that time but, rather, to continue recruitment, for example, to allow a conclusion to be reached regarding clinically important secondary endpoints. There are situations in which the need to evaluate interactions may also result in a Statistical Trigger not leading, immediately, to a Platform Conclusion, although if superiority or inferiority has been demonstrated all patients in the REMAP will receive the superior intervention or no longer be exposed to inferior intervention(s), respectively.

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

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

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

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

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

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

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

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

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

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

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

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

2. INTRODUCTION

2.1. Relationship between interpandemic REMAP-CAP and REMAP-CAP for COVID-19 patients (REMAP-COVID) design and documents

REMAP CAP is a large on-going international adaptive platform trial specifically designed to run in both inter-pandemic and pandemic periods, focusing on optimal care of patients with severe pneumonia. It is governed by a core protocol and statistical analysis plan together with appendices to the core that describe:

- domains and interventions being tested (domain-specific appendices)
- regional features (region-specific appendices)
- additional appendices (e.g., the pandemic appendix, which describes the general features governing the transition between inter-pandemic and pandemic modes for the trial).

All study materials, including current versions of these protocols and appendices, can be found at www.remapcap.org.

This document is the core protocol for sites and regions that are participating in REMAP-CAP exclusively for the enrollment of patients with COVID-19 and require a stream-lined set of documents delineating only those issues pertinent to COVID-19. Sites and regions can still use the entire set of REMAP-CAP documents if they wish. If sites expand to non-COVID-19 patients, they must adopt the full REMAP CAP documents.

Thus, this REMAP-CAP COVID-19 core protocol is 'core' for COVID-19 patients, but is a subcore to the overall REMAP-CAP core protocol. It contains a modification of the REMAP-CAP core protocol and pandemic appendix to reflect only those study design features and procedures relevant to the study of patients with COVID-19. It has the following features.

- It is based on the overall REMAP-CAP protocol, except all elements that are not relevant to the study of COVID-19 patients are removed.
- It provides background information on COVID-19.
- It incorporates all design considerations contained in the main pandemic appendix that have been specifically incorporated for the COVID-19 pandemic. Thus, there is no additional 'pandemic appendix' attached to this document.
- It clarifies that, although REMAP-CAP has traditionally only enrolled patients requiring ICU care for cardiovascular or respiratory insufficiency (state = 'severe'), modifications to REMAP COVID-19 include the option to expand enrollment criteria for ALL hospitalized patients (defined as 'severe' or 'moderate', assuming 'mild' are managed as out-patients) with COVID-19, depending on the domain. In those instances, using the REMAP-CAP design principles, patients are stratified based on whether, at enrollment, they are in the state of

meeting the traditional REMAP CAP ICU and cardiorespiratory entry criteria (severe) or not (moderate).

- Recognizing the very large number of trials being launched in the setting of COVID-19, it provides expanded discussion of co-enrollment and alignment with other trials.
- The REMAP-COVID core protocol is also accompanied by a Statistical Analysis Plan (SAP) Appendix. This SAP is a sub-SAP to the overarching REMAP-CAP SAP (just as the REMAP-COVID core protocol is a sub-core to the overarching REMAP-CAP core protocol). It delineates the pandemic model implemented for COVID-19 patients, including the handling of domain assignments to patients in the severe and moderate states.
- For those regions using the REMAP-COVID core protocol, there will also be region-specific appendices. Regions using the full REMAP-CAP protocol will provide any COVID-19 specific updates within their existing region-specific appendix.
- Domain-specific appendices will be attached to the REMAP-COVID protocol for all domains used in COVID-19 patients. Those domains (e.g., corticosteroid DSA) that exist in REMAP-CAP but require modification (e.g., changed primary endpoint in the COVID19 pandemic model) for evaluation in COVID-19 patients will be provided as sub-DSAs, akin to the 'sub' documents described above. Those domains generated specifically for COVID-19 will be appendices to this protocol (as well as to the master REMAP-CAP protocol).

2.2. WHO endorsement

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

2.3. Synopsis

Background: Since SARS-CoV-2-coronavirus (COVID-19) emerged from Wuhan, China in late 2019, continual reports of disease now tally over 200,000 confirmed cases with almost 10,000 deaths worldwide. On March 11, 2020, the World Health Organization (WHO) announced COVID-19 as a pandemic (situation report 51, https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10) signaling the inevitable spread of this respiratory illness around the world.

With no effective treatments for COVID-19, the evaluation of potential treatments in randomized clinical trials is essential to mitigate the potential catastrophic loss of human life inherent to pandemics. Recognizing the importance of structured data capture for off-label uses of medications in a pandemic environment, the WHO urges use of unproven therapies only within the clinical trial context (https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf).

Current conventional clinical trials methods to assess the efficacy of treatments for any pneumonia, including acute viral pneumonia due to COVID-19, generally compare two treatment options (either two options for the same treatment modality, where both are in common use; or a new treatment against no treatment or placebo where the effectiveness of the new treatment is not known). Using this approach, in a series of separate and sequential trials, it will take an inordinate length of time to study all the treatment options. Additionally, with conventional trial designs it is not possible to evaluate interactions between treatment options. Though initiated prior to COVID-19, REMAP-CAP was specifically designed to address these issues. REMAP-CAP has already transitioned to pandemic mode, and is already enrolling patients with the goal of finding effective COVID-19 treatments.

Aim: The primary objective of this trial is to identify the effect of a range of interventions to improve outcome as defined by 21-day intensive care unit (ICU) free days for patients who present with suspected or proven COVID-19 infection.

Methods: The study will enroll adult patients who present with suspected or proven COVID-19 infection using a design known as a REMAP, which is a type of adaptive platform trial. Within this REMAP, eligible participants will be randomized to receive one intervention in each of one or more domains (a domain is a category of treatment that contains one or more options, termed interventions, with each intervention option being mutually exclusive). In addition to the primary outcome of 21-day ICU free days, there will also be both general and domain-specific secondary outcome measures.

In a conventional trial, enrollment continues until a pre-specified sample size is obtained, at which time enrollment ceases, and the trial data are analyzed to obtain a result. The possible results are that a difference is detected or that no difference is detected. However, when the conclusion of the statistical test is “no difference”, this could be that there truly is no meaningful difference, or that the result is indeterminate (i.e., it is possible that if more patients had been enrolled a clinically relevant difference may have been detected).

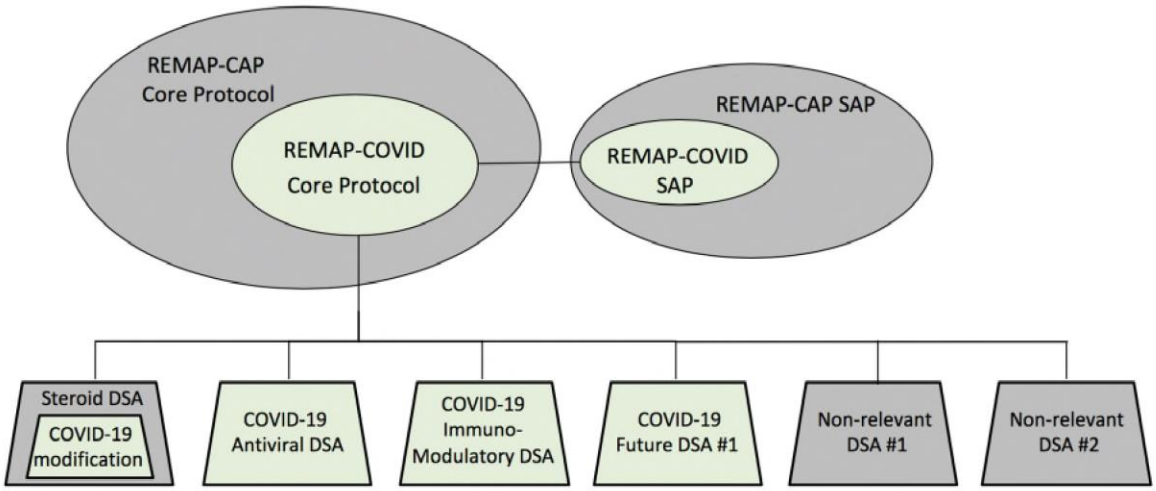
In comparison to a conventional trial, this REMAP uses an adaptive design, relying on pre-specified criteria for adaptation, that: avoids indeterminate results; concludes an answer to a question when sufficient data have accrued (not when a pre-specified sample is reached); evaluates the effect of treatment options in pre-defined subgroups of patients (termed strata); utilizes already accrued data to increase the likelihood that patients within the trial are randomized to treatments that are more

likely to be beneficial; is multifactorial, evaluating multiple questions simultaneously; is intended to be perpetual (or at least open-ended), substituting new questions in series as initial questions are answered; and can evaluate the interaction between interventions in different domains. Bayesian statistical methods will be used to establish the superiority, inferiority, or equivalence of interventions within a domain. Interventions determined to be superior will be incorporated into standard care within the ongoing REMAP. Interventions determined to be inferior will be discontinued. While a limited number of initial treatments and treatment domains have been specified at initiation, it is planned that this REMAP will continue to evaluate other treatments in the future. Each new treatment that is proposed to be evaluated within the REMAP will be submitted for prospective ethical review.

2.4. Protocol Structure

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

Figure 1: Protocol Structure. The REMAP-COVID is a subset of the REMAP-CAP structure, which studies both inter- pandemic and pandemic pneumonia. The DSAs are thus part of a family of DSAs that belong to REMAP-CAP, but some of these DSAs are not relevant in regions or sites only studying patients with COVID-19. Portions of REMAP-CAP relevant to regions, sites and patients in the REMAP-COVID only-program are shown in green. For illustration purposes, RSAs and othermiscellaneous appendices are not shown.



The protocol has multiple modules, comprising a Core Protocol, multiple DSAs, and a Statistical Analysis Appendix. A Simulations Appendix is updated periodically as an operational document.

2.4.1 Core Protocol

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

- The background and rationale for studying COVID-19 infection
- The background and rationale for the research approach
- The trial design including study setting, the criteria that define eligibility for the REMAP, treatment allocation, strata (see glossary for a definition of this term), principles of application of trial interventions, trial endpoints, methods to control bias, principles of statistical analysis, and criteria for termination of the trial
- The trial conduct including recruitment methods, time-lines for sites, delivery of trial interventions, data collection, data management, and management of participant safety
- The overall trial governance structures and ethical considerations

2.4.2 Domain-Specific Appendices

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

of interventions within an existing domain, as well as removal and addition of entire domains. Each DSA has the following structure:

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

2.4.3 Region-Specific Appendices

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

- the definition of the region
- the organization of trial management and administration within the region
- information about availability of domains and interventions
- data management and randomization procedures
- ethical issues that are specific to a region.

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

2.4.4 Statistical Analysis Appendix and Simulations Appendix

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

The Simulations Appendix is an operational document that contains the results of Monte Carlo simulations that are conducted to describe and understand the operating characteristics of the REMAP across a range of plausible assumptions regarding outcomes, treatment effects, and interactions between interventions in different domains. The statistical power of the study (likelihood of type II error) and the likelihood of type I error are evaluated using these simulations. As the trial adapts, with, for example, the introduction of new interventions, the trial simulations are

updated and the Simulations Appendix is amended. The Simulations Appendix is not part of the formal protocol.

2.4.5 Version History

Version 1: Finalized for submission on 27 March 2020

2.5. Lay Description

COVID-19 is a viral respiratory infection caused by the SARS-CoV-2-coronavirus. Early in their course, reports indicate that those infected often experience fever and cough similar to a common cold. During this phase, these patients are highly contagious, capable of broadly spreading COVID-19 to others. Physical decline resulting in hospitalization is attributed to pneumonia, an infection involving the lungs, which is a common reason for admission to an ICU. Severe pneumonia is associated not only with failure of lungs supplying oxygen to the body, but also failure of other organ systems that is due to an uncontrolled immune response to infection.

With patients suspected to have COVID-19 presenting to hospital, enrollment into this pandemic clinical trial will begin with preliminary domains to attempt to mitigate viral load and prevent disease progression. In the event a patient's condition worsens and they should require admission to an ICU, additional domains are available which include medications that may modify the immune system and provide supportive treatments to support failing organs.

In a conventional clinical trial, selected patients are allocated to receive one treatment from a short list of alternatives, typically one or two. This trial differs from conventional clinical trials by being randomized, embedded, multifactorial, adaptive, and a platform (a "REMAP"). (Angus, 2015) In this type of trial, we will test many alternative treatments ("multifactorial") by replacing *ad hoc* treatment decisions with "randomized" treatment allocation ("embedded"). Although treatments will be allocated randomly, patients will preferentially be allocated to treatments that statistical models derived from trial data indicate are more likely to be the most effective treatments. The trial will "adapt" in multiple ways including answering questions as soon as sufficient data have accrued to answer the question of the effectiveness of each treatment and by changing the treatments that are being tested over-time so as to progressively determine the best package of treatments for pre-defined categories of patients with severe pneumonia. Once a treatment is identified as being optimal it is subsequently routinely provided to all eligible patients within the REMAP.

2.6. Trial registration

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

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

2.7. Funding of the trial

At initiation of REMAP-CAP, the trial had funding from the following sources.

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

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

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

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

Since the onset of the COVID-19 pandemic, additional funding has been secured from multiple sources, including several governments and healthcare systems, and including in additional regions, such as the United States. Additional funding is being sought in other regions and countries.

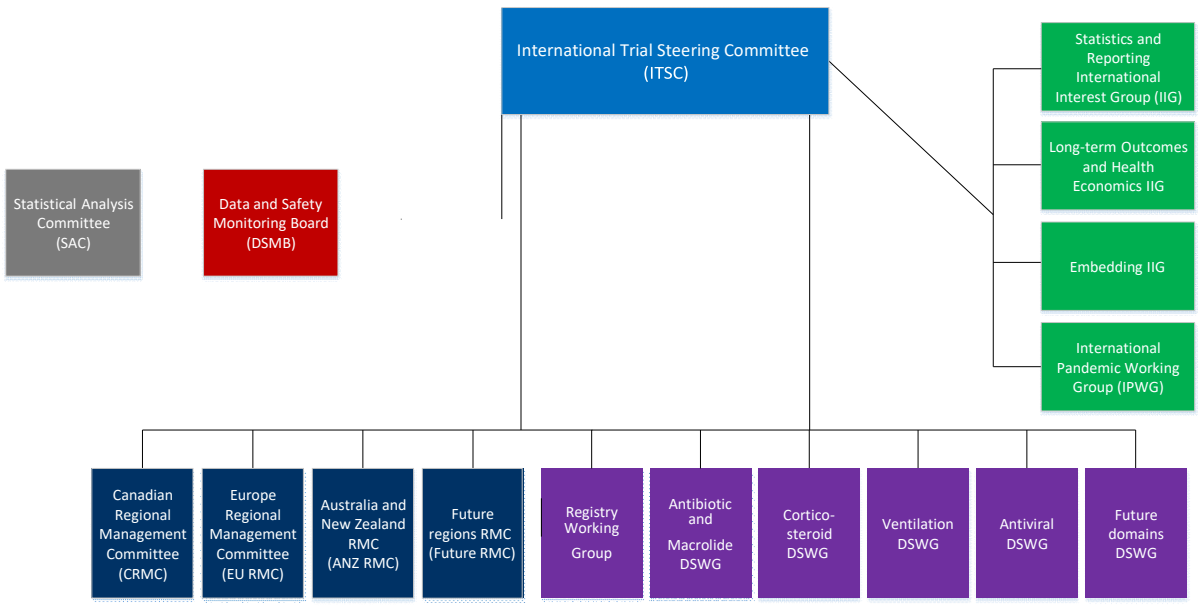
3. STUDY ADMINISTRATION STRUCTURE

The study administration structure is designed to provide appropriate management of all aspects of the study, taking into account multiple factors including availability of skills and expertise related to trial conduct and statistical analysis, and content knowledge regarding COVID-19 and pneumonia and the interventions that are being evaluated. The administration model is designed to provide effective operational and strategic management of the REMAP that operates in multiple sites as well as changes in the domains and interventions that are being evaluated.

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

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

Figure 2: REMAP-CAP (including interpandemic and REMAP-COVID) Organization Chart



3.1. International Trial Steering Committee

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

3.1.1 Responsibilities

The responsibilities of the ITSC are:

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

3.1.2 Members

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

Professor Derek Angus, Chair Corticosteroid DSWG and Foundation member

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

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

Ms. Zahra Bhimani, Canadian Project Manager

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

Professor Frank Brunkhorst, member EU RMC

Professor Allen Cheng, Chair Antibiotic Domain and Macrolide Duration DSWG

Professor Menno De Jong, member Antiviral DSWG

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

Professor Herman Goossens, Principal Investigator for PREPARE

Professor Anthony Gordon, member EU RMC

Mr. Cameron Green, Global Project Manager

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

Dr. Ed Litton, member Australian and New Zealand (ANZ) RMC

Professor John Marshall, Canadian Executive Director

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

Dr. Shay McGuinness, Chair ANZ RMC

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

Professor Alistair Nichol, Chair Ventilation DSWG

Associate Professor Rachael Parke, member ANZ RMC

Ms. Jane Parker, Australian Project Manager

Professor Kathy Rowan, member EU RMC

Ms. Anne Turner, New Zealand Project Manager

Professor Steve Webb, ANZ Executive Director and Foundation member

3.1.3 Contact Details

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

3.2. Regional Management Committees

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

3.2.1 Responsibilities

The responsibilities of each RMC are:

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

- liaison with the sponsor(s) for that region
- management of systems for randomization and data management for that region

3.3. Domain-Specific Working Groups

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

3.3.1 Responsibilities

The responsibilities of each DSWG are:

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

3.3.2 Members

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

3.4. International Interest Groups

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

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

3.4.1 Role

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

3.5. Sponsors

In relation to recruitment that occurs in:

- countries in Europe the sponsor is University Medical Center Utrecht.
- Australia the sponsor is Monash University.

- New Zealand the sponsor is the Medical Research Institute of New Zealand.
- Canada the sponsor is Unity Health Toronto.
- United States the sponsor is the Global Coalition for Adaptive Research.

3.5.1 Role of sponsor

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

3.5.2 Insurance

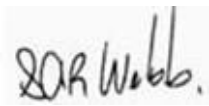
The provision of insurance is specified in each RSA.

4. INTERNATIONAL TRIAL STEERING COMMITTEE AUTHORIZATION

This document is a summation of the master REMAP-CAP core protocol (version 3.0, 10th July, 2019) and the Pandemic Appendix (version 1.1, 12th February, 2020) to that core. The master REMAP-CAP core protocol, version 3.0 was read and authorized by the ITSC. Signed by the ITSC,

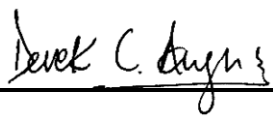
EU Executive Director
Marc Bonten

ANZ Executive Director
Steve Webb

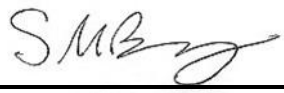


ANZ Deputy Director
Colin McArthur

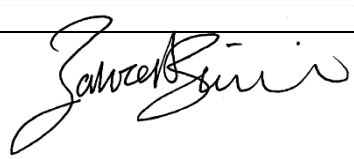
ITSC Member
Derek Angus



ITSC Member
Wilma van Bentum-Puijk



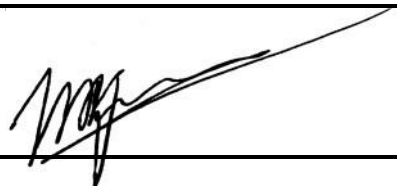
ITSC Member
Scott Berry



ITSC Member
Zahra Bhimani

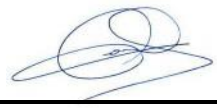
ITSC Member
Frank Brunkhorst

ITSC Member
Allen Cheng



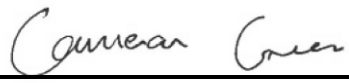
ITSC Member
Menno De Jong

ITSC Member
Lennie Derde



ITSC Member
Herman Goossens

ITSC Member
Anthony Gordon



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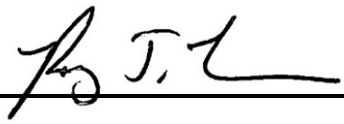
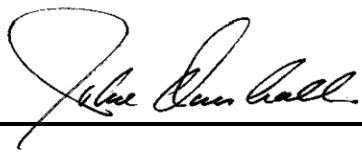


ITSC Member
Roger Lewis

ITSC Member
Ed Litton



ITSC Member
John Marshall

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Shay McGuinness

ITSC Member
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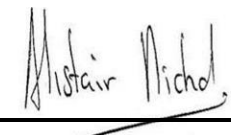
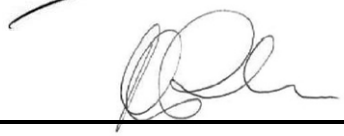
Alistair Nichol



ITSC Member
Rachael Parke



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Jane Parker

ITSC Member
Kathy Rowan

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Anne Turner

5. BACKGROUND & RATIONALE

5.1. COVID-19

5.1.1. Introduction

This section, within the Core Protocol, provides background on the epidemiology, causes, treatment categories, and evidence base for the management of patients with COVID-19. Detailed information regarding the rationale for specific interventions to which patients will be randomized within the REMAP can be found in a corresponding DSA. As the trial is intended to be perpetual, if background information changes, appropriate amendments to the protocol documents will occur periodically, but it is anticipated that this will occur predominantly by amendment of DSAs.

5.1.2. Epidemiology

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, the sensitivity of diagnostic methods, possible limitation on the number of diagnostic tests that can be performed, and changing case-definitions. Nevertheless, it is recognized that fatal pneumonia is common. COVID-19 is now a pandemic with more than 200,000 cases worldwide.

The clinical course of COVID-19 is variable, with many patients who progress to severe pneumonia, with a significant proportion requiring mechanical ventilation and some reports of multi-organ dysfunction. In a report of 3 patients who developed clinical and radiographic features of pneumonia, one patient required mechanical ventilation and died subsequently (Zhu et al., 2020) In a study of 41 hospitalized patients with laboratory-confirmed COVID-19 infection, 13 (32%) patients were admitted to an ICU and six (15%) died. Invasive mechanical ventilation was required in four (10%) patients, with two patients (5%) receiving extracorporeal membrane oxygenation as salvage therapy (Huang et al.). In another study of 99 hospitalized patients with COVID-19 pneumonia, 23 (23%) were admitted to ICU, 17 (17%) developed acute respiratory distress syndrome (ARDS), 3 (3%) acute renal failure and 4 (4%) septic shock. (Jens et al., 2012) (Jens et al., 2012) In a study of 138 patients with COVID-19 infection, 36/138 required ICU care. Patients admitted to ICU were older and were more likely to have underlying comorbidities. In the ICU, four patients (11.1% 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 2 patients received renal replacement therapy (Wang et al., 2020). Thus, COVID-19 infections have demonstrated a variable clinical course, which requires further investigation in order to draw meaningful conclusions.

5.1.3. Standard care for patients with COVID-19

While preventative efforts such as community awareness and social distancing serve to minimize the spread of COVID-19, for those infected, there are no known effective treatments. This REMAP will serve to evaluate several potential interventions to treat COVID-19 infection.

5.2. Randomized Embedded Multifactorial Adaptive Platform Trials

5.2.1 Generating clinical evidence

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

5.2.2 Underlying Principles of the Study Design

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

A conventional RCT (i.e. a non-platform trial) makes a wide range of assumptions at the time of design. These assumptions include the plausible size of the treatment effect, the incidence of the primary outcome, the planned sample size, the (typically, small number of) treatments to be tested, and that treatment effects are not influenced by concomitant treatment options. These assumptions are held constant until the trial completes recruitment and is analyzed. (Barker et al., 2009, Berry, 2012, Connor et al., 2013) Participants who are enrolled in a conventional RCT are not able to benefit from knowledge accrued by the trial because no results are made available until the trial completes. A REMAP uses five approaches to minimize the impact of assumptions on trial efficiency and also maximizes the benefit of participation for individuals who are enrolled in the trial. (Angus, 2015, Berry et al., 2015, Aikman et al., 2013, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016)

These design features are:

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

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

5.2.3 Particular advantages of the REMAP design in a pandemic

There are several particular advantages of this design when studying a new disease in a pandemic setting, such as COVID-19. First, multiple therapies can be evaluated simultaneously, without the

requirement of requiring pre-set sample sizes, which are hazardous to estimate, given the limited understanding of the disease and potential effectiveness of any therapy. Second, therapies performing poorly can be quickly discarded, preserving most 'learning' for the evaluation of therapies that are most promising. Third, the design allows the testing of potential heterogeneity of treatment effect due to treatment-by-subgroup interactions and treatment-by-treatment interactions. Again, in a previously unencountered disease, such flexibility is crucial. Fourth, the use of multiple assignments with a common control, coupled with RAR, means that only a few patients are assigned control care, the control care can continually improve, and patients are preferentially assigned the best performing interventions. Thus, patients are being treated while therapies are being studied.

5.2.4 Nomenclature

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

5.2.5 Randomization and Response Adaptive Randomization

The study will randomly allocate participants to one or more interventions, with each intervention nested within a domain. In this regard, a platform trial is no different to other forms of RCT in that randomization provides the basis for causal inference. However, unlike a conventional RCT, the proportion of participants who are randomized to each available intervention within a domain will not be fixed. Rather, the trial will incorporate RAR. RAR utilizes random allocation with a weighted probability for each intervention, with the weighted probability being proportional to the extent to which similar participants recruited earlier in the trial benefited or not from each particular intervention. (Angus, 2015, Berry, 2012, Connor et al., 2013, Aikman et al., 2013, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016) RAR will result in participants in each particular stratum being randomized with greater probability to interventions that are performing better within that stratum. At the initiation of a new domain or when a new intervention is added to a domain the randomization proportion of all new interventions is balanced and only changes, with the application of RAR, that takes into account uncertainty about treatment effect so as to avoid excessive variability in proportions generated by RAR until sufficient sample size has accrued.

The major consequence of RAR is that better therapies move through the evaluation process faster, resulting in trial efficiency gains. (Berry, 2012, Connor et al., 2013) The platform “learns” more quickly about the treatments we ultimately care about, i.e. those that work best. Moreover, as data accrues, newly randomized participants are more likely to receive interventions from which they benefit. (Berry, 2012, Connor et al., 2013, Meurer et al., 2012, Angus, 2015, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016) This is a highly ethical fusion of trial science with continuous quality improvement and a learning healthcare system. (Institute of Medicine, 2013) Assuming at least some interventions are better than others, the total mortality within the trial population will be lower than would have occurred with a fixed randomization

proportion. It is also particularly relevant to the ethical conduct of trials that enroll critically ill patients where unanticipated increases in mortality have been seen (Dellinger et al., 2013) and to the conduct of trials during a pandemic in which there is in-built implementation of the therapies that are more likely to be beneficial during the trial. The simulations underpinning REMAP-COVID demonstrate that, in instances where particular interventions are indeed superior to others, the use of RAR will, on average, increase the odds of discovering the superiority not only with lower sample size, but with fewer participants exposed to the less efficacious therapies and, thus, fewer deaths or adverse outcomes.

There are potential disadvantages associated with RAR. It is intended that participating sites and trial investigators will be blind to the RAR proportions. One disadvantage is that, for interventions that are provided without blinding, the treating clinicians may be able to draw inference about the RAR proportions and, as a consequence, draw inference about the interim standing of interventions that are being tested in the REMAP. This could have adverse consequences including that clinicians are influenced to not enroll participants within a domain but rather directly prescribe the treatment that they believe to be doing better outside the trial. However, a number of factors mitigate this potential concern. First, it can be difficult to distinguish between patterns of sequential allocation status that are derived from fixed versus RAR. Second, extreme proportions will not be used (except where a Statistical Trigger but not a Platform Conclusion has been reached, see later). Finally, for many conditions, team-based management means that an individual clinician will directly observe only a small proportion of all participants enrolled within the trial at each participating site. Another disadvantage of RAR is that, under certain allocation rules, statistical power can be reduced. This concern is mitigated via pre-trial simulation to test the effects of different allocation rules. Furthermore, a REMAP that comprises multiple domains with multiple interventions within each domain will generally have higher, rather than lower, power as a consequence of the use of RAR. Finally, by deploying RAR rules to minimize the odds of exposure to inferior interventions, the design is intended to motivate embedding in clinical practice, thereby resulting in more rapid recruitment.

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

5.2.6 Embedding

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

electronic health records will be utilized to enhance screening and recruitment and specify the 'order set' for participants, including those orders that are determined by allocation status within the REMAP. While screening and recruitment for a REMAP can be conducted by research staff, it is not intended that recruitment should be dependent on research staff, particularly as such staff are typically only present during office hours and since limiting potential exposure of non-essential personnel given the highly contagious nature of COVID-19 is preferred. In addition to the facilitation of recruitment and high-fidelity delivery of the intervention, a further advantage is that the results of the trial can be translated rapidly within the ongoing REMAP so that all appropriate participants receive a treatment declared to be superior with continued allocation to that treatment option within the REMAP used to ensure implementation.

5.2.7 Multifactorial

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

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

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

5.2.8 Adaptive

5.2.8.1 *Frequent adaptive analyses*

Adaptive analyses using Bayesian statistical methods will be undertaken using Markov Chain Monte Carlo (MCMC) estimates of the Bayesian posterior probability distributions. The trial will utilize a set of pre-specified rules to reach conclusions regarding the effectiveness of interventions that are being evaluated. It is these pre-specified rules that determines how the trial "adapts" to the information contained in accumulating participant data. An analogy is that the 'routes' that a trial can take are pre-specified, within the protocol, but the exact route that the trial takes is determined by the data that accrues. Such adaptation improves statistical efficiency substantially. As this REMAP addresses the enrollment of patients during a pandemic, the frequency of adaptive analyses will occur with greater frequency to permit rapid data evaluation. Modeling to impute missing data will be used, as necessary.

5.2.8.2 *Analysis of data to reach conclusions*

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

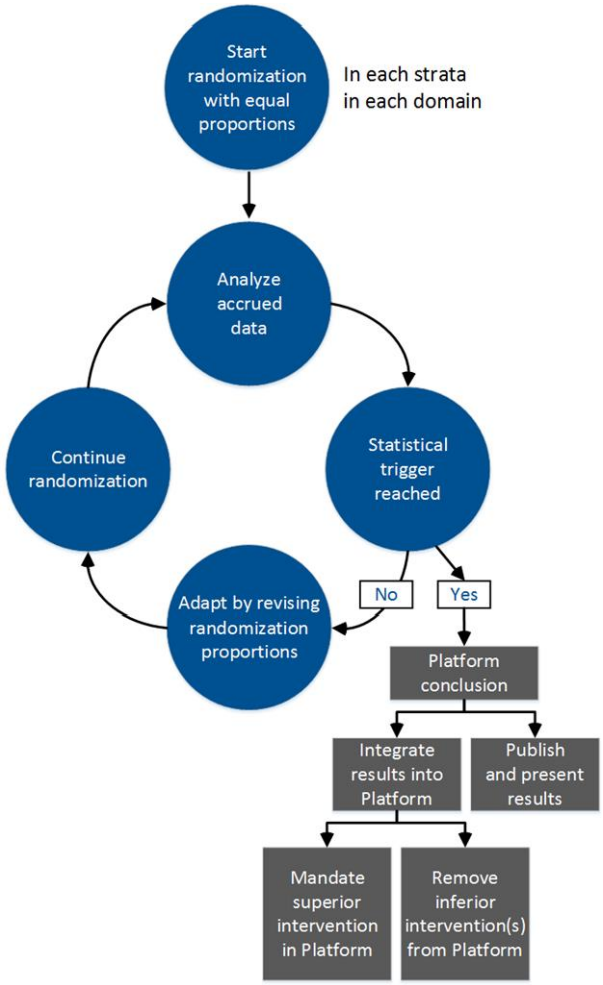
The occurrence of a Statistical Trigger is communicated immediately to the trial DSMB by the SAC. The DSMB has primary responsibility for determining if a Statistical Trigger should lead to a Platform Conclusion. The declaration of a Platform Conclusion results in the removal of inferior intervention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

The algorithm by which a Platform Conclusion is reached is different for Statistical Triggers of superiority or inferiority, compared to those triggers that arise because of equivalence. Where the Statistical Trigger is for superiority or inferiority, so long as the DSMB is satisfied that the Statistical Trigger has been met validly, the default position is that the DSMB will declare this result as a Platform Conclusion. The only exception to this situation is if there is a need to evaluate potential interactions between treatments in different domains. In this circumstance the randomization schedule will be adapted (all participants receive the superior intervention or randomization to one or more inferior interventions is removed) but Public Disclosure may be delayed until evaluation of the interaction is completed.

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

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

Figure 3: Adaptive Analyses



5.2.8.3 *Probability thresholds*

In this REMAP the pre-specified rules are that, at any adaptive analysis, an intervention will be declared "superior," if it is has at least a 0.95 posterior probability of being the best intervention within its domain. An intervention will be declared "inferior" if it has a less than 0.05 probability of being the best intervention within its domain. Intervention equivalence is declared between two factors when there is at least a 0.90 posterior probability of the rate of the primary endpoint falls within a pre-specified delta.

5.2.8.4 *Analysis within and between strata*

The frequent adaptive analyses will evaluate the primary endpoint, *within one or more stratum*. Where specified, the statistical models for each strata will be able to 'borrow' information from adjacent strata leading to the declaration of a Statistical Trigger in one, more, or all strata. The extent to which borrowing occurs is dependent on the pre-specified structure of the model and the degree of statistical congruence of treatment effect between stratum. Where treatment effects are divergent between stratum there is less 'borrowing'. The capacity to evaluate strata is particularly important for interventions that might plausibly have differential, including opposite, treatment effects in different strata. (Dellinger et al., 2013, Finfer et al., 2004, The Acute Respiratory Distress Syndrome Network, 2000) In traditional trial designs, divergent treatment effects among sub-groups may cancel each other out and this is one plausible explanation for the trials that report no overall

difference in outcome. It should be noted that strata can be different for different domains and that strata can be changed over time (in conjunction with amendment of the protocol).

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

5.2.8.5 *Frequency of adaptive analyses*

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

5.2.8.6 *Advantages of adaptive analysis*

The major advantage of this type of analysis approach is that a conclusion is reached when there is sufficient information to support the conclusion, rather than when enrollment reaches a predetermined sample size. This approach allows a result to be obtained as quickly as possible with appropriate sample size. It also avoids indeterminate results by continuing randomization until either superiority, inferiority, or equivalence is concluded. (Barker et al., 2009, Berry, 2012, Connor et al., 2013, Meurer et al., 2012, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016) An additional advantage is that dissemination of such results does not interrupt the conduct of the platform. In a single REMAP, there is no need for the "start-and-stop" periods that would typically occur under the alternative approach of multiple separate trials. These "downtime" periods can be quite extensive and carry a number of disadvantages. First, there is a lot of duplicative effort every time a near-identical treatment protocol goes through the appropriate development and approval processes. Second, clinical investigation units must maintain a certain infrastructure, and that infrastructure can be expensive to maintain during periods when participants are not being enrolled or expensive to recreate if the infrastructure degrades. Third, downtime is simply one more contributor to delay in the production of scientific knowledge. Participants at large benefit from earlier production of knowledge regardless of whether new information demonstrates a therapy is effective or ineffective. Finally, the inevitable start up delay before a trial can "go live" can wipe out any possibility of conducting effective research during time-critical situations such as a pandemic.

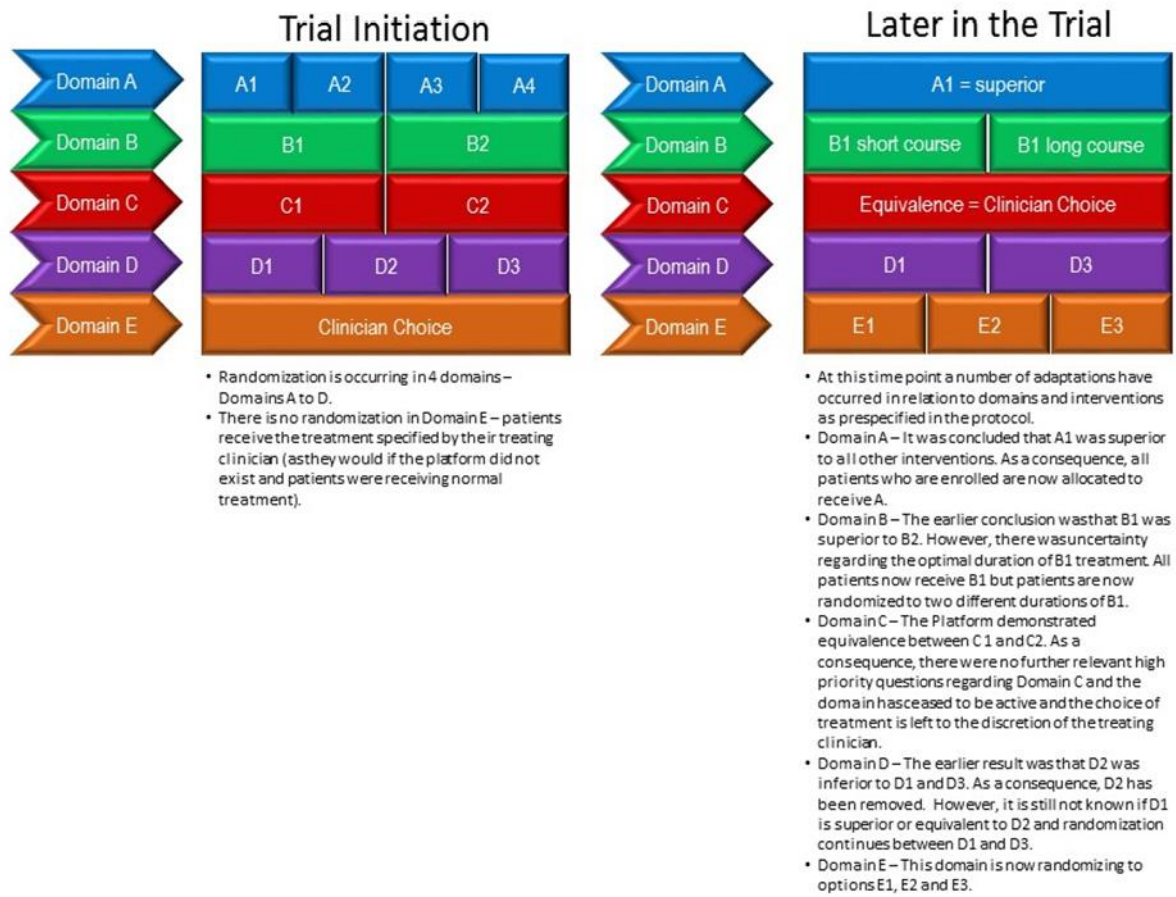
5.2.8.7 *Substitution of new domains and interventions within the REMAP*

It is intended that the REMAP will be 'perpetual'. In conjunction with a Platform Conclusion being reached, the TSC takes responsibility for determining what new questions will be introduced to the REMAP including adding one or more new interventions to a domain or adding one or more new domains. In a REMAP, the sample size is not fixed, rather maximum use is made of the available

sample and more questions may be asked for the same monetary investment. (Barker et al., 2009, Berry, 2012, Connor et al., 2013, Meurer et al., 2012, Aikman et al., 2013, Bhatt and Mehta, 2016, Park et al., 2016) The only limit on the duration of a platform trial is the availability of ongoing funding, the availability of new interventions to evaluate, and that the disease continues to be a public health problem. The TSC responsible for the REMAP will develop appropriate processes for identifying and prioritizing the selection of new interventions and domains that are introduced progressively into the REMAP over time.

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

Figure 4: REMAP Evolution Over Time



5.2.9 Nesting of the REMAP within a Registry

The REMAP can also be nested within a registry, with the registry recording information (typically a subset of the trial Case Report Form (CRF)) in all participants who met the REMAP entry criteria, or an expanded set of entry criteria, but who, for any reason, were not randomized. Examples could include registries of COVID-19 patients enrolled using the ISARIC/WHO clinical characterisation protocol (www.isaric.tghn.org). Information obtained from eligible but not randomized participants can be useful for evaluating the external validity of results and optimizing recruitment. Evaluation of non-randomized treatments received by all participants, both randomized and non-randomized, can be used to identify the consequences of natural variation in care so as to identify interventions that should be prioritized for evaluation by randomization within the REMAP. (Byrne and Kastrati, 2013) The design features of the trial and the conceptual advantages associated with each design feature are summarized in Table 2.

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

5.2.10 Platform

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

Table 1: Features of a REMAP that contribute to advantages of the design

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

6. OBJECTIVES

6.1. Primary objective

The primary objective of this REMAP is, for adult patients with either suspected or proven COVID-19 infection, to identify the effect of a range of interventions to improve outcome as defined by 21-day ICU free days. Depending on the domain, these interventions will be assessed in all patients admitted to hospital or all patients admitted to an ICU with cardiovascular or respiratory compromise.

6.2. Secondary objectives

The secondary objective is to determine the effect of COVID-19 treatments on additional endpoints, including the World Health Organization 8-point ordinal scale measured at day 15 after enrollment,

all-cause mortality measured at ICU discharge, hospital discharge, and at day 90, ICU and hospital length of stay (LOS), ventilator free days (VFDs) and other endpoints as indicated for specific domains.

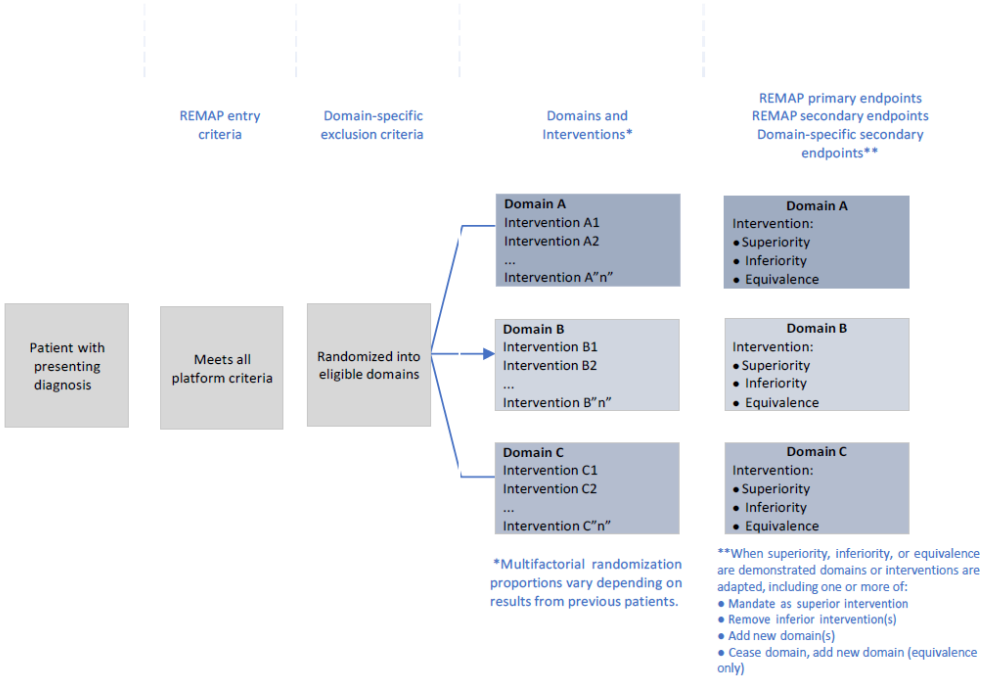
7. SUMMARY OF TRIAL DESIGN

7.1. Introduction

This is a REMAP that aims to test many interventions in a number of domains with the primary outcome being the 21-day ICU free days. Frequent adaptive analyses will be performed to determine if an intervention is superior, inferior, or equivalent to one or more other interventions to which it is being compared, within a domain. A Bayesian analysis method will be used to evaluate superiority, inferiority, or equivalence, as well as to inform the adaptive randomization strategy within each domain. Where it is anticipated that interactions between interventions in different domains may be likely the statistical models will allow evaluation of such interactions. Where the statistical models evaluate such an interaction the models can incorporate the relative likelihood of such interactions, but with possibly low prior probability in cases where it is biologically implausible for interactions to occur. Each intervention within each domain will be evaluated within prospectively defined and mutually exclusive strata (sub-groups) of participants but information from one stratum may be used (via 'borrowing') to contribute to the analysis of the effect of that intervention in other strata. Interventions that are found to be inferior, for a specific stratum, are removed from use in that stratum, and will, typically, be removed from the REMAP allowing new interventions or domains or both to be introduced. An RAR algorithm will be used to preferentially randomize participants to interventions that appear to be performing better. Extensive simulation studies have been performed to define the type I error, power to detect specified differences, and demonstration of equivalence as well as a broad range of operating characteristics. It is planned that further simulation studies will be conducted in conjunction with consideration of the introduction of new interventions or domains or both into the REMAP. The intention-to-treat (ITT) principle will be used for all primary analyses.

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

Figure 5: REMAP Structure



7.2. Nomenclature

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

7.3. Study setting and participating regions

The trial will recruit only participants who are hospitalized with suspected or proven COVID-19. Those who are suspected or confirmed to have COVID-19 infection will have access to specific pre-ICU domains. In the event a participant is admitted to an ICU and meets severity criteria, additional ICU domains would be available. An ICU is defined as a location that identifies itself as an ICU (or high dependency unit) and is able to provide at least non-invasive ventilation and continuous administration of vasoactive medications. The definition of an ICU may include a general ward in which a patient is under the care of an Intensive Care Specialist (Intensivist), but resource limitations prevent the immediate delivery of care occurring in the ICU. Broader definition of an ICU under a surge of pandemic COVID-19 cases is also permitted (see below). It is intended that the trial will be conducted in multiple regions. A region is defined as a country or collection of countries with study sites for which a RMC is responsible. The country or countries for which a RMC are responsible, as well as all aspects of trial conduct that are specific to each region, are described in the RSAs.

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

The current regions are:

- Europe, with funding from a European Union FP7 grant (FP7-HEALTH-2013-INNOVATION-1, grant number 602525), to support the enrollment of 4000 participants. This funding terminates in 2021.
- Australia and New Zealand. In Australia the project has received funding from a NHMRC Project Grant (APP1101719), to support the enrollment of 2000 participants. This funding terminates in December 2021, although some extension may be feasible. In New Zealand the project has received funding from a HRC Programme Grant (16/631), to support the enrollment of 800 participants. This funding terminates in November 2021.
- Canada. In Canada the project has received funding for a CIHR grant (158584), to support the enrollment of 300 participants. This funding terminates in 2022.
- United States. In the US, funding has been received from UPMC health system for recruitment internally at all UPMC hospitals (>40) and to support a US regional coordinating center. Philanthropic support is being provided through GCAR. Additional funds are being pursued.

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

7.4. Eligibility criteria

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

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

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

7.4.1. REMAP Inclusion Criteria

In order to be eligible to participate in COVID-19 aspects of REMAP-CAP, a patient must meet the following criteria:

3. Adult patient (age >/= 18 years of age) who is hospitalized with suspected or proven COVID-19

infection. “Suspected COVID-19 infection” means the patient is clinically diagnosed based on symptoms and/or exposure and for whom a microbiology test for COVID-19 has been/will be ordered, but for whom the result is pending. “Proven COVID-19 infection” means the patient has a confirmed positive result for COVID-19 based on microbiological testing.

In order to participate in all existing REMAP-CAP 'ICU-based' domains, a patient must also meet the following criteria (required to be characterized in the severe COVID-19 state):

4. Admitted to an ICU with the following features suggestive of COVID-19-related pneumonia within 48 hours of hospital admission
    a. symptoms or signs or both that are consistent with lower respiratory tract infection (for example, acute onset of dyspnea, cough, pleuritic chest pain) AND
    b. Radiological evidence of new onset infiltrate of infective origin (in patients with pre-existing radiological changes, evidence of new infiltrate)
5. Up to 48 hours after ICU admission, receiving organ support with one or more of:
    a. Non-invasive or invasive ventilatory support;
    b. Receiving infusion of vasopressor or inotropes or both

7.4.2. REMAP Exclusion Criteria

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

8. Death is deemed to be imminent and inevitable during the next 24 hours
9. Previous participation in this REMAP within the last 90 days

7.4.3. Study setting: definition of an ICU

During the COVID-19 pandemic, there may be insufficient ICU beds available to care for all critically ill patients resulting in provision of advanced organ support occurring in locations other than an ICU. Thus, an ICU is defined as area within the hospital that is able to deliver one or more of the qualifying organ failure supports specified in the Core Protocol (non-invasive ventilation, invasive ventilation, and vasopressor therapy) will meet the definition of an ICU. It is preferred in such circumstances that the patient is under the care of a specialist who is trained in the provision of critical care, but this is not an essential requirement.

7.4.4. Domain-Specific Entry criteria

Each domain may have additional, domain-specific eligibility criteria, typically just exclusion criteria, although a combination of inclusion and exclusion criteria can be specified. Patients who fulfill the Overall REMAP Eligibility Criteria will be assessed for enrollment into all domains that are active at a site. A participant enrolled in the trial will receive the number of REMAP-specific interventions equivalent to the number of Domains to which they are enrolled. The additional eligibility criteria that are specific to a domain are provided in each DSA.

Where a participant has an exclusion criterion to one or more interventions within a domain, but there are at least two interventions within that domain to which the participant is eligible the

patient will be randomized to receive one of the interventions to which the participant is eligible.

7.5. Interventions

7.5.1. Domain-Specific Information

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

7.5.2. Treatment allocation and Response Adaptive Randomization

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

The proportions that are specified by RAR are determined only by analysis of the primary outcome measure in participants who have completed 21 days of follow-up from the time of enrollment. By only including participants in the analysis models that determine the RAR proportions potential bias that arises from different events occurring with different patterns of timing within the 21 day follow up period is avoided. The same statistical model will be used to both analyze the results of the REMAP as well as specify the randomization proportions.

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

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

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

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

7.5.3. Adaptation of Domains and Interventions

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

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

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

7.6. Endpoints

The primary outcome for this REMAP will apply to all domains. Secondary outcomes generic to all Domains are provided in this Core Protocol below. Secondary outcomes specific to individual domains are provided in the relevant DSAs.

7.6.1. Primary Endpoint

The primary endpoint for all domains will be a composite endpoint that comprises the number of whole and part study days for which the patient is alive and not admitted to any ICU until the end of study day 21. All patients who die before discharge from an acute hospital, irrespective of whether this occurs before or after day 21, will be coded as zero days. Patients who die between day 21 and discharge from an acute hospital will be updated at the time of the next adaptive analysis. All whole

and part days after discharge from an acute hospital and before day 21 will be counted as being not admitted to an ICU. Hospital readmission that included a new admission to ICU between first discharge from an acute hospital and day 21 will not contribute to the primary endpoint.

7.6.2. Secondary Endpoints

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

The generic secondary endpoints for the trial are:

- World Health Organization 8-point ordinal scale
    1. Ambulatory with no limitation of activities
    2. Ambulatory with limitation of activities
    3. Hospitalized not receiving oxygen therapy
    4. Hospitalized receiving oxygen therapy by mask or nasal prongs
    5. Hospitalized receiving noninvasive ventilation or high-flow oxygen
    6. Hospitalized receiving invasive mechanical ventilation but no other additional organ support
    7. Hospitalized receiving invasive mechanical ventilation plus additional organ support (e.g., vasopressors, RRT, and/or ECMO)
    8. Deceased
- ICU outcomes:
    - ICU mortality censored at 90 days;
    - ICU LOS censored at 90 days;
    - VFDs censored at 28 days;
    - OFFDs censored at 28 days;
    - Proportion of intubated participants who receive a tracheostomy censored at 28 days;

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

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

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

- Longer follow-up:

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

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

7.7. Bias Control

7.7.1. Randomization

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

7.7.2. Allocation concealment

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

7.7.3. Blinding of treatment allocation

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

7.7.4. Blinding of outcome adjudication

The primary outcome of 21-day ICU free days is not subject to ascertainment bias. Wherever possible, trial management personnel, who are blinded to allocation status, will conduct any follow up after discharge.

7.7.5. Follow up and missing data

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

7.8. Principles of Statistical Analysis

7.8.1. Preface

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

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

7.8.2. Introduction

Within the REMAP, two or more interventions within a domain are evaluated and sequential Bayesian statistical analyses are used over time to incorporate new trial outcome information to determine if an intervention is superior, if one or more interventions are inferior in comparison to all other interventions, or if one or more pairs of interventions are equivalent, with respect to the

primary endpoint. Every participant will be assigned a set of interventions, comprising one intervention from each domain for which the participant is eligible. The combination of interventions to which a participant is assigned comprises the regimen and the regimens are the available arms in the trial. Participants will be classified by membership in different populations defined by one or more strata. The unit-of-analysis for a domain is the most granular level, defined by one or more stratum, or a state, within which the treatment effect of interventions within that domain may vary in the statistical model. Participants are also classified by the criteria that determine eligibility for each domain.

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

Whenever a model hits a predefined threshold for any of superiority, inferiority, or equivalence for an intervention with respect to the primary endpoint, this is termed a Statistical Trigger. At any given adaptive analysis, a Statistical Trigger may be reached for all participants or for one or more stratum and will be reviewed immediately by the DSMB. When a Statistical Trigger is confirmed by the DSMB, based on a thorough review of the data including an evaluation of the proportion of patients for whom monitoring of variables that contribute to the model has been completed, and totality of evidence, and where no compelling reason exists not to reach a conclusion (see Section 7.8.9) regarding that question the result that has led to a Statistical Trigger will be specified to be a Platform Conclusion. The declaration of a Platform Conclusion will lead to appropriate modification of the interventions available within that domain and a Public Disclosure of the result. A Statistical Trigger can be considered as a mathematical threshold, whereas a Platform Conclusion is a decision regarding one or more interventions within a domain.

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

7.8.3.1 *Introduction*

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

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

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

The appropriate statistical handling of the analysis of patients who become eligible for a domain as a consequence of entering a state, after the time of enrollment, requires the use of models that take into account that the likelihood of entering the state after enrollment may have been influenced by the allocation status for other domains that specified the initiation of interventions that commenced at the time prior to entry into the state.

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

7.8.3.2 *Stratum*

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

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

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

The *a priori* defined strata that are used for determination of results and for RAR may be changed during the life of the REMAP as knowledge is accumulated and, if this occurs, will result in

amendment of one or both of the Core Protocol and DSAs. Data from patients enrolled before the change in the strata can be used to determine priors that are incorporated into the model at the outset of the incorporation of the new strata into the model.

7.8.3.3 *Treatment-by-strata interactions: borrowing between strata*

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

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

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

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

7.8.3.4 *Analysis set for strata, timing of enrollment and timing of informationregarding strata membership*

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

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

7.8.3.5 *State*

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

The number of state variables and the number of states within the REMAP may be varied, depending on the impact of such decisions on statistical power, as determined by simulations. The same state may be shared by one or more domains but may be different in different domains. The *a priori* defined states that are used for determination of results and for RAR may be changed during the life of the REMAP as knowledge is accumulated or as domains change and, if this occurs, will result in amendment of one or both of the Core Protocol or DSAs. Data from patients enrolled before the change in the state can be used to determine priors that are incorporated into the model at the outset of the incorporation of the new state into the model.

7.8.3.6 *Timing of randomization and revealing of allocation status*

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

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

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

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

Another situation applies when eligibility is determined by information that relates to the condition of the patient at the time of initial assessment of eligibility and is relevant to determination of eligibility but is not known until later. In this circumstance, the participant's allocation status can be revealed when the additional information becomes available. Examples of this type of information include the results of microbiological tests and the outcome of a request for consent. Information

related to the safety of an intervention in individuals that may change between the time of initial assessment of eligibility and initiation of an intervention may also be reassessed and be used to determine if an allocation status will be revealed. Where initiation of the intervention is deferred pending availability of this additional information, this is referred to as **Randomization with Deferred Reveal.** It is noted that submission of information regarding microbiological results, consent, or safety information occurs without knowledge of allocation status.

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

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

7.8.3.7 *Treatment-by-treatment interactions*

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

In this REMAP, only three options are permitted with respect to specifying the lambda parameter for each domain-domain pair. Firstly, lambda may be set to zero. The effect of this is that there are no

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

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

7.8.3.8 *Nested analysis of interventions within a domain*

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

In situations in which interventions may be more similar than others, the model may nest the more similar interventions within a higher-level intervention category that comprises all the interventions deemed similar. In this situation, and to evaluate the occurrence of a Statistical Trigger, there are two models for analysis. Firstly, all patients receiving the nested interventions, treated as a single combined intervention, are compared with all other interventions in the domain. Secondly, all interventions are modeled individually. In this analysis, the interventions within a nest are modeled using a BHM incorporating the nesting structure. The BHM has a hyperprior specified for the shrinkage across interventions within the nest. This analysis will compare all interventions within a domain to all other interventions. This BHM analysis is used for the RAR assignments.

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

7.8.3.9 *Current strata and states*

Prior to COVID-19, REMAP-CAP enrolled patients with severe CAP who were admitted to the ICU with either shock or respiratory failure. The key states in which these patients could be classified were:

- Shock, defined in 2 categories, present or absent, with present defined as the patient is receiving continuous infusion of intravenous vasopressor or inotrope medications at the time of enrollment
- Hypoxemia, defined in 3 categories, comprising participants who are not receiving invasive mechanical ventilation; participants who are receiving invasive mechanical ventilation and have a ratio of arterial partial pressure of oxygen to fractional inspired concentration of oxygen (P:F ratio) of ≥ 200 mmHg or are receiving invasive mechanical ventilation with the

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

Of these states, 'shock at presentation' was also incorporated as a stratum in the model.

In response to the COVID-19 pandemic, the ITSC has adopted a COVID-19-specific pandemic model. In that model, the existing structure for patients admitted to the ICU and stratified by shock remains unchanged. However, in addition, as per section 7.4.3 of the Pandemic Appendix to the REMAP-CAP core protocol, the entry criteria have been broadened to allow patients to be enrolled who present in an additional state characterized as meeting the criteria for COVID-19 pneumonia, but not meeting the severity threshold of ICU admission and either cardiovascular or respiratory failure.

Thus, these two states are called:

- **severe**: meets the original REMAP CAP criteria
- **moderate**: hospitalized but not meeting the REMAP CAP criteria for ICU admission plus either cardiovascular or respiratory insufficiency

Patients who are seen, suspected or proven to have COVID-19, but are not admitted to hospital are assumed to be mild, but that state is not currently evaluated in the REMAP. The new moderate state can be used by domains that test interventions suitable for patients who present to hospital with lower acuity, and is incorporated in the pandemic statistical model (see Statistical Analysis Plan Appendix). The state at enrollment can be used as a strata (moderate versus severe) for the evaluation of differential treatment effects, dependent on the state at which they were initiated.

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

7.8.3.10 *Confirmation of COVID-19 infection strata*

Both confirmed and suspected patients are enrolled. Confirmation of COVID-19 infection is subsequently defined in two categories, present or absent, based on the results of microbiological tests. Any patient with clinically suspected COVID-19 who is not tested or the result is not yet known will be deemed positive. The availability and interpretation of microbiological tests for COVID-19 are changing. An operational document will be used to specify how different tests are interpreted. It is noted that COVID-19 confirmed status is defined by the final results of testing for the pandemic organism, which may include analysis of samples collected after enrollment where it is reasonable to presume that the sample reflected COVID-19 status at time of enrollment.

Because the sensitivity of microbiological testing for COVID-19, like other pandemic organisms, may not be known at the beginning or even during the pandemic(Iwasenko et al., 2010), it is anticipated that initial analysis will occur without application of this confirmation status strata. However, this would be applied when there was sufficient confidence about the operating characteristics of diagnostic tests. If the COVID-19 confirmation status is applied, the probabilities derived from patients who have confirmed infection will be used to determine the RAR proportions for patients

receiving treatment assignments in the COVID-19 domains. Further details are provided in the master REMAP CAP documents.

7.8.3.11 *Pre-specified subgroup analysis after achievement of a Platform Conclusion*

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

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

7.8.4. Bayesian Statistical modeling

Inferences in this trial are based on a Bayesian statistical model, that will calculate the probability of superiority, inferiority, and equivalence of the interventions (known as a posterior probability distribution) within a unit-of-analysis that is defined by one or more stratum, taking into account the evidence accumulated during the trial (based on data on the outcomes of participants) and on assumed prior knowledge (known as a prior distribution). For the evaluation of the main effects of interventions within a domain (and evaluation of regimens) the default design assumes that parameters in the model have uninformative prior distributions at the first adaptive analysis. This means that any subsequent Platform Conclusion is not capable of being influenced by any discretionary choice regarding the pre-trial choice of prior distribution (i.e. it is the most conservative approach, making no assumptions regarding the prior distribution). At each subsequent adaptive analysis, the prior distribution is determined by all accumulated data available at the time of the adaptive analysis. The Bayesian approach is seen as continually updating the distribution of the model parameters.

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

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

This method of statistical analysis differs from conventional (frequentist) trials. Frequentist statistics calculate the probability of seeing patterns in the data from a trial if a hypothesis is true (including patterns not observed). This approach relies on assumptions about frequency distributions of trial results that would arise if the same trial were repeated *ad infinitum*. Thus, it requires specific sample sizes, which in turn requires pre-experiment assumptions regarding plausible effect sizes and

outcome rates. Although many clinicians are comfortable with this approach, the pre-trial assumptions are frequently incorrect, and the design lacks the flexibility either to easily address the complex questions more reflective of clinical practice or to make mid-trial corrections when the pre-trial assumptions are wrong without concern that the integrity of the final analysis is violated. To allow increased flexibility and yet still generate robust statistical inferences, REMAP relies on an overarching Bayesian, rather than frequentist, framework for statistical inference.

A Bayesian approach calculates the probability a hypothesis is true, given the observed data and, optionally, prior information and beliefs. The advantage of this approach is that, as more data are accrued, the probability can be continually updated (the updated probability is called the posterior probability). In this trial, frequent adaptive analyses will be performed, creating a very complicated sample space, and hence the Bayesian approach is a very natural one for these adaptive designs. The characterization of the risk of false positive error, or power, are done through Monte Carlo trial simulation. In contrast to frequentist confidence intervals which have awkward direct interpretation, Bayesian analyses return probability estimates that are directly interpretable as probabilities that statements are true (like the probability that one intervention is superior to another).

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

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

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

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

7.8.5. Statistical Handling of Ineligible Participants

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

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

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

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

7.8.6. Intervention Superiority Statistical Trigger

At any adaptive analysis, if a single intervention has at least a 0.95 posterior probability of being a member of the optimal regimen, for that unit-of-analysis, then that intervention will be deemed as being superior to all other interventions in that domain in that target population. This Statistical Trigger may also be applied for a state that defines the target population for a domain.

7.8.7. Intervention Inferiority Statistical Trigger

At any adaptive analysis, if a single intervention has less than a 0.05 posterior probability of being a member of the optimal regimen, for a unit-of-analysis, then that intervention will be deemed as being inferior for that target population. If superiority and inferiority were to be discovered simultaneously (for example when there are two interventions), the result will be interpreted as

demonstrating superiority. An asymmetrical inferiority statistical trigger may be set when an active intervention is evaluated against no active treatment within the same domain. This Statistical Trigger may also be applied for a state that defines the target population for a domain.

7.8.8. Intervention Equivalence Statistical Trigger

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

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

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

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

7.8.9. Action when a Statistical Trigger is achieved

7.8.9.1 *Introduction*

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

7.8.9.2 *Actions following Statistical Trigger for superiority*

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

patients suspected or proven infected with COVID-19 will be conveyed promptly to public health authorities by the ITSC and DSMB.

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

7.8.9.3 *Actions following Statistical Trigger for inferiority*

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

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

7.8.9.4 *Actions following Statistical Trigger for equivalence*

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

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

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

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

Factors that should be taken into account by the DSMB and the TSC include the results of the primary analysis, analysis of clinically relevant secondary end-points, the possibility of treatment-by-treatment interactions, the relative burden and cost of the two interventions, the clinical

interpretation of the adequacy of the delta, and the possibility that ongoing randomization with a smaller delta might also allow a Statistical Trigger for superiority (with a small effect size).

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

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

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

In a domain that comprises three or more interventions, but in which two or more interventions are analyzed in a nested manner, the nested group may be combined for analyses of equivalence. Where compression converts a domain with three or more interventions into a domain with two interventions (and data continues to support equivalence of the compressed interventions) such a

domain will be regarded as a two-intervention domain for the purposes of evaluation of Statistical Triggers for superiority, inferiority, and equivalence.

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

7.8.10. Analysis set for reporting

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

7.8.11. Simulations and statistical power

The design of the trial, at initiation, and in conjunction with the planning of the introduction of new interventions within a domain or of new domains, will be informed by the conduct of extensive simulations using standard Monte Carlo methods. Simulations will be updated whenever a new intervention is added within a domain or whenever a new domain is added to the REMAP. However, simulations will not be updated when an intervention is removed from a domain because of the declaration of a Platform Conclusion that the intervention is inferior. These simulations will evaluate the impact of a range of plausible scenarios on the statistical properties of the trial.

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

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

7.8.12. Updating model after monitoring

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

7.9. Co-enrollment with other trials

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

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

7.10.1. Cooperation of the entire REMAP-CAP program with other trials

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

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

7.10.2. Cooperation of the REMAP-COVID component of REMAP-CAP with other trials

There are a large number of trials registered for the study of COVID-19 (www.covid19-trials.org). As noted above, this REMAP is open label and highly flexible with regard to co-enrollment. In particular, the ITSC will work with other trial steering committees to explore rapid sharing of allocation assignments pertinent to any adaptive trial decisions both in this REMAP and in other adaptive trials, under appropriate data protections. This REMAP will also explore structured relationships with other trials that can exploit a coordinated approach around treatment assignments and states.

For example, in a given region, a cooperation could be established between this REMAP and another trial where this REMAP restricts enrollment to the severe state (the traditional enrollment criteria for REMAP-CAP) while the other trial enrolls patients earlier at hospital arrival (the moderate state).

In such a setting, if the other trial assigns a patient in the moderate state to an intervention that also exists within one of this REMAP's domains, and the patient subsequently progresses to the severe state and is enrolled in this REMAP, the intervention assignment from the earlier trial can, and the patient will only be randomized to interventions within the other domains. The REMAP-COVID pandemic model has the capability to account for these random assignment-state relationships, including if the assignment occurred within another trial (see Statistical Analysis Plan Appendix).

7.11. Registry of non-randomized patients

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

7.12. Criteria for termination of the trial

The COVID-19 portion of REMAP-CAP is designed to allow continued research in acutely ill COVID-19 patients. The platform allows for the study to be perpetual, with multiple different domains that can be evaluated at any one time, and over time. Frequent adaptive analyses are performed to determine whether the interventions under evaluation are still eligible for further testing or randomization should be stopped due to demonstrated inferiority, superiority or equivalence.

It is anticipated that after inclusion of the initially planned sample size, the COVID-19 portion would continue to include additional participants and test additional domains and/or interventions until one of the following occurs:

- COVID-19 is no longer deemed to be a public health problem
- The effectiveness and/or cost-effectiveness of all interventions are known and there are no new plausible interventions to test

The decision to cease the study of COVID-19 patients specifically is to be made by the ITSC. At this time, data from COVID-19 patients can also be incorporated back within the broader REMAP CAP program and combined with that of other patients, as specified in the master REMAP CAP core protocol, pandemic appendix, and statistical analysis plan (www.remapcap.org). Should the whole REMAP CAP study be stopped, the end of trial is the date of the last scheduled follow up for any participant.

8. TRIAL CONDUCT

8.1. Site time-lines

8.1.1. Initiation of participation at a site

A range of options are available for the sequence of activities by which a site commences participation. The following outlines the default sequence of participation. The first level of participation is termed ‘observational only’. During this stage eligible participants will be identified, preferably using a process of embedding with recognition by clinical staff and registration on the study website as soon as eligibility is recognized. Treatment decisions will be made by that site’s

clinical staff, and observational data using the study CRF or a sub-set of the CRF will be collected. The next level of participation is termed 'single domain'. During this time period, eligible participants are identified and randomized, but only within a single domain. The next level of participation is termed 'multiple domains' although this would typically include only the addition of a single domain at any one time-point with staggered introduction of additional domains. Decisions about transition through levels would be made by the site, in conjunction with the RCC, and would be influenced by factors including speed and accuracy of identification of eligible participants, accuracy of information provided at time of randomization, compliance with allocated treatment status, and timeliness of reporting of outcome variables that are used to determine RAR algorithms. It is also permissible to commence the trial with multiple domains being active at initiation.

8.1.2. Vanguard sites

In each region or at the initiation of a new domain or both, the trial may consider commencing with only a small number of vanguard sites. The purpose of commencing the trial at vanguard sites is to learn about the effectiveness of different options for trial processes so that this information about the most effective trial processes can be shared with subsequent non-vanguard sites. If a site is acting as a vanguard site this will be specified in any application for ethical approval at that site.

8.2. Recruitment of participants including embedding

8.2.1. Embedding

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

The success of embedding can be evaluated by the proportion of eligible participants who are recruited and randomized, that recruitment and randomization occurs as soon as possible after eligibility occurs, and that there is compliance with the allocated intervention. Successful embedding will enhance the internal and external validity of the results generated by the trial.

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

8.2.2. Participant recruitment procedures at participating sites

Once screened and identified as eligible the clinical staff (medical or nursing) or research staff will randomize the participant. Standard Operating Procedures (SOPs) will be developed to guide staff who undertake randomization. For example, in ICUs with an eCIS, an integrated website link may be used to allow direct access to the trial randomization webpage and, where possible, provide a

summary (or direct population from the eCIS) of information that is required to be entered into the randomization web-site. To complement this system the research staff in each ICU will review patients admitted each day to assess the suitability of patients deemed not eligible out of hours, either because they were missed on screening or because the clinical situation has changed.

8.3. Treatment allocation

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

8.4. Delivery of interventions

8.4.1. Treatment allocation and protocol adherence at participating units

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

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

8.5. Unblinding of allocation status

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

8.6. Criteria for discontinuation of a participant in the trial

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

Criteria for discontinuation from the REMAP interventions entirely include:

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

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

8.7. Concomitant care and co-interventions

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

8.8. Data collection

8.8.1. Principles of data collection

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

8.8.2. Variables to be collected

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

8.8.2.1 *Baseline and required for randomization*

- Overall REMAP Inclusion / exclusion check list
- Date and time of hospital admission
- Date and time of first ICU admission (if relevant)
- Domain-specific exclusion checklist
- Shock status
- Hypoxemia status

8.8.2.2 *Baseline but not required for randomization*

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

8.8.2.3 *Daily from ICU admission until discharge from ICU or Day-21 whichever comes first*

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

8.8.2.4 *ICU Outcome data*

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

8.8.2.5 *Hospital outcome data*

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

8.8.2.6 *Antimicrobial Administration*

- Administration of antibiotic medications
- Administration of antiviral medications

8.8.2.7 *Outcome data*

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

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

8.8.2.8 *Process-related outcomes*

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

8.8.3. Data required to inform Response Adaptive Randomization

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

3. Baseline and allocation status
    a. Unique trial-specific number
    b. Location (Site code)
    c. Date and time of randomization
    d. Eligibility for each domain
    e. Intervention allocation for each domain
    f. Reveal status for each intervention allocation for each domain
    g. Age category
    h. Strata
        i. Shock or no shock
    i. State
    j. Location in ICU or not
4. Outcome

a. 21-day ICU free days

Data fields required to inform the adaptive randomization process and Statistical Trigger will be pre-specified and will be required to be entered into the eCRF or electronically captured from the electronic health record within 7 days of death and within 28 days of enrollment in the REMAP if the participant is alive at day 28.

8.8.4. Blinding of outcome assessment

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

8.9. Data management

8.9.1. Source Data

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

8.9.2. Confidentiality

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

8.10. Quality assurance and monitoring

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

8.10.1. Plans for improving protocol adherence and complete data

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

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

- Start-up meeting for all research coordinators and investigators will be held prior to study commencement to ensure consistency in procedures;

- A detailed dictionary will define the data to be collected on the CRF;
- The data management center will perform timely validation of data, queries and corrections if errors are found during quality control checks;
- Data monitoring will occur as described below.

8.10.2. Data Monitoring

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

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

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

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

8.11. Data safety and monitoring board

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

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

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

8.12. Safety monitoring and reporting

8.12.1. Principles

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

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

8.12.2. Definition

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

8.12.3. Reporting Procedures for Serious Adverse Events

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

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

- Unique trial-specific number
- Date(s) of the event
- Nature of the event, including its outcome, and the rationale for attribution to a trial intervention

- Whether treatment was required for the event and, if so, what treatment was administered

8.12.4. Attribution of serious events to study interventions

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

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

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

9. GOVERNANCE AND ETHICAL CONSIDERATIONS

9.1. Management of participating sites and trial coordination

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

9.2. Ethics and regulatory issues

9.2.1. Guiding principles

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

9.2.2. Ethical issues relevant to this study

Patients who will be eligible for this study are critically ill, and many eligible patients will be receiving sedative medications for comfort, safety and to facilitate standard life saving emergency and ICU procedures. In patients who are not necessarily receiving sedative medications, the presence of critical illness, itself, leads commonly to an altered mental state that will affect the patient's mental capacity. The presence of these factors may mean that some patients who are eligible for the study may not be able to provide prospective consent for participation. Additionally, many interventions within this trial must be initiated urgently, either because there is an immediate time critical

imperative to initiate the intervention or because the most valid evaluation of the intervention occurs if the trial intervention is initiated at the same time-point as would occur in clinical practice.

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

- Patients who, in the opinion of the treating clinician, are competent to consent will be provided with information about the trial and invited to participate
- The vast majority of patients who are eligible for the REMAP will not be competent to consent. For such patients, and as permitted by local laws and requirements for ethical approval:
    - For domains in which all interventions available at the participating site are regarded as being part of the spectrum of acceptable standard care by the clinicians at that site, entry to the study is preferred to be via waiver-of-consent or some form of delayed consent. If required by local laws or ethical requirements and alternative to this pathway will be participation in conjunction with the agreement of an authorized representative of the participant.
    - For domains in which at least one intervention available at the participating site is regarded as experimental or not part of the spectrum of acceptable standard care then prospective agreement by an authorized representative will be required. An exception to this principle is recognized when there is a time-imperative need to commence the intervention which would routinely preclude obtaining the prospective agreement by an authorized representative.
    - For domains in which eligibility may develop after initial enrollment in the trial it is permissible to obtain contingent consent from the participant or contingent agreement from an authorized representative, i.e. there is contingent approval to randomize the participant if the participant meets eligibility criteria for a domain subsequently.
    - Where any participant is enrolled without having provided their own consent, the participant's authorized representative will be informed as soon as appropriate and informed of processes to cease trial participation. If required by local laws or processes for ethical approval, the authorized representative will be asked to provide agreement to on-going participation. In undertaking these trial processes research staff will be cognizant of the need to avoid unnecessary distress or create unnecessary confusion for authorized representatives and all other persons who have an interest in the participant's welfare.
    - Where any participant is enrolled without having provided their own consent, the participant should be informed of their enrollment after regaining competency, in accordance with local practice and jurisdictional requirements. Where any participant is

enrolled and does not regain competency (due to their death or neurological impairment) the default position, subject to local laws and ethical review processes, will be that the enrolled person will continue to be a participant in the trial.

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

9.2.3. Approvals

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

9.3. Protocol modifications

9.3.1. Amendments

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

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

All substantial amendments to the original approved documents, including all modifications of interventions available within a domain and the addition of interventions within a new domain will be submitted for approval to all relevant ethical and regulatory review bodies that were required for original approvals.

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

9.4. Confidentiality

The principles of confidentiality that will apply to this trial, are that all trial staff will ensure that the confidentiality of all participants information will be maintained and preserved at all times. The participants will be identified only by a unique trial-specific number on all documents and electronic databases that contain any information specific to the participating individual. Each site will

maintain a separate file that links each participant's unique trial-specific number to the participant's name and other identifying information such as date of birth, address, and other contact information. No other information will be maintained in the file that links the participant unique trial-specific number to participant identifying information.

9.5. Declarations of interest

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

9.6. Post-trial care

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

9.7. Communication

9.7.1. Reporting

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

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

9.7.2. Communication of trial results

Trial results will be communicated by presentation and publication.

9.8. Publication policy

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

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

9.9. Data access and ownership

9.9.1. Data ownership

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

9.9.2. Access to Data

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

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

- There is complete academic independence with regard to the design and conduct of all aspects of the trial including analysis and reporting of trial results
- May agree to provide a pre-publication version of presentations or manuscripts to a commercial organization but that the commercial organization has no authority to prevent or modify presentation or publication
- That all data are owned by the trial and the commercial organization has no authority to access data

9.10. Consent form

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

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Domain-Specific Appendix: COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN

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

COVID-19 Immunoglobulin Therapy Domain-Specific Appendix Version 2.5 dated 03 August 2020

Summary

In this domain of the REMAP-CAP trial, participants meeting the platform-entry criteria with microbiological testing confirmed SARS-CoV-2 infection will be randomized to receive one of two interventions:

- No immunoglobulin against SARS-CoV-2
- Convalescent plasma

This DSA applies to the following states and stratum:

<table>
<tr><td>Stratum</td><td colspan="3">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="3">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 colspan="2">Moderate State</td><td>Severe State</td><td>Severe State</td></tr>
<tr><td>Interventions specified in this DSA</td><td colspan="2">No immunoglobulin against SARS-CoV-2
Convalescent plasma</td><td>No immunoglobulin against SARS-CoV-2
Convalescent plasma</td><td>Not available</td></tr>
<tr><td>Interventions submitted for approval in this jurisdiction</td><td colspan="2">☐ No immunoglobulin against SARS-CoV-2
☐ Convalescent plasma</td><td>☐ No immunoglobulin against SARS-CoV-2
☐ Convalescent plasma</td><td>Not available</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>☐ No immunoglobulin against SARS-CoV-2
☐ Convalescent plasma</td><td>☐ No immunoglobulin against SARS-CoV-2
☐ Convalescent plasma</td><td>☐ No immunoglobulin against SARS-CoV-2
☐ Convalescent plasma</td><td>Not available</td></tr>
</table>

REMAP-CAP: Immunoglobulin Therapy Domain Summary	
Interventions	• No immunoglobulin against COVID-19 • Convalescent plasma (up to 2 units within 48 hours)
Unit-of-analysis and Strata and States	The default unit-of-analysis for this domain will be the pandemic infection suspected or confirmed (PISOP) stratum with SARS-CoV-2 infection strata applied. 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. Borrowing is permitted between states. Response Adaptive Randomization will be applied to using probabilities derived from the SARS-CoV-2 confirmed stratum.
Evaluable treatment-by-treatment Interactions	No interaction will be evaluated with any other domain.
Nesting	None
Timing of Reveal	Randomization with Deferred Reveal at time of confirmation of infection by microbiological testing.
Inclusions	Inclusion criteria are the same as those specified in the relevant core protocol documents, and • SARS-CoV-2 infection is confirmed by microbiological testing
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • If in ICU, more than 48 hours have elapsed since ICU admission • Patient has already received treatment with any non-trial prescribed antibody therapy (monoclonal antibody, hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this hospital admission • **Enrolment in a trial evaluating any antibody therapy directed against COVID-19, where the protocol of the trial requires continuation of the treatment assignment specified in that trial** • More than 14 days have elapsed since 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 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 previous history of transfusion-related acute lung injury will exclude a patient from receiving convalescent plasma • Known objection to receiving plasma products will exclude a patient from receiving any plasma components
Outcome measures	Primary REMAP endpoint: refer to the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol. Secondary REMAP endpoints refer to the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol

	Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrolment): • All-cause mortality at 28 days • Confirmed deep venous thrombosis • Confirmed pulmonary embolism • Confirmed ischemic stroke • Confirmed acute myocardial infarction • Other confirmed thrombotic events • Serious treatment-related adverse events (SAE) as defined in this appendix • Serious Adverse Events (SAE) as defined in Core Protocol

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1. ABBREVIATIONS

ADE	Antibody-dependent enhancement
CCP	Clinical Characterization Protocol
CRP	C-reactive protein
CVA	Cerebrovascular accident
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
DVT	Deep vein thrombosis
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
MERS-CoV	Middle East respiratory syndrome coronavirus
NHS	National Health Service of the United Kingdom
NHSBT	National Health Service Blood and Transplant
PAtC	Pandemic Appendix to the Core Protocol
PE	Pulmonary Embolism
PISOP	Pandemic Infection Suspected or Proven
PT	Prothrombin time
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS	Serious Acute Respiratory Syndrome
TACO	Transfusion-Associated Circulatory Overload
TRALI	Transfusion-related acute lung injury
TTI	Transfusion-Associated Circulatory Overload
WHO	World Health Organization

2. PROTOCOL APPENDIX STRUCTURE

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

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models) and 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 Regions-Specific Appendices (RSA) (detailing regional management and governance).

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

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

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

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

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

3. COVID-19 IMMUNOGLOBULIN DOMAIN-SPECIFIC APPENDIX VERSION

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

3.1. Version history

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

Version 2: Approved by the COVID-19 Immunoglobulin Therapy Domain-Specific Working Group (DSWG) on 30 June 2020

Version 2.5: Approved by the New Zealand members of the COVID-19 Immunoglobulin Therapy DSWG on 03 August 2020

4. COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN GOVERNANCE

4.1. Domain members

Chair:

Dr. Lise Estcourt*

Country Leads:

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Canada	Dr. Alexis Turgeon[2]
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Members:

Dr. Donald Arnold[2]
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Ms. Helen Thomas[1]
Dr. Alan Tinmouth[2]
Prof. Tim Walsh[1]
Prof. Steve Webb[4]
Prof. Erica Wood[4]

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5. COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

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

Chair Lise Estcourt		Date 30 June 2020
Country lead Tom Hills		03 August 2020
Country lead Colin McArthur		03 August 2020

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP platform to test the effectiveness of different strategies for immunoglobulin therapy for microbiological testing-confirmed SARS-CoV-2 infection in patients with acute illness due to suspected or proven COVID-19.

This is the version of the COVID-19 Immunoglobulin Therapy Domain that will apply in New Zealand and has the version number 2.5. It is anticipated that this domain may also enroll patients in other countries. However, because of differences in nature and supply of product, or timing of availability of product, it is anticipated that differences in the DSA will be necessary. Versions used in other countries, that are derived from this DSA, will be numbered sequentially with a new number after the decimal point (i.e. 1.1, 1.2 etc.) each applying to new countries. A major revision to the DSA will be allocated a new number before the decimal point, i.e. 2.0.

6.2. Domain-specific background

6.2.1. COVID-19 Infection

The first report of infection with SARS-CoV-2 (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 millions of reported cases across the globe, with hundreds of thousands of deaths, and documented sustained human-to-

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/newsroom/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)). Due to previous experience with other 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 is to understand the effectiveness of COVID-19 treatments. Clinical guidance issued by the WHO indicates that unproven therapies should be administered preferably only within the setting of a clinical trial (https://www.who.int/docs/defaultsource/coronaviruse/clinical-management-of-novel-cov.pdf).

Globally, as of 20 June 2020 there are 8,666,697 confirmed cases, 460,066 deaths and 4,247,527 patients have recovered from SARS-CoV-2 illness (https://coronavirus.jhu.edu/map.html; Accessed on 20 June 2020). Estimates of the burden of critical illness among patients infected with COVID-19 vary and the corresponding case-fatality estimates are affected by factors such as health system capacity including the availability of diagnostic testing and critical care beds. Nevertheless, it is recognized that fatal critical illness, especially from severe respiratory failure from pneumonitis is high. In reports from China and from Italy (Grasselli et al., 2020, Huang et al., 2020, Remuzzi and Remuzzi, 2020), the proportion of confirmed COVID-19 cases requiring organ support in critical care units varies between 16% to 32% of all hospitalized SARS-CoV-2 illness. Although the overall case fatality rate is estimated as 5.7% (95% confidence intervals 5.5% – 5.9%) for COVID-19 disease for hospitalized patients (Baud et al., 2020), the mortality in critically ill patients with COVID-19 disease, especially those requiring mechanical ventilation, is much higher (Yang et al., 2020).

Interim guidance from the WHO for clinical care of infected patients focus upon supportive care, including organ support as needed, prevention of complications, and no specific anti-COVID-19 therapies. The WHO have recommended that any specific therapy targeted to COVID-19 infection should be provided only as part of a research protocol (https://www.who.int/publications/i/item/clinical-management-of-covid-19).

6.2.2. Convalescent Plasma

Convalescent plasma treatment, containing high titers of polyclonal antibody (Ab), has been used to treat severe viral pneumonia. Many studies have been poorly controlled but such series have shown decreased mortality in Spanish Influenza A (H1N1) infections in 1915-1917 (Luke et al., 2006, McGuire and Redden, 1918), Influenza A (H1N1)pdm09 infections in 2009/2010 (Hung et al., 2011, Ortiz et al., 2013) and of more relevance to this trial, SARS-CoV infections in 2003 (Cheng et al., 2005, Soo et al., 2004). A systematic review and meta-analysis performed identified 699 treated patients with SARS coronavirus infection or severe influenza and 568 untreated “controls” (Mair-Jenkins et al., 2015) found consistent reports of a reduction in mortality. Post hoc meta-analysis showed a statistically significant reduction in the pooled odds of mortality following treatment, compared with placebo or no therapy (odds ratio, 0.25; 95% CI:0.14–0.45) (Mair-Jenkins et al., 2015).

Several trials have shown that convalescent plasma had some efficacy in the treatment of SARS-CoV infection. Eight observational studies reported improved mortality after patients with SARS-CoV – infection received various amounts of convalescent plasma (Mair-Jenkins et al., 2015). For example, a small retrospective case-comparison study (19 vs 21 patients) showed a 23% (95% CI: 6%-42%,

p≤0.05) reduction in mortality after treatment with 200-400 ml of convalescent plasma, when compared with continuation of high-dose methylprednisolone (Soo et al., 2004). In a case series of 80 patients treated with 160-640 ml of convalescent plasma 12.5% died compared with the overall SARS-related mortality rate in Hong-Kong of 17% (Cheng et al., 2005). In this limited series, convalescent plasma given before 14 days after the onset of symptoms was associated with better outcome, however such post-hoc analyses are fraught with confounding factors but do suggest early treatment may be more efficacious.

Reports on the use of convalescent plasma to treat COVID-19 have emerged from the early stages of the pandemic in China (Duan et al., 2020, Shen et al., 2020, Zhang et al., 2020). The largest study showed that 10 patients hospitalized with COVID-19 each given 200ml of convalescent plasma with a neutralizing antibody titer of >1:640 described an improvement in clinical, laboratory and radiological parameters. However, this study was not adequately controlled or powered to allow robust conclusions (Duan et al., 2020).

Subsequently, the effectiveness of convalescent plasma has been assessed in an open-label, multicenter, randomized clinical trial in China comparing convalescent plasma with standard of care in 103 patients with 'severe' or 'life-threatening' COVID-19 (Li et al., 2020). There was a higher rate of nasopharyngeal SARS-CoV-2 PCR negativity at 72 hours in the convalescent plasma group (87.2% vs 37.5%, OR, 11.39 [95% CI, 3.91-33.18]; P < 0.001). In patients with 'severe' COVID-19, clinical improvement, defined as either hospital discharge or reduction of 2 points on a 6-point disease severity scale ranging from 6=death to 1=discharge, occurred in 91.3% (21/23) of the convalescent plasma group and 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; P = 0.03). However, this clinical improvement with convalescent plasma was not seen in patients with 'life-threatening' COVID-19. Overall, the secondary outcome of 28-day mortality was not significantly reduced with convalescent plasma treatment (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46]; P = 0.30).

6.2.2.1. *Adverse effects of convalescent plasma*

Minor side effects have been reported with convalescent plasma, such as fever or chills (Luke et al., 2006), or allergic transfusion reactions (Beigel et al., 2019). More significantly two reports of possible transfusion-related acute lung injury (TRALI) following convalescent plasma have been documented in one patient with Ebola disease and one patient with MERS-CoV, although no anti-HLA or anti-HNA antibodies were identified in donor plasma (Chun et al., 2016, Mora-Rillo et al., 2015). However, none of the 84 patients in the Ebola randomized controlled trial developed any serious adverse events due to the transfusion (Van Griensven et al., 2016). Convalescent plasma has now been given to more than 20,000 COVID-19 patients in the United States of America through an expanded access program (Joyner et al., 2020). In a convenience sample of 20,000 of these patients, mostly with 'severe' or 'life-threatening' COVID-19, the administration of convalescent plasma was generally safe with a low rate of serious adverse events. Specifically, transfusion reactions (n=89; <1%), thromboembolic or thrombotic events (n=87; <1%), and cardiac events (n=680, ~3%) were uncommon and the majority of thromboembolic/thrombotic (55/87) and cardiac events (562/680) were deemed to be unrelated to the convalescent plasma therapy.

6.2.2.2. *Antibody Dependent Enhancement*

Antibody-dependent enhancement (ADE) occurs when antibodies facilitate viral entry into host cells and enhance viral infection in these cells (Wan et al., 2019). Potential toxicity associated with convalescent plasma remains a concern, and this is very relevant to COVID-19 patients who exhibit a spectrum of lung pathology from acute lung injury to acute respiratory disease syndrome and death.

In SARS-CoV-associated disease, antibodies may mediate pathology if they target a different serotype of the virus (Wan et al., 2019, Wang et al., 2014). Furthermore, a novel mechanism for ADE where a neutralizing antibody binding to the surface protein of a coronavirus-like viral receptor triggers viral cell entry has been recently proposed. This ADE pathway was shown not only to be antibody dose dependent but also likely mediated by presence of non-neutralizing antibodies (Ricke and Malone, 2020). For these reasons, we plan to collect convalescent plasma at the earliest 28 days after recovery so that antibody response has matured in terms of titer and affinity.

There is currently no evidence of ADE occurring in the current epidemic, and a small trial of 10 patients in China with COVID-19 treated in a single infusion of 200ml of convalescent plasma showed neither pulmonary injury nor infection enhancement. The high levels of neutralizing antibodies (>1:640), timely transfusion (median time from onset of symptoms to hospital admission and CP transfusion was 6 days (IQR, 2.5–8.5 days) and 16.5 days (IQR 11.0–19.3 days), respectively, and appropriate plasma volume (200ml) were thought to contribute to the absence of side-effects (Duan et al., 2020).

6.2.2.3. *Collection of Convalescent Plasma*

New Zealand Blood Service (NZBS) has commenced collecting convalescent plasma from recovered COVID-19 infected individuals. Donors are eligible if they have a history of confirmed COVID-19, are at least 28 days from COVID-19 symptom resolution (defined as the date they become afebrile) and meet eligibility criteria for acceptance as blood donors. In addition to the usual donor and donation screening, donors must meet NZBS's standard TRALI risk mitigation controls (i.e. un-transfused male or HLA antibody tested female donors). Donor plasma will be tested for SARS-CoV-2 serology, and if reactive, a neutralising assay will be performed. All donations will be tested for SARS-CoV-2 RNA. Convalescent plasma will be collected and processed in exactly the same pathway as clinical plasma and will meet all regulatory requirements for use as clinical plasma.

6.2.2.4. *Administration of convalescent plasma*

Administration of convalescent plasma is more likely to be beneficial early in the course of the disease (up to 10 to 14 days after onset of symptoms) (Chen et al., 2020).

6.2.2.5. *Need for a clinical trial*

Thus far, the available literature indicates that convalescent plasma has been used to treat thousands of patients with COVID-19 and that, in this setting, rates of serious adverse effects are low. There is a lack of high-quality evidence to determine whether convalescent plasma is an effective therapy for hospitalized patients with COVID-19 and crucial questions remain unanswered, including whether convalescent plasma reduces mortality in hospitalized patients and whether it improves outcomes in the critically unwell.

6.2.3. Intervention Strategy for this domain

It is intended that this domain of REMAP-CAP will evolve, taking into account evidence derived from other clinical trials, as well as availability of potentially effective immunoglobulin therapies. WHO guidance notes the flexibility associated with REMAP-CAP as a platform for the testing of multiple agents, including serial testing of additional interventions (https://apps.who.int/iris/bitstream/handle/10665/330680/WHO-HEO-RDBlueprint%28nCoV%29-2020.1-eng.pdf?ua=1).

At the commencement of this domain, a control group is included (i.e. some patients will not receive any immunoglobulin therapy that is intended to be active against COVID-19 infection). This is

appropriate for two reasons. Firstly, there is relatively limited trial or clinical experience with the administration of immunoglobulin therapies and it is not reasonable to presume that such agents do not cause net harm. Secondly, designs that include only active interventions are not able to ascertain if any option is better or worse than no treatment. If, during the evolution of this domain, there is sufficient evidence of effectiveness of agents or clinical practice changes to include the routine use of such agents or both, the control intervention that specifies that no immunoglobulin therapy is administered will be abandoned. Although this domain will commence with a single immunoglobulin therapy, it is intended that additional agents can be added (allowing evaluation of several agents against a common control intervention) as well as allowing introduction of combinations of agents (to evaluate potential synergy). Any changes to the intervention structure of the domain will be specified using one or more amendments to this DSA with implementation occurring only after ethical approval has been obtained. The initial selection of immunoglobulin therapy to be evaluated is convalescent plasma. If at any stage evidence of harm or definitive evidence of absence of effectiveness in critically ill patients emerges for any intervention specified in this domain, the ITSC, as advised by the DSWG, may remove an intervention prior to declaration of a Platform Conclusion. If this occurs, presentation and publication of results that relate to that intervention will occur, so as to contribute additional weight of evidence available in the public domain.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of Immunoglobulin Therapy for patients who are eligible for the platform and who have microbiological testing-confirmed COVID-19.

We hypothesize that the probability of the occurrence of the primary end-point specified in the relevant core protocol documents will differ based on the immunoglobulin therapy intervention. The following interventions will be available:

- No immunoglobulin against SARS-CoV-2
- Convalescent plasma

Each participating site has the option to opt-in to two or more interventions to be included in the randomization schedule depending on local clinical preference, usual practice, acceptable practice, and the availability of the intervention at that site. As long as the ‘no immunoglobulin therapy for COVID-19’ intervention is retained in the platform it is strongly preferred that this intervention is always included by participating sites and is mandatory so long as there is only a single active intervention within the domain.

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial. Treatment allocation will be adaptive, as described in either the REMAP-CAP Core Protocol +/- Pandemic Appendix or the REMAP-COVID Core Protocol.

8.1. Population

The REMAP enrolls patients with severe pneumonia admitted to ICU and patients with acute illness due to suspected or proven COVID-19 admitted to hospital, including patients admitted to ICU).

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in either the REMAP-CAP Core Protocol +/- Pandemic Appendix or the REMAP-COVID Core Protocol. Patients eligible for REMAP-CAP may have conditions that exclude them from the COVID-19 Immunoglobulin Therapy Domain.

8.2.1. Domain inclusion criteria

Patients are eligible for this domain if:

- SARS-CoV-2 infection is confirmed by microbiological testing

8.2.2. Domain exclusion criteria

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

- If currently in ICU, 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)
- Patient has already received treatment with any non-trial prescribed antibody therapy (monoclonal antibody, hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this hospital admission
- **Enrolment in a trial evaluating any antibody therapy directed against COVID-19, where the protocol of the trial requires continuation of the assignment specified in that trial**
- More than 14 days have elapsed since hospital admission
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

8.2.3. Intervention exclusion criteria

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons.

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 who are not eligible for this domain 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/allergy to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
- Known previous history of transfusion-related acute lung injury will exclude a patient from receiving convalescent plasma

- Known objection to receiving plasma products will exclude a patient from receiving any plasma components

8.3. Interventions

8.3.1. Immunoglobulin Therapy Interventions

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

- No immunoglobulin against COVID-19
- Convalescent plasma

If the domain evolves to comprise 3 or more interventions, it is required that all sites will participate in the 'No immunoglobulin against COVID-19' intervention, and each site has the option to opt-in to one or more of the remaining interventions based on local practice and availability of the intervention.

8.3.2. No immunoglobulin against SARS-CoV-2

Patients assigned to this intervention will not receive any preparation of immunoglobulin intended to neutralize SARS-CoV-2 during the index hospitalization. Administration of such a preparation is considered a protocol deviation.

8.3.3. Convalescent Plasma

8.3.3.1. *Dosing of convalescent plasma*

Patients assigned to receive plasma will receive at least one and not more than two adult units of ABO compatible convalescent plasma (total volume 550ml ± 150ml) within 48 hours of randomization. If no ABO compatible convalescent plasma units are available, consideration may be given to the use of low-titer non-ABO compatible convalescent plasma. Volume of convalescent plasma administered will be recorded and where available the level of antibodies within each unit will be tested.

8.3.3.2. *Duration of administration of convalescent plasma*

Those receiving plasma will receive a unit of ABO compatible convalescent plasma on the first day of the study. If the patient has no serious adverse reactions to the transfusion the second unit of convalescent plasma will be given. There must be a minimum of 12 hours between transfusions to allow appropriate assessment of adverse reactions to the initial transfusion. Both transfusions should be given within 48 hours from randomization.

8.3.4. Discontinuation of study therapy

An immunoglobulin for SARS-CoV-2 infection should be discontinued if there is development of an SAE. Immunoglobulin therapy can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

8.4. Concomitant care

In patients who have received an allocation status in the COVID-19 Antiviral Domain, and have microbiological testing confirmed SARS-CoV-2 infection, continuation of antiviral agent will be as per the COVID-19 Antiviral Domain-Specific Appendix (Section 8.3). Additional agents intended to be active against SARS-CoV-2 infection should not be administered, unless they have become standard of care during the trial or specified in another trial protocol. All 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 (occurring during the index hospitalization, censored at 90 days after enrollment) will be:

- All-cause mortality at 28 days
- Confirmed deep vein thrombosis
- Confirmed pulmonary embolus
- Confirmed ischemic cerebrovascular event
- Confirmed acute myocardial infarction
- Other confirmed thrombotic events
- Serious treatment-related adverse events (see section 11.2 of this appendix)
- Serious Adverse Events (SAE) as defined in core protocol documents and qualified in this appendix.

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 and any additional testing, which may differ between locations, is specified below.

Sites that are participating in this domain are encouraged to also participate in the Clinical Characterization Protocol (CCP) for patients with COVID-19 that has been established by the International Severe Acute Respiratory and Emerging Infectious Consortium

(https://isaric.tghn.org/CCP/). This protocol specifies the collection of biological samples from patients with COVID-19. Samples collected in patients who are enrolled in the CCP may be made available to REMAP-CAP investigators to evaluate aspects of host or pathogen biology associated with assignment in this domain. Ethical approval at such sites and agreement from patients to undertake the CCP will be obtained separately.

9.2. Domain-specific data collection

Additional domain-specific data will be collected for the index hospitalization:

- Administration of immunoglobulin therapies
- Neutralizing antibody titer of trial immunoglobulin therapies (where available)
- Deep vein thrombosis
- Pulmonary embolism
- Ischemic cerebrovascular events
- Peak troponin
- Acute myocardial infarction (using fourth international definition)

Additional domain-specific data will be collected on all participants from clinically indicated testing where available at baseline: neutrophil count, lymphocyte count, prothrombin time (PT), fibrinogen, and C-reactive protein, D-dimers and troponin. It is recommended that a baseline serum sample (prior to receipt of convalescent plasma) is obtained to allow the measurement of SARS-CoV-2 antibodies and neutralizing antibodies.

9.3. Criteria for discontinuation

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

9.4. Blinding

9.4.1. Blinding

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

9.4.2. Unblinding

Not applicable.

10. STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

The following Platform Conclusions are possible in this domain:

- Superiority of convalescent plasma compared to no immunoglobulin against SARS-CoV-2

- Futility of convalescent plasma compared to no immunoglobulin against SARS-CoV-2

Additional Platform Conclusions may be possible if further interventions are added to the domain.

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

10.2. Unit-of-analysis and strata

This domain is analyzed only in the pandemic statistical model and includes only patients who are SARS-CoV-2 infection confirmed. 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. Borrowing is permitted between states and strata. Response Adaptive Randomization will be applied in each illness severity state, using probabilities derived from the SARS-CoV-2 confirmed stratum.

The shock strata will not contribute to unit-of-analysis for this domain, as this strata is not applied in the Pandemic Statistical Model.

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

10.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal or Randomization with Deferred Reveal if confirmation of microbiological diagnosis is not known at the time of initial assessment of eligibility (see relevant core protocol documents)

10.4. Interactions with interventions in other domains

An a priori interaction with the Antibiotic Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the Macrolide Duration Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Influenza Antiviral Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the COVID-19 Antiviral Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Immune Modulation Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Corticosteroid Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Statin Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Vitamin C Domain is either not considered possible and will not be incorporated into the statistical model used to evaluate this domain in the pandemic statistical model or is not able to be evaluated for PINSNP patients as analysis occurs in different statistical models.

No interaction is evaluable between the Ventilation Domain and this domain.

10.5. Nesting of interventions

Nesting is not applicable to this domain

10.6. Threshold probability for superiority, effectiveness and inferiority

The threshold odds ratio delta for superiority, effectiveness and inferiority in this domain are those specified in the relevant core protocol documents

10.7. Threshold odds ratio delta for equivalence or futility

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 an active intervention.

10.8. Informative priors

This domain will launch with priors that are not informative for main effects. If new immunoglobulin agents are added to the domain, consideration will be given to the use of informative priors at the time of amendment of the DSA.

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. Data for post-trial sub-group analysis may not be available from all regions or for all patients in a region. The a priori patient sub-groups of interest are:

- Proven concomitant bacterial co-infection, defined as having isolation or detection of a known pathogen that causes pneumonia from blood, pleural fluid, or lower respiratory tract specimen.
- Receiving invasive mechanical ventilation at baseline
- Patients with undetectable virus at baseline (convalescent plasma intervention)
- Patients with different levels of neutralizing antibodies at baseline (convalescent plasma intervention)
- Dose of neutralizing antibodies received (convalescent plasma intervention, based on volume of transfusion and titer measurement, where available)
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

10.10. Domain-specific secondary and exploratory analyses

- Number of SAEs (excluding thrombotic events) from randomization until 72 hours after randomization, per day at risk; described by intervention.
- Number of thrombotic events from randomization up to the end of acute hospitalization, per day at risk. These will be analyzed using Poisson regression.
- Analyses of the data from any country-specific sub-studies will be specified in separate analysis plans.

10.11. Data sharing

Not applicable.

11. ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, effectiveness, inferiority, futility or equivalence of different interventions with respect to the primary endpoints are possible, and if equivalence is demonstrated, determination of the optimal intervention may be based on secondary endpoints, such as all-cause mortality at 28 days.

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 are required.

11.2. Potential domain-specific adverse events

11.2.1. Convalescent Plasma

The following possible treatment-related adverse events should be reported in all patients in this domain, irrespective of intervention allocation. In addition, site staff are responsible for reporting all transfusion-related adverse events to their national or regional hemovigilance system

- Severe allergic reaction or anaphylaxis
- Transfusion-associated Acute Lung Injury (TRALI)
- Transfusion-associated Circulatory Overload (TACO)

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

11.3. Domain-specific consent issues

As noted in the background, and endorsed by the WHO, in the absence of evidence of effectiveness of specific treatments for COVID-19, the use of a no treatment control is both appropriate and ethical.

For patients who are not competent to consent, either prospective agreement or entry via waiver of-consent or some form of deferred consent can be applied, as required by an appropriate ethical review body.

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.

Clinicians are directed to not enrol an individual patient if the treating clinician believes that participation in this domain is not in the best interests of the patient.

12. GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the core protocol documents. Further additional funding may be obtained during the life-time of the domain.

12.2. Funding of domain interventions and outcome measures

The New Zealand Blood Service will supply the convalescent plasma for the trial and arrange for distribution to 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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Domain-Specific Appendix: COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN

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

COVID-19 Immunoglobulin Therapy Domain-Specific Appendix Version 2.4.2 dated 23 July 2020

Summary

In this domain of the REMAP-CAP trial, participants meeting the platform-entry criteria with microbiological testing confirmed SARS-CoV-2 infection will be randomized to receive one of two interventions:

- No immunoglobulin against SARS-CoV-2
- Convalescent plasma

This DSA applies to the following states and stratum:

<table>
<tr><td>Stratum</td><td colspan="3">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="3">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 colspan="2">Moderate State</td><td>Severe State</td><td>Severe State</td></tr>
<tr><td>Interventions specified in this DSA</td><td colspan="2">No immunoglobulin against SARS-CoV-2
Convalescent plasma</td><td>No immunoglobulin against SARS-CoV-2
Convalescent plasma</td><td>Not available</td></tr>
<tr><td>Interventions submitted for approval in this jurisdiction</td><td colspan="2">☐ No immunoglobulin against SARS-CoV-2
☐ Convalescent plasma</td><td>☐ No immunoglobulin against SARS-CoV-2
☐ Convalescent plasma</td><td>Not available</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>☐ No immunoglobulin against SARS-CoV-2
☐ Convalescent plasma</td><td>☐ No immunoglobulin against SARS-CoV-2
☐ Convalescent plasma</td><td>☐ No immunoglobulin against SARS-CoV-2
☐ Convalescent plasma</td><td>Not available</td></tr>
</table>

REMAP-CAP: Immunoglobulin Therapy Domain Summary	
Interventions	• No immunoglobulin against COVID-19 • Convalescent plasma (up to 2 units within 48 hours)
Unit-of-analysis and Strata and States	The default unit-of-analysis for this domain will be the pandemic infection suspected or confirmed (PISOP) stratum with SARS-CoV-2 infection strata applied. 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. Borrowing is permitted between states. Response Adaptive Randomization will be applied to using probabilities derived from the SARS-CoV-2 confirmed stratum.
Evaluable treatment-by-treatment Interactions	Treatment-treatment interactions will be evaluated between interventions in this domain and interventions in the Corticosteroid Domain and the COVID-19 Antiviral Therapy Domain. No other interactions will be evaluated with any other domain.
Nesting	None
Timing of Reveal	Randomization with Deferred Reveal at time of confirmation of infection by microbiological testing.
Inclusions	Inclusion criteria are the same as those specified in the relevant core protocol documents, and • SARS-CoV-2 infection is confirmed by microbiological testing
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • If in ICU, more than 48 hours have elapsed since ICU admission • Patient has already received treatment with any non-trial prescribed antibody therapy (monoclonal antibody, hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this hospital admission • **Enrolment in a trial evaluating any antibody therapy directed against COVID-19, where the protocol of the trial requires continuation of the treatment assignment specified in that trial** • More than 14 days have elapsed since 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 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 previous history of transfusion-related acute lung injury will exclude a patient from receiving convalescent plasma • Known objection to receiving plasma products will exclude a patient from receiving any plasma components
Outcome measures	Primary REMAP endpoint: refer to the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol. Secondary REMAP endpoints refer to the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol

	Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrolment): • All-cause mortality at 28 days • Confirmed deep venous thrombosis • Confirmed pulmonary embolism • Confirmed ischemic stroke • Confirmed acute myocardial infarction • Other confirmed thrombotic events • Serious treatment-related adverse events (SAE) as defined in this appendix • Serious Adverse Events (SAE) as defined in Core Protocol Domain-specific exploratory outcomes • Nil

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1. ABBREVIATIONS

ADE	Antibody-dependent enhancement
CCP	Clinical Characterization Protocol
CRP	C-reactive protein
CVA	Cerebrovascular accident
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
DVT	Deep vein thrombosis
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
MERS-CoV	Middle East respiratory syndrome coronavirus
NHS	National Health Service of the United Kingdom
NHSBT	National Health Service Blood and Transplant
PAtC	Pandemic Appendix to the Core Protocol
PE	Pulmonary Embolism
PISOP	Pandemic Infection Suspected or Proven
PT	Prothrombin time
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS	Serious Acute Respiratory Syndrome
TACO	Transfusion-Associated Circulatory Overload
TRALI	Transfusion-related acute lung injury
TTI	Transfusion-Associated Circulatory Overload
WHO	World Health Organization

2. PROTOCOL APPENDIX STRUCTURE

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

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models) and 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 Regions-Specific Appendices (RSA) (detailing regional management and governance).

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

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

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

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

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

3. COVID-19 IMMUNOGLOBULIN DOMAIN-SPECIFIC APPENDIX VERSION

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

3.1. Version history

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

Version 2: Approved by the COVID-19 Immunoglobulin Therapy Domain-Specific Working Group (DSWG) on 30 June 2020

Version 2.4: Approved by the Australian members of the COVID-19 immunoglobulin Therapy DSWG on 04 July 2020

4. COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN GOVERNANCE

4.1. Domain members

Chair:

Dr. Lise Estcourt*

Country Leads:

United Kingdom	Dr. Lise Estcourt[1]
	Dr. Manu Shankar-Hari[1]
Canada	Dr. Alexis Turgeon[2]
	Dr. Ryan Zarychanski[2]
USA	Dr. Bryan McVerry[3]
Australia	A/Prof. Zoe McQuilten[4]
New Zealand	Dr. Tom Hills[5]
	Dr. Colin McArthur[5]
Ireland	Prof. Alistair Nicol[6]

Members:

Dr. Donald Arnold[2]
Dr. Phillipe Bégin[2]
A/Prof. Scott Berry
Dr. Richard Charlewood[5]
Dr. Michaël Chassé[2]
A/Prof. Mark Coyne[6]
Prof. Jamie Cooper[4]

Dr. James Daly[4]
Prof. Dean Fergusson[2]
Prof. Anthony Gordon[1]
Prof. Iain Gosbell[4]
Dr. Heli Harvala-Simmonds[1]
Dr. Sheila MacLennan[1]
Dr. John Marshall[2]
Prof. David Menon[1]
Dr. Susan Morpeth[5]
Mr. Paul Mouncey
Dr. Srinivas Murthy[2]
Dr. Nicole Pridee[1]
Prof. David Roberts[1]
Prof. Kathy Rowan[1]
Ms. Helen Thomas[1]
Dr. Alan Tinmouth[2]
Prof. Tim Walsh[1]
Prof. Steve Webb[4]
Prof. Erica Wood[4]

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[2] Members leading the Canadian COVID-19 Immunoglobulin Therapy Domain
[3] Members leading the USA COVID-19 Immunoglobulin Therapy Domain
[4] Members leading the Australian COVID-19 Immunoglobulin Therapy Domain
[5] Members leading the New Zealand COVID-19 Immunoglobulin Therapy Domain
[6] Members leading the Irish COVID-19 Immunoglobulin Therapy Domain

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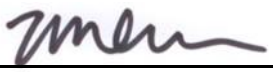
5. COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

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

Chair  Date 30 June 2020
Lise Estcourt

Country lead  Date 04 July 2020
Zoe McQuilten

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP platform to test the effectiveness of different strategies for immunoglobulin therapy for microbiological testing-confirmed SARS-CoV-2 infection in patients with acute illness due to suspected or proven COVID-19.

This is the version of the COVID-19 Immunoglobulin Therapy Domain that will apply in Australia and has the version number 2.4. It is anticipated that this domain may also enroll patients in other countries. However, because of differences in nature and supply of product, or timing of availability of product, it is anticipated that differences in the DSA will be necessary. Versions used in other countries, that are derived from this DSA, will be numbered sequentially with a new number after the decimal point (i.e. 1.1, 1.2 etc.) each applying to new countries. A major revision to the DSA will be allocated a new number before the decimal point, i.e. 2.0.

6.2. Domain-specific background

6.2.1. COVID-19 Infection

The first report of infection with SARS-CoV-2 (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 millions of reported cases across the globe, with hundreds of thousands of deaths, and documented sustained human-to-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/newsroom/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)). Due to previous experience with other 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 is to understand the effectiveness of COVID-19 treatments. Clinical guidance issued by the WHO indicates that unproven therapies should be administered preferably only within the setting of a clinical trial (https://www.who.int/docs/defaultsource/coronaviruse/clinical-management-of-novel-cov.pdf).

Globally, as of 20 June 2020 there are 8,666,697 confirmed cases, 460,066 deaths and 4,247,527 patients have recovered from SARS-CoV-2 illness (https://coronavirus.jhu.edu/map.html; Accessed on 20 June 2020). Estimates of the burden of critical illness among patients infected with COVID-19 vary and the corresponding case-fatality estimates are affected by factors such as health system capacity including the availability of diagnostic testing and critical care beds. Nevertheless, it is recognized that fatal critical illness, especially from severe respiratory failure from pneumonitis is high. In reports from China and from Italy (Grasselli et al., 2020, Huang et al., 2020, Remuzzi and Remuzzi, 2020), the proportion of confirmed COVID-19 cases requiring organ support in critical care units varies between 16% to 32% of all hospitalized SARS-CoV-2 illness. Although the overall case fatality rate is estimated as 5.7% (95% confidence intervals 5.5% – 5.9%) for COVID-19 disease for hospitalized patients (Baud et al., 2020), the mortality in critically ill patients with COVID-19 disease, especially those requiring mechanical ventilation, is much higher (Yang et al., 2020).

Interim guidance from the WHO for clinical care of infected patients focus upon supportive care, including organ support as needed, prevention of complications, and no specific anti-COVID-19 therapies. The WHO have recommended that any specific therapy targeted to COVID-19 infection should be provided only as part of a research protocol (https://www.who.int/publications/i/item/clinical-management-of-covid-19).

6.2.2. Convalescent Plasma

Convalescent plasma treatment, containing high titers of polyclonal antibody (Ab), has been used to treat severe viral pneumonia. Many studies have been poorly controlled but such series have shown decreased mortality in Spanish Influenza A (H1N1) infections in 1915-1917 (Luke et al., 2006, McGuire and Redden, 1918), Influenza A (H1N1)pdm09 infections in 2009/2010 (Hung et al., 2011, Ortiz et al., 2013) and of more relevance to this trial, SARS-CoV infections in 2003 (Cheng et al., 2005, Soo et al., 2004). A systematic review and meta-analysis performed identified 699 treated patients with SARS coronavirus infection or severe influenza and 568 untreated “controls” (Mair-Jenkins et al., 2015) found consistent reports of a reduction in mortality. Post hoc meta-analysis showed a statistically significant reduction in the pooled odds of mortality following treatment, compared with placebo or no therapy (odds ratio, 0.25; 95% CI:0.14–0.45) (Mair-Jenkins et al., 2015).

Several trials have shown that convalescent plasma had some efficacy in the treatment of SARS-CoV infection. Eight observational studies reported improved mortality after patients with SARS-CoV – infection received various amounts of convalescent plasma (Mair-Jenkins et al., 2015). For example, a small retrospective case-comparison study (19 vs 21 patients) showed a 23% (95% CI: 6%-42%, $p \leq 0.05$) reduction in mortality after treatment with 200-400 ml of convalescent plasma, when compared with continuation of high-dose methylprednisolone (Soo et al., 2004). In a case series of 80 patients treated with 160-640 ml of convalescent plasma 12.5% died compared with the overall SARS-related mortality rate in Hong-Kong of 17% (Cheng et al., 2005). In this limited series, convalescent plasma given before 14 days after the onset of symptoms was associated with better outcome, however such post-hoc analyses are fraught with confounding factors but do suggest early treatment may be more efficacious.

Reports on the use of convalescent plasma to treat COVID-19 have emerged from the early stages of the pandemic in China (Duan et al., 2020, Shen et al., 2020, Zhang et al., 2020). The largest study showed that 10 patients hospitalized with COVID-19 each given 200ml of convalescent plasma with a neutralizing antibody titer of >1:640 described an improvement in clinical, laboratory and radiological parameters. However, this study was not adequately controlled or powered to allow robust conclusions (Duan et al., 2020).

Subsequently, the effectiveness of convalescent plasma has been assessed in an open-label, multicenter, randomized clinical trial in China comparing convalescent plasma with standard of care in 103 patients with 'severe' or 'life-threatening' COVID-19 (Li et al., 2020). There was a higher rate of nasopharyngeal SARS-CoV-2 PCR negativity at 72 hours in the convalescent plasma group (87.2% vs 37.5%, OR, 11.39 [95% CI, 3.91-33.18]; P < 0.001). In patients with 'severe' COVID-19, clinical improvement, defined as either hospital discharge or reduction of 2 points on a 6-point disease severity scale ranging from 6=death to 1=discharge, occurred in 91.3% (21/23) of the convalescent plasma group and 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; P = 0.03). However, this clinical improvement with convalescent plasma was not seen in patients with 'life-threatening' COVID-19. Overall, the secondary outcome of 28-day mortality was not significantly reduced with convalescent plasma treatment (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46]; P = 0.30).

6.2.2.1. *Adverse effects of convalescent plasma*

Minor side effects have been reported with convalescent plasma, such as fever or chills (Luke et al., 2006), or allergic transfusion reactions (Beigel et al., 2019). More significantly two reports of possible transfusion-related acute lung injury (TRALI) following convalescent plasma have been documented in one patient with Ebola disease and one patient with MERS-CoV, although no anti-HLA or anti-HNA antibodies were identified in donor plasma (Chun et al., 2016, Mora-Rillo et al., 2015). However, none of the 84 patients in the Ebola randomized controlled trial developed any serious adverse events due to the transfusion (Van Griensven et al., 2016). Convalescent plasma has now been given to more than 20,000 COVID-19 patients in the United States of America through an expanded access program (Joyner et al., 2020). In a convenience sample of 20,000 of these patients, mostly with 'severe' or 'life-threatening' COVID-19, the administration of convalescent plasma was generally safe with a low rate of serious adverse events. Specifically, transfusion reactions (n=89; <1%), thromboembolic or thrombotic events (n=87; <1%), and cardiac events (n=680, ~3%) were uncommon and the majority of thromboembolic/thrombotic (55/87) and cardiac events (562/680) were deemed to be unrelated to the convalescent plasma therapy.

6.2.2.2. *Antibody Dependent Enhancement*

Antibody-dependent enhancement (ADE) occurs when antibodies facilitate viral entry into host cells and enhance viral infection in these cells (Wan et al., 2019). Potential toxicity associated with convalescent plasma remains a concern, and this is very relevant to COVID-19 patients who exhibit a spectrum of lung pathology from acute lung injury to acute respiratory disease syndrome and death. In SARS-CoV-associated disease, antibodies may mediate pathology if they target a different serotype of the virus (Wan et al., 2019, Wang et al., 2014). Furthermore, a novel mechanism for ADE where a neutralizing antibody binding to the surface protein of a coronavirus-like viral receptor triggers viral cell entry has been recently proposed. This ADE pathway was shown not only to be antibody dose dependent but also likely mediated by presence of non-neutralizing antibodies (Ricke and Malone, 2020). For these reasons, we plan to collect convalescent plasma at the earliest 28 days after recovery so that antibody response has matured in terms of titer and affinity.

There is currently no evidence of ADE occurring in the current epidemic, and a small trial of 10 patients in China with COVID-19 treated in a single infusion of 200ml of convalescent plasma showed neither pulmonary injury nor infection enhancement. The high levels of neutralizing antibodies (>1:640), timely transfusion (median time from onset of symptoms to hospital admission and CP transfusion was 6 days (IQR, 2.5–8.5 days) and 16.5 days (IQR 11.0–19.3 days), respectively, and appropriate plasma volume (200ml) were thought to contribute to the absence of side-effects (Duan et al., 2020).

6.2.2.3. *Collection of Convalescent Plasma*

The Australian Red Cross Lifeblood will collect convalescent plasma from recovered COVID-19 infected individuals. Donors will be eligible if they have a history of prior COVID-19 infection, meet eligibility criteria for acceptance of blood donors, and are at least 28 days from COVID-19 symptom resolution. We will use existing Lifeblood TRALI risk mitigation strategies, and only use convalescent plasma collected from male donors. Donor samples will also undergo routine blood group and infectious disease testing as for any fresh blood component by Lifeblood. Donor plasma will be tested for SARS-CoV-2 serology, and if reactive, a neutralising assay will be performed. Testing will be performed in a Therapeutic Goods Administration accredited laboratory. Convalescent plasma will be collected and processed in exactly the same pathway as clinical plasma. It will be preferentially collected by apheresis and the final product will be 250-310 mL volume, stored at or below minus 25 degrees Celsius, and will meet all regulatory requirements for use as clinical plasma.

6.2.2.4. *Administration of convalescent plasma*

Administration of convalescent plasma is more likely to be beneficial early in the course of the disease (up to 10 to 14 days after onset of symptoms) (Chen et al., 2020).

6.2.2.5. *Need for a clinical trial*

Thus far, the available literature indicates that convalescent plasma has been used to treat thousands of patients with COVID-19 and that, in this setting, rates of serious adverse effects are low. There is a lack of high-quality evidence to determine whether convalescent plasma is an effective therapy for hospitalized patients with COVID-19 and crucial questions remain unanswered, including whether convalescent plasma reduces mortality in hospitalized patients and whether it improves outcomes in the critically unwell.

6.2.3. Intervention Strategy for this domain

It is intended that this domain of REMAP-CAP will evolve, taking into account evidence derived from other clinical trials, as well as availability of potentially effective immunoglobulin therapies. WHO guidance notes the flexibility associated with REMAP-CAP as a platform for the testing of multiple agents, including serial testing of additional interventions (https://apps.who.int/iris/bitstream/handle/10665/330680/WHO-HEO-RDBlueprint%28nCoV%29-2020.1-eng.pdf?ua=1).

At the commencement of this domain, a control group is included (i.e. some patients will not receive any immunoglobulin therapy that is intended to be active against COVID-19 infection). This is appropriate for two reasons. Firstly, there is relatively limited trial or clinical experience with the administration of immunoglobulin therapies and it is not reasonable to presume that such agents do not cause net harm. Secondly, designs that include only active interventions are not able to ascertain if any option is better or worse than no treatment. If, during the evolution of this domain, there is sufficient evidence of effectiveness of agents or clinical practice changes to include the routine use

of such agents or both, the control intervention that specifies that no immunoglobulin therapy is administered will be abandoned. Although this domain will commence with a single immunoglobulin therapy, it is intended that additional agents can be added (allowing evaluation of several agents against a common control intervention) as well as allowing introduction of combinations of agents (to evaluate potential synergy). Any changes to the intervention structure of the domain will be specified using one or more amendments to this DSA with implementation occurring only after ethical approval has been obtained. The initial selection of immunoglobulin therapy to be evaluated is convalescent plasma. If at any stage evidence of harm or definitive evidence of absence of effectiveness in critically ill patients emerges for any intervention specified in this domain, the ITSC, as advised by the DSWG, may remove an intervention prior to declaration of a Platform Conclusion. If this occurs, presentation and publication of results that relate to that intervention will occur, so as to contribute additional weight of evidence available in the public domain.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of Immunoglobulin Therapy for patients who are eligible for the platform and who have microbiological testing-confirmed COVID-19.

We hypothesize that the probability of the occurrence of the primary end-point specified in the relevant core protocol documents will differ based on the immunoglobulin therapy intervention. The following interventions will be available:

- No immunoglobulin against SARS-CoV-2
- Convalescent plasma

Each participating site has the option to opt-in to two or more interventions to be included in the randomization schedule depending on local clinical preference, usual practice, acceptable practice, and the availability of the intervention at that site. As long as the 'no immunoglobulin therapy for COVID-19' intervention is retained in the platform it is strongly preferred that this intervention is always included by participating sites and is mandatory so long as there is only a single active intervention within the domain.

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial. Treatment allocation will be adaptive, as described in either the REMAP-CAP Core Protocol +/- Pandemic Appendix or the REMAP-COVID Core Protocol.

8.1. Population

The REMAP enrolls patients with severe pneumonia admitted to ICU and patients with acute illness due to suspected or proven COVID-19 admitted to hospital, including patients admitted to ICU).

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in either the REMAP-CAP Core Protocol +/- Pandemic

Appendix or the REMAP-COVID Core Protocol. Patients eligible for REMAP-CAP may have conditions that exclude them from the COVID-19 Immunoglobulin Therapy Domain.

8.2.1. Domain inclusion criteria

Patients are eligible for this domain if:

- SARS-CoV-2 infection is confirmed by microbiological testing

8.2.2. Domain exclusion criteria

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

- If currently in ICU, 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)
- Patient has already received treatment with any non-trial prescribed antibody therapy (monoclonal antibody, hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this hospital admission
- **Enrolment in a trial evaluating any antibody therapy directed against COVID-19, where the protocol of the trial requires continuation of the assignment specified in that trial**
- More than 14 days have elapsed since hospital admission
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

8.2.3. Intervention exclusion criteria

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons.

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 who are not eligible for this domain 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/allergy to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
- Known previous history of transfusion-related acute lung injury will exclude a patient from receiving convalescent plasma
- Known objection to receiving plasma products will exclude a patient from receiving any plasma components

8.3. Interventions

8.3.1. Immunoglobulin Therapy Interventions

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

- No immunoglobulin against COVID-19
- Convalescent plasma

If the domain evolves to comprise 3 or more interventions, it is required that all sites will participate in the 'No immunoglobulin against COVID-19' intervention, and each site has the option to opt-in to one or more of the remaining interventions based on local practice and availability of the intervention.

8.3.2. No immunoglobulin against SARS-CoV-2

Patients assigned to this intervention will not receive any preparation of immunoglobulin intended to neutralize SARS-CoV-2 during the index hospitalization. Administration of such a preparation is considered a protocol deviation.

8.3.3. Convalescent Plasma

8.3.3.1. *Dosing of convalescent plasma*

Patients assigned to receive plasma will receive two adult units of ABO compatible convalescent plasma (total volume 550ml ± 150ml) within 48 hours of randomization unless there was a reason to withhold the second unit (for example, if the patient had a reaction to the first unit). Volume of convalescent plasma administered will be recorded and where available the level of antibodies within each unit will be tested.

8.3.3.2. *Duration of administration of convalescent plasma*

Those receiving plasma will receive a unit of ABO compatible convalescent plasma on the first day of the study. If the patient has no serious adverse reactions to the transfusion the second unit of convalescent plasma will be given. There must be a minimum of 12 hours between transfusions to allow appropriate assessment of adverse reactions to the initial transfusion. Both transfusions should be given within 48 hours from randomization.

8.3.4. Discontinuation of study therapy

An immunoglobulin for SARS-CoV-2 infection should be discontinued if there is development of an SAE. Immunoglobulin therapy can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

8.4. Concomitant care

In patients who have received an allocation status in the COVID-19 Antiviral Domain, and have microbiological testing confirmed SARS-CoV-2 infection, continuation of antiviral agent will be as per the COVID-19 Antiviral Domain-Specific Appendix (Section 8.3). Additional agents intended to be active against SARS-CoV-2 infection should not be administered, unless they have become standard of care during the trial or specified in another trial protocol. All 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 (occurring during the index hospitalization, censored at 90 days after enrollment) will be:

- All-cause mortality at 28 days
- Confirmed deep vein thrombosis
- Confirmed pulmonary embolus
- Confirmed ischemic cerebrovascular event
- Confirmed acute myocardial infarction
- Other confirmed thrombotic events
- Serious treatment-related adverse events (see section 11.2 of this appendix)
- Serious Adverse Events (SAE) as defined in core protocol documents and qualified in this appendix.

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 and any additional testing, which may differ between locations, is specified below.

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

9.2. Domain-specific data collection

Additional domain-specific data will be collected for the index hospitalization:

- Administration of immunoglobulin therapies
- Neutralizing antibody titer of trial immunoglobulin therapies (where available)
- SARS-CoV-2 antibody titer at baseline (where available but strongly recommended)
- Deep vein thrombosis
- Pulmonary embolism
- Ischemic cerebrovascular events
- Peak troponin
- Acute myocardial infarction (using fourth international definition)

Additional domain-specific data will be collected on all participants from clinically indicated testing where available at baseline: neutrophil count, lymphocyte count, prothrombin time (PT), fibrinogen, and C-reactive protein, D-dimers and troponin.

9.2.1. Laboratory sub-study

There will involve collection and storage of biological samples for a sub-set of participants. Sites can elect to participate in the sub-study dependent on their capacity for additional sample collection and storage.

Please see Appendix 1 for schedule of sampling. We will aim for 50 participants in each study intervention to be included in the sub-study. Full details are included in the Laboratory SOP.

9.3. Criteria for discontinuation

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

9.4. Blinding

9.4.1. Blinding

All interventions 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:

- Superiority of convalescent plasma compared to no immunoglobulin against SARS-CoV-2
- Futility of convalescent plasma compared to no immunoglobulin against SARS-CoV-2

Additional Platform Conclusions may be possible if further interventions are added to the domain.

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

10.2. Unit-of-analysis and strata

This domain is analyzed only in the pandemic statistical model and includes only patients who are SARS-CoV-2 infection confirmed. 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. Borrowing is permitted between states and strata. Response Adaptive Randomization will be applied in each illness severity state, using probabilities derived from the SARS-CoV-2 confirmed stratum.

The shock strata will not contribute to unit-of-analysis for this domain, as this strata is not applied in the Pandemic Statistical Model.

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

10.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal or Randomization with Deferred Reveal if confirmation of microbiological diagnosis is not known at the time of initial assessment of eligibility (see relevant core protocol documents)

10.4. Interactions with interventions in other domains

An a priori interaction with the Antibiotic Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the Macrolide Duration Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Influenza Antiviral Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the COVID-19 Antiviral Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Immune Modulation Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Corticosteroid Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Statin Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Vitamin C Domain is either not considered possible and will not be incorporated into the statistical model used to evaluate this domain in the pandemic statistical model or is not able to be evaluated for PINSNP patients as analysis occurs in different statistical models.

No interaction is evaluable between the Ventilation Domain and this domain.

10.5. Nesting of interventions

Nesting is not applicable to this domain

10.6. Threshold probability for superiority, effectiveness and inferiority

The threshold odds ratio delta for superiority, effectiveness and inferiority in this domain are those specified in the relevant core protocol documents

10.7. Threshold odds ratio delta for equivalence or futility

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 an active intervention.

10.8. Informative priors

This domain will launch with priors that are not informative for main effects. If new immunoglobulin agents are added to the domain, consideration will be given to the use of informative priors at the time of amendment of the DSA.

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. Data for post-trial sub-group analysis may not be available from all regions or for all patients in a region. The a priori patient sub-groups of interest are:

- Proven concomitant bacterial co-infection, defined as having isolation or detection of a known pathogen that causes pneumonia from blood, pleural fluid, or lower respiratory tract specimen.
- Receiving invasive mechanical ventilation at baseline
- Patients with undetectable virus at baseline (convalescent plasma intervention)
- Patients with different levels of neutralizing antibodies at baseline (convalescent plasma intervention)
- Dose of neutralizing antibodies received (convalescent plasma intervention, based on volume of transfusion and titer measurement, where available)
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

10.10. Domain-specific secondary and exploratory analyses

- Number of SAEs (excluding thrombotic events) from randomization until 72 hours after randomization, per day at risk; described by intervention.
- Number of thrombotic events from randomization up to the end of acute hospitalization, per day at risk. These will be analyzed using Poisson regression.
- Analyses of the data from any country-specific sub-studies will be specified in separate analysis plans.

10.11. Data sharing

Not applicable.

11. ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, effectiveness, inferiority, futility or equivalence of different interventions with respect to the primary endpoints are possible, and if equivalence is demonstrated, determination of the optimal intervention may be based on secondary endpoints, such as all-cause mortality at 28 days.

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 are required.

11.2. Potential domain-specific adverse events

11.2.1. Convalescent Plasma

The following possible treatment-related adverse events should be reported in all patients in this domain, irrespective of intervention allocation. In addition, site staff are responsible for reporting all transfusion-related adverse events to their national or regional hemovigilance system

- Severe allergic reaction or anaphylaxis
- Transfusion-associated Acute Lung Injury (TRALI)
- Transfusion-associated Circulatory Overload (TACO)

- Uncommon and new complications of Transfusion not fitting into other transfusion reaction categories.

Other SAEs should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see relevant core protocol documents).

11.3. Domain-specific consent issues

As noted in the background, and endorsed by the WHO, in the absence of evidence of effectiveness of specific treatments for COVID-19, the use of a no treatment control is both appropriate and ethical.

For patients who are not competent to consent, either prospective agreement or entry via waiver of-consent or some form of deferred consent can be applied, as required by an appropriate ethical review body.

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.

Clinicians are directed to not enrol an individual patient if the treating clinician believes that participation in this domain is not in the best interests of the patient.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the core protocol documents. This domain has received domain-specific funding from the Australian Medical Research Future Fund (MRFF).

12.2. Funding of domain interventions and outcome measures

The Australian Red Cross Lifeblood will supply the convalescent plasma for the trial and arrange for distribution to 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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14. APPENDIX 1: SCHEDULE OF SAMPLE COLLECTION

	Enrolment	**Day 3***	**Day 15***
Time window for sample collection	Baseline, prior to convalescent plasma	Day 3	Day 15
Blood sample, 1 x 9ml serum-separating tube (SST)	x	x	x

*only required to be collected if still an inpatient

15. APPENDIX 2: TRANSFUSION REACTIONS

Type of SAE	Diagnostic criteria	Where should cases should be reported
Allergic Acute Transfusion Reaction (Report within 24 hours of a transfusion)	**Severe** Bronchospasm, stridor, angioedema or circulatory problems which require urgent medical intervention AND/OR, directly result in or prolong hospital stay, or Anaphylaxis (severe, life-threatening, generalized or systemic hypersensitivity reaction with rapidly developing airway AND/OR breathing AND/OR circulation problems, usually associated with skin and mucosal changes)	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank/transfusion service with details of the patient's trial number
Allergic Acute Reaction (Report within first 72 hours of the trial)		Must be reported on the REMAP-CAP trial SAE form
Transfusion-Associated Circulatory Overload (TACO) (Report within 12 hours of a transfusion)	* Required criteria (A and/or B) A. Acute or worsening respiratory compromise and/or B. Evidence of acute or worsening pulmonary edema based on: • clinical physical examination, and/or • radiographic chest imaging and/or other noninvasive assessment of cardiac function Additional criteria: C. Evidence for cardiovascular system changes not explained by the patient's underlying medical condition, including development of tachycardia, hypertension, jugular venous distension, enlarged cardiac silhouette and/or peripheral edema	Patients classified with TACO should have: At least one required criterion* with onset during or up to 24 hours after transfusion Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number

	D. Evidence of fluid overload including any of the following: a positive fluid balance; clinical improvement following diuresis E. Supportive result of a relevant biomarker, e.g. an increase of B-type natriuretic peptide levels (BNP) or N terminal-pro brain natriuretic peptide) NT-pro BNP to greater than 1.5 times baseline value **A total of 3 or more criteria** i.e. *A and/or B, and total of at least 3 (A to E) Acute or worsening respiratory compromise Defined as fever and other symptoms/signs of hemolysis confirmed by fall of Hb AND one or more of the following: • Rise in LDH • Rise in bilirubin • Positive DAT • Positive crossmatch	
Transfusion-Related Acute Lung Injury (TRALI)	Acute dyspnea with hypoxia and bilateral pulmonary infiltrates during or within six hours of transfusion, not due to circulatory overload or other likely causes	Suspected TRALI should be reported – further investigations are required to confirm cases Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank/transfusion service with details of the patient's trial number. These will be reported to ARCL as per usual practice.
Uncommon and new Complications of	Pathological reaction or adverse effect in temporal	Suspected ADE should be reported

Transfusion not fitting into any of the other categories	association with transfusion which cannot be attributed to already defined side effects and with no risk factor other than transfusion and do not fit under any of the other reportable categories. Including cases of antibody dependent enhancement of infection (ADE)	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank/transfusion service with details of the patient's trial number

Domain-Specific Appendix: COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

COVID-19 Immunoglobulin Therapy Domain-Specific Appendix Version 2.3 dated 03 August 2020

Summary

In this domain of the REMAP-CAP trial, participants meeting the platform-entry criteria with microbiological testing confirmed SARS-CoV-2 infection will be randomized to receive one of two interventions:

- No immunoglobulin against SARS-CoV-2
- Convalescent plasma

This DSA applies to the following states and stratum:

Stratum	Pandemic infection suspected or proven (PISOP)			Pandemic infection neither suspected nor proven (PINSNP)
Core protocol documents	REMAP-CAP Core Protocol + Pandemic Appendix, or REMAP-COVID Core Protocol			REMAP-CAP Core Protocol
Illness Severity State	Moderate State		Severe State	Severe State
Interventions specified in this DSA	No immunoglobulin against SARS-CoV-2 Convalescent plasma		No immunoglobulin against SARS-CoV-2 Convalescent plasma	Not available
Interventions submitted for approval in this jurisdiction	☐ No immunoglobulin against SARS-CoV-2 ☐ Convalescent plasma		☐ No immunoglobulin against SARS-CoV-2 ☐ Convalescent plasma	Not available
Interventions offered at this site	Ward	ICU	ICU	ICU
	☐ No immunoglobulin against SARS-CoV-2 ☐ Convalescent plasma	☐ No immunoglobulin against SARS-CoV-2 ☐ Convalescent plasma	☐ No immunoglobulin against SARS-CoV-2 ☐ Convalescent plasma	Not available

REMAP-CAP: Immunoglobulin Therapy Domain Summary	
Interventions	• No immunoglobulin against COVID-19 • Convalescent plasma (up to 2 units within 48 hours)
Unit-of-analysis and Strata and States	The default unit-of-analysis for this domain will be the pandemic infection suspected or confirmed (PISOP) stratum with SARS-CoV-2 infection strata applied. 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. Borrowing is permitted between states. Response Adaptive Randomization will be applied to using probabilities derived from the SARS-CoV-2 confirmed stratum.
Evaluable treatment-by-treatment Interactions	No interaction will be evaluated with any other domain.
Nesting	None
Timing of Reveal	Randomization with Deferred Reveal at time of confirmation of infection by microbiological testing.
Inclusions	Inclusion criteria are the same as those specified in the relevant core protocol documents, and • SARS-CoV-2 infection is confirmed by microbiological testing
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • If in ICU, more than 48 hours have elapsed since ICU admission • Patient has already received treatment with any non-trial prescribed antibody therapy (monoclonal antibody, hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this hospital admission • **Enrolment in a trial evaluating any antibody therapy directed against COVID-19, where the protocol of the trial requires continuation of the treatment assignment specified in that trial** • More than 14 days have elapsed since 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 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 previous history of transfusion-related acute lung injury will exclude a patient from receiving convalescent plasma • Known objection to receiving plasma products will exclude a patient from receiving any plasma components
Outcome measures	Primary REMAP endpoint: refer to the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol. Secondary REMAP endpoints refer to the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol

	Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrolment): • All-cause mortality at 28 days • Confirmed deep venous thrombosis • Confirmed pulmonary embolism • Confirmed ischemic stroke • Confirmed acute myocardial infarction • Other confirmed thrombotic events • Serious treatment-related adverse events (SAE) as defined in this appendix • Serious Adverse Events (SAE) as defined in Core Protocol Domain-specific exploratory outcomes in a subset of patients • Percentage of participants who cleared SARS-CoV-2 infection in respiratory samples after transfusion • Reduction in SARS-CoV-2 viral load • Change in SARS-CoV-2 neutralizing antibody levels

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1. ABBREVIATIONS

ADE	Antibody-dependent enhancement
CCP	Clinical Characterization Protocol
CRP	C-reactive protein
CVA	Cerebrovascular accident
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
DVT	Deep vein thrombosis
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
MERS-CoV	Middle East respiratory syndrome coronavirus
NHS	National Health Service of the United Kingdom
NHSBT	National Health Service Blood and Transplant
PAtC	Pandemic Appendix to the Core Protocol
PE	Pulmonary Embolism
PISOP	Pandemic Infection Suspected or Proven
PT	Prothrombin time
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS	Serious Acute Respiratory Syndrome
TACO	Transfusion-Associated Circulatory Overload
TRALI	Transfusion-related acute lung injury
TTI	Transfusion-Associated Circulatory Overload
WHO	World Health Organization

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While, all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see glossary, Section 1.2 Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models) and 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 Regions-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject of a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change overtime in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the relevant Core Protocol (either REMAP-CAP Core Protocol +/- Pandemic Appendix or REMAP-COVID Core Protocol), DSAs, RSAs, and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org).

3. COVID-19 IMMUNOGLOBULIN DOMAIN-SPECIFIC APPENDIX VERSION

The version of the COVID-19 Immunoglobulin Therapy Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the COVID-19 Immunoglobulin Therapy Domain-Specific Working Group (DSWG) on 19th April 2020

Version 2: Approved by the COVID-19 Immunoglobulin Therapy Domain-Specific Working Group (DSWG) on 30 June 2020

Version 2.3 Approved by the United States of America members of the COVID-19 Immunoglobulin Therapy DSWG on 03 August 2020

4. COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN GOVERNANCE

4.1. Domain members

Chair:

Dr. Lise Estcourt*

Country Leads:

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5. COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The COVID-19 Immunoglobulin Therapy Domain-Specific Working Group (DSWG) have read the appendix and authorize it as the official COVID-19 Immunoglobulin Therapy Domain-Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair _____ Date 30 June 2020
Lise Estcourt

Country lead _____ 03 August 2020
Bryan McVerry

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP platform to test the effectiveness of different strategies for immunoglobulin therapy for microbiological testing-confirmed SARS-CoV-2 infection in patients with acute illness due to suspected or proven COVID-19.

This is the version of the COVID-19 Immunoglobulin Therapy Domain that will apply in the United States of America and has the version number 2.3. It is anticipated that this domain may also enroll patients in other countries. However, because of differences in nature and supply of product, or timing of availability of product, it is anticipated that differences in the DSA will be necessary. Versions used in other countries, that are derived from this DSA, will be numbered sequentially with a new number after the decimal point (i.e. 1.1, 1.2 etc.) each applying to new countries. A major revision to the DSA will be allocated a new number before the decimal point, i.e. 2.0.

6.2. Domain-specific background

6.2.1. COVID-19 Infection

The first report of infection with SARS-CoV-2 (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 millions of reported cases across the globe, with hundreds of thousands of deaths, and documented sustained human-to-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/newsroom/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)). Due to previous experience with other 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 is to understand the effectiveness of COVID-19 treatments. Clinical guidance issued by the WHO indicates that unproven therapies should be administered preferably only within the setting of a clinical trial (https://www.who.int/docs/defaultsource/coronaviruse/clinical-management-of-novel-cov.pdf).

Globally, as of 20 June 2020 there are 8,666,697 confirmed cases, 460,066 deaths and 4,247,527 patients have recovered from SARS-CoV-2 illness (https://coronavirus.jhu.edu/map.html; Accessed on 20 June 2020). Estimates of the burden of critical illness among patients infected with COVID-19 vary and the corresponding case-fatality estimates are affected by factors such as health system capacity including the availability of diagnostic testing and critical care beds. Nevertheless, it is recognized that fatal critical illness, especially from severe respiratory failure from pneumonitis is high. In reports from China and from Italy (Grasselli et al., 2020, Huang et al., 2020, Remuzzi and Remuzzi, 2020), the proportion of confirmed COVID-19 cases requiring organ support in critical care units varies between 16% to 32% of all hospitalized SARS-CoV-2 illness. Although the overall case fatality rate is estimated as 5.7% (95% confidence intervals 5.5% – 5.9%) for COVID-19 disease for hospitalized patients (Baud et al., 2020), the mortality in critically ill patients with COVID-19 disease, especially those requiring mechanical ventilation, is much higher (Yang et al., 2020).

The corresponding figures in the United States are 4,339,997 confirmed cases and 148,866 deaths (3.4%, www.cdc.gov). In the US, the critical care case-mix of COVID19 has been projected by The Institute for Health Metrics and Evaluation (IHME, https://covid19.healthdata.org; Accessed on 30th July 2020). IHME projects 14,507 inpatient beds needed for COVID-19 care, of which 5,941 are intensive care unit beds. Of the 5941 ICU patients, 5679 are mechanically ventilated, 903 are projected to die. The predictions for all health care systems globally, including the US, are that the demands on critical care requirements are likely to persist and any intervention that accelerates illness resolution, ideally by reducing both mortality and by reducing critical care length of stay is essential.

Interim guidance from the WHO for clinical care of infected patients focus upon supportive care, including organ support as needed, prevention of complications, and no specific anti-COVID-19 therapies. The WHO have recommended that any specific therapy targeted to COVID-19 infection should be provided only as part of a research protocol (https://www.who.int/publications/i/item/clinical-management-of-covid-19).

6.2.2. Convalescent Plasma

Convalescent plasma treatment, containing high titers of polyclonal antibody (Ab), has been used to treat severe viral pneumonia. Many studies have been poorly controlled but such series have shown decreased mortality in Spanish Influenza A (H1N1) infections in 1915-1917 (Luke et al., 2006, McGuire and Redden, 1918), Influenza A (H1N1)pdm09 infections in 2009/2010 (Hung et al., 2011, Ortiz et al., 2013) and of more relevance to this trial, SARS-CoV infections in 2003 (Cheng et al., 2005, Soo et al., 2004). A systematic review and meta-analysis performed identified 699 treated patients with SARS coronavirus infection or severe influenza and 568 untreated “controls” (Mair-

Jenkins et al., 2015) found consistent reports of a reduction in mortality. Post hoc meta-analysis showed a statistically significant reduction in the pooled odds of mortality following treatment, compared with placebo or no therapy (odds ratio, 0.25; 95% CI:0.14–0.45) (Mair-Jenkins et al., 2015).

Several trials have shown that convalescent plasma had some efficacy in the treatment of SARS-CoV infection. Eight observational studies reported improved mortality after patients with SARS-CoV – infection received various amounts of convalescent plasma (Mair-Jenkins et al., 2015). For example, a small retrospective case-comparison study (19 vs 21 patients) showed a 23% (95% CI: 6%-42%, p≤0.05) reduction in mortality after treatment with 200-400 ml of convalescent plasma, when compared with continuation of high-dose methylprednisolone (Soo et al., 2004). In a case series of 80 patients treated with 160-640 ml of convalescent plasma 12.5% died compared with the overall SARS-related mortality rate in Hong-Kong of 17% (Cheng et al., 2005). In this limited series, convalescent plasma given before 14 days after the onset of symptoms was associated with better outcome, however such post-hoc analyses are fraught with confounding factors but do suggest early treatment may be more efficacious.

Reports on the use of convalescent plasma to treat COVID-19 have emerged from the early stages of the pandemic in China (Duan et al., 2020, Shen et al., 2020, Zhang et al., 2020). The largest study showed that 10 patients hospitalized with COVID-19 each given 200ml of convalescent plasma with a neutralizing antibody titer of >1:640 described an improvement in clinical, laboratory and radiological parameters. However, this study was not adequately controlled or powered to allow robust conclusions (Duan et al., 2020).

Subsequently, the effectiveness of convalescent plasma has been assessed in an open-label, multicenter, randomized clinical trial in China comparing convalescent plasma with standard of care in 103 patients with ‘severe’ or ‘life-threatening’ COVID-19 (Li et al., 2020). There was a higher rate of nasopharyngeal SARS-CoV-2 PCR negativity at 72 hours in the convalescent plasma group (87.2% vs 37.5%, OR, 11.39 [95% CI, 3.91-33.18]; P < 0.001). In patients with ‘severe’ COVID-19, clinical improvement, defined as either hospital discharge or reduction of 2 points on a 6-point disease severity scale ranging from 6=death to 1=discharge, occurred in 91.3% (21/23) of the convalescent plasma group and 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; P = 0.03). However, this clinical improvement with convalescent plasma was not seen in patients with ‘life-threatening’ COVID-19. Overall, the secondary outcome of 28-day mortality was not significantly reduced with convalescent plasma treatment (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46]; P = 0.30).

6.2.2.1. *Adverse effects of convalescent plasma*

Minor side effects have been reported with convalescent plasma, such as fever or chills (Luke et al., 2006), or allergic transfusion reactions (Beigel et al., 2019). More significantly two reports of possible transfusion-related acute lung injury (TRALI) following convalescent plasma have been documented in one patient with Ebola disease and one patient with MERS-CoV, although no anti-HLA or anti-HNA antibodies were identified in donor plasma (Chun et al., 2016, Mora-Rillo et al., 2015). However, none of the 84 patients in the Ebola randomized controlled trial developed any serious adverse events due to the transfusion (Van Griensven et al., 2016). Convalescent plasma has now been given to more than 20,000 COVID-19 patients in the United States of America through an expanded access program (Joyner et al., 2020). In a convenience sample of 20,000 of these patients, mostly with ‘severe’ or ‘life-threatening’ COVID-19, the administration of convalescent plasma was generally safe with a low rate of serious adverse events. Specifically, transfusion reactions (n=89; <1%),

thromboembolic or thrombotic events (n=87; <1%), and cardiac events (n=680, ~3%) were uncommon and the majority of thromboembolic/thrombotic (55/87) and cardiac events (562/680) were deemed to be unrelated to the convalescent plasma therapy.

6.2.2.2. *Antibody Dependent Enhancement*

Antibody-dependent enhancement (ADE) occurs when antibodies facilitate viral entry into host cells and enhance viral infection in these cells (Wan et al., 2019). Potential toxicity associated with convalescent plasma remains a concern, and this is very relevant to COVID-19 patients who exhibit a spectrum of lung pathology from acute lung injury to acute respiratory disease syndrome and death. In SARS-CoV-associated disease, antibodies may mediate pathology if they target a different serotype of the virus (Wan et al., 2019, Wang et al., 2014). Furthermore, a novel mechanism for ADE where a neutralizing antibody binding to the surface protein of a coronavirus-like viral receptor triggers viral cell entry has been recently proposed. This ADE pathway was shown not only to be antibody dose dependent but also likely mediated by presence of non-neutralizing antibodies (Ricke and Malone, 2020). For these reasons, we plan to collect convalescent plasma at the earliest 28 days after recovery so that antibody response has matured in terms of titer and affinity.

There is currently no evidence of ADE occurring in the current epidemic, and a small trial of 10 patients in China with COVID-19 treated in a single infusion of 200ml of convalescent plasma showed neither pulmonary injury nor infection enhancement. The high levels of neutralizing antibodies (>1:640), timely transfusion (median time from onset of symptoms to hospital admission and CP transfusion was 6 days (IQR, 2.5–8.5 days) and 16.5 days (IQR 11.0–19.3 days), respectively, and appropriate plasma volume (200ml) were thought to contribute to the absence of side-effects (Duan et al., 2020).

6.2.2.3. *Collection of Convalescent Plasma*

Individuals who have documented COVID-19 infections are identified through hospital records with assistance from the local or regional County Health Departments. Recovered individuals will be evaluated in clinic as potential donors for convalescent plasma (CP). US criteria for CP donors has been outlined by the FDA and includes evidence of prior COVID-19 infection, absence of symptoms for a minimum of 14 days (we will be using 21 days for local donors), a negative nasopharyngeal swab by PCR and a positive IgG/ IgA ELISA antibody test (EuroImmun IgG/IgA against the spike protein - S1 domain). A positive result with this assay indicates a titer>=100. CP donor samples will be saved to determine maximum titer. Donors must also meet all regular volunteer donor criteria. We will only use plasma from male donors, non-parous female donors or parous female donors who have tested negative for HLA antibodies.

6.2.2.4. *Administration of convalescent plasma*

Administration of convalescent plasma is more likely to be beneficial early in the course of the disease (up to 10 to 14 days after onset of symptoms) (Chen et al., 2020).

6.2.2.5. *Need for a clinical trial*

Thus far, the available literature indicates that convalescent plasma has been used to treat thousands of patients with COVID-19 and that, in this setting, rates of serious adverse effects are low. There is a lack of high-quality evidence to determine whether convalescent plasma is an effective therapy for hospitalized patients with COVID-19 and crucial questions remain unanswered, including whether convalescent plasma reduces mortality in hospitalized patients and whether it improves outcomes in the critically unwell.

6.2.3. Intervention Strategy for this domain

It is intended that this domain of REMAP-CAP will evolve, taking into account evidence derived from other clinical trials, as well as availability of potentially effective immunoglobulin therapies. WHO guidance notes the flexibility associated with REMAP-CAP as a platform for the testing of multiple agents, including serial testing of additional interventions (https://apps.who.int/iris/bitstream/handle/10665/330680/WHO-HEO-RDBlueprint%28nCoV%29-2020.1-eng.pdf?ua=1).

At the commencement of this domain, a control group is included (i.e. some patients will not receive any immunoglobulin therapy that is intended to be active against COVID-19 infection). This is appropriate for two reasons. Firstly, there is relatively limited trial or clinical experience with the administration of immunoglobulin therapies and it is not reasonable to presume that such agents do not cause net harm. Secondly, designs that include only active interventions are not able to ascertain if any option is better or worse than no treatment. If, during the evolution of this domain, there is sufficient evidence of effectiveness of agents or clinical practice changes to include the routine use of such agents or both, the control intervention that specifies that no immunoglobulin therapy is administered will be abandoned. Although this domain will commence with a single immunoglobulin therapy, it is intended that additional agents can be added (allowing evaluation of several agents against a common control intervention) as well as allowing introduction of combinations of agents (to evaluate potential synergy). Any changes to the intervention structure of the domain will be specified using one or more amendments to this DSA with implementation occurring only after ethical approval has been obtained. The initial selection of immunoglobulin therapy to be evaluated is convalescent plasma. If at any stage evidence of harm or definitive evidence of absence of effectiveness in critically ill patients emerges for any intervention specified in this domain, the ITSC, as advised by the DSWG, may remove an intervention prior to declaration of a Platform Conclusion. If this occurs, presentation and publication of results that relate to that intervention will occur, so as to contribute additional weight of evidence available in the public domain.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of Immunoglobulin Therapy for patients who are eligible for the platform and who have microbiological testing-confirmed COVID-19.

We hypothesize that the probability of the occurrence of the primary end-point specified in the relevant core protocol documents will differ based on the immunoglobulin therapy intervention. The following interventions will be available:

- No immunoglobulin against SARS-CoV-2
- Convalescent plasma

Each participating site has the option to opt-in to two or more interventions to be included in the randomization schedule depending on local clinical preference, usual practice, acceptable practice, and the availability of the intervention at that site. As long as the 'no immunoglobulin therapy for COVID-19' intervention is retained in the platform it is strongly preferred that this intervention is always included by participating sites and is mandatory so long as there is only a single active intervention within the domain.

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial. Treatment allocation will be adaptive, as described in either the REMAP-CAP Core Protocol +/- Pandemic Appendix or the REMAP-COVID Core Protocol.

8.1. Population

The REMAP enrolls patients with severe pneumonia admitted to ICU and patients with acute illness due to suspected or proven COVID-19 admitted to hospital, including patients admitted to ICU).

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in either the REMAP-CAP Core Protocol +/- Pandemic Appendix or the REMAP-COVID Core Protocol. Patients eligible for REMAP-CAP may have conditions that exclude them from the COVID-19 Immunoglobulin Therapy Domain.

8.2.1. Domain inclusion criteria

Patients are eligible for this domain if:

- SARS-CoV-2 infection is confirmed by microbiological testing

8.2.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- If currently in ICU, 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)
- Patient has already received treatment with any non-trial prescribed antibody therapy (monoclonal antibody, hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this hospital admission
- **Enrolment in a trial evaluating any antibody therapy directed against COVID-19, where the protocol of the trial requires continuation of the assignment specified in that trial**
- More than 14 days have elapsed since hospital admission
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

8.2.3. Intervention exclusion criteria

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons.

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 who are not eligible for this domain 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/allergy to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
- Known previous history of transfusion-related acute lung injury will exclude a patient from receiving convalescent plasma
- Known objection to receiving plasma products will exclude a patient from receiving any plasma components

8.3. Interventions

8.3.1. Immunoglobulin Therapy Interventions

Patients will be randomly assigned to receive one of the following open-label strategies. All interventions will be commenced immediately after allocation status is revealed.

- No immunoglobulin against COVID-19
- Convalescent plasma

If the domain evolves to comprise 3 or more interventions, it is required that all sites will participate in the 'No immunoglobulin against COVID-19' intervention, and each site has the option to opt-in to one or more of the remaining interventions based on local practice and availability of the intervention.

8.3.2. No immunoglobulin against SARS-CoV-2

Patients assigned to this intervention will not receive any preparation of immunoglobulin intended to neutralize SARS-CoV-2 during the index hospitalization. Administration of such a preparation is considered a protocol deviation.

8.3.3. Convalescent Plasma

8.3.3.1. *Dosing of convalescent plasma*

Patients assigned to receive plasma will receive at least one and not more than two adult units of ABO compatible convalescent plasma (total volume 550ml ± 150ml) within 48 hours of randomization. Volume of convalescent plasma administered will be recorded and where available the level of antibodies within each unit will be tested.

8.3.3.2. *Duration of administration of convalescent plasma*

Patients will be randomized to receive ABO compatible convalescent plasma plus standard care upon admission to the hospital or standard care alone. Those receiving convalescent plasma will receive a up to two adult units of convalescent plasma (minimum 200mL each) supply permitting as early as possible following randomization. The antibody titer of the plasma will be tested in each unit as well as documenting the volume transfused.

8.3.4. Discontinuation of study therapy

An immunoglobulin for SARS-CoV-2 infection should be discontinued if there is development of an SAE. Immunoglobulin therapy can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

8.4. Concomitant care

In patients who have received an allocation status in the COVID-19 Antiviral Domain, and have microbiological testing confirmed SARS-CoV-2 infection, continuation of antiviral agent will be as per the COVID-19 Antiviral Domain-Specific Appendix (Section 8.3). Additional agents intended to be active against SARS-CoV-2 infection should not be administered, unless they have become standard of care during the trial or specified in another trial protocol. All 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 (occurring during the index hospitalization, censored at 90 days after enrollment) will be:

- All-cause mortality at 28 days
- Confirmed deep vein thrombosis
- Confirmed pulmonary embolus
- Confirmed ischemic cerebrovascular event
- Confirmed acute myocardial infarction
- Other confirmed thrombotic events
- Serious treatment-related adverse events (see section 11.2 of this appendix)
- Serious Adverse Events (SAE) as defined in core protocol documents and qualified in this appendix.

Domain-specific exploratory outcomes in a subset of patients:

- Percentage of participants who cleared SARS-CoV-2 infection in respiratory samples after transfusion
- Reduction in SARS-CoV-2 viral load
- Change in SARS-CoV-2 neutralizing antibody levels

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 and any additional testing, which may differ between locations, is specified below.

Sites that are participating in this domain are encouraged to also participate in the Clinical Characterization Protocol (CCP) for patients with COVID-19 that has been established by the International Severe Acute Respiratory and Emerging Infectious Consortium (https://isaric.tghn.org/CCP/). This protocol specifies the collection of biological samples from patients with COVID-19. Samples collected in patients who are enrolled in the CCP may be made available to REMAP-CAP investigators to evaluate aspects of host or pathogen biology associated with assignment in this domain. Ethical approval at such sites and agreement from patients to undertake the CCP will be obtained separately.

9.2. Domain-specific data collection

Additional domain-specific data will be collected for the index hospitalization:

- Administration of immunoglobulin therapies
- Neutralizing antibody titer of trial immunoglobulin therapies (where available)
- Deep vein thrombosis
- Pulmonary embolism
- Ischemic cerebrovascular events
- Peak troponin
- Acute myocardial infarction (using fourth international definition)

Type and cross-match will be performed locally for all participants so that ABO compatible convalescent plasma can be administered.

Samples will be taken on Day 1 prior to administration of convalescent plasma to assess the level of antibodies and neutralizing antibodies detectable prior to treatment on Day 1 (6 mL plasma).

Patients may be enrolled in a separate biosampling registry and subsequently blood will be sampled on days 5 and 10 after randomization (plasma 6ml) to assess the level of antibodies and neutralizing antibodies detectable.

Samples will be obtained by research personnel or from excess blood form the central lab sent for clinical testing purposes.

9.3. Criteria for discontinuation

Refer to relevant core protocol documents for criteria for discontinuation of participation in the trial.

9.4. Blinding

9.4.1. Blinding

All interventions 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:

- Superiority of convalescent plasma compared to no immunoglobulin against SARS-CoV-2
- Futility of convalescent plasma compared to no immunoglobulin against SARS-CoV-2

Additional Platform Conclusions may be possible if further interventions are added to the domain.

In all other respects the stopping rules for this domain are those outlined in the core protocol documents.

10.2. Unit-of-analysis and strata

This domain is analyzed only in the pandemic statistical model and includes only patients who are SARS-CoV-2 infection confirmed. 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. Borrowing is permitted between states and strata. Response Adaptive Randomization will be applied in each illness severity state, using probabilities derived from the SARS-CoV-2 confirmed stratum.

The shock strata will not contribute to unit-of-analysis for this domain, as this strata is not applied in the Pandemic Statistical Model.

The influenza strata will not contribute to unit-of-analysis for this domain.

10.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal or Randomization with Deferred Reveal if confirmation of microbiological diagnosis is not known at the time of initial assessment of eligibility (see relevant core protocol documents)

10.4. Interactions with interventions in other domains

An a priori interaction with the Antibiotic Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the Macrolide Duration Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Influenza Antiviral Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the COVID-19 Antiviral Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Immune Modulation Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Corticosteroid Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Statin Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Vitamin C Domain is either not considered possible and will not be incorporated into the statistical model used to evaluate this domain in the pandemic statistical model or is not able to be evaluated for PINSNP patients as analysis occurs in different statistical models.

No interaction is evaluable between the Ventilation Domain and this domain.

10.5. Nesting of interventions

Nesting is not applicable to this domain

10.6. Threshold probability for superiority, effectiveness and inferiority

The threshold odds ratio delta for superiority, effectiveness and inferiority in this domain are those specified in the relevant core protocol documents

10.7. Threshold odds ratio delta for equivalence or futility

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 an active intervention.

10.8. Informative priors

This domain will launch with priors that are not informative for main effects. If new immunoglobulin agents are added to the domain, consideration will be given to the use of informative priors at the time of amendment of the DSA.

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. Data for post-trial sub-group analysis may not be available from all regions or for all patients in a region. The a priori patient sub-groups of interest are:

- Proven concomitant bacterial co-infection, defined as having isolation or detection of a known pathogen that causes pneumonia from blood, pleural fluid, or lower respiratory tract specimen.
- Receiving invasive mechanical ventilation at baseline
- Patients with undetectable virus at baseline (convalescent plasma intervention)
- Patients with different levels of neutralizing antibodies at baseline (convalescent plasma intervention)
- Dose of neutralizing antibodies received (convalescent plasma intervention, based on volume of transfusion and titer measurement, where available)
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

10.10. Domain-specific secondary and exploratory analyses

- Number of SAEs (excluding thrombotic events) from randomization until 72 hours after randomization, per day at risk; described by intervention.

- Number of thrombotic events from randomization up to the end of acute hospitalization, per day at risk. These will be analyzed using Poisson regression.

- Analyses of the data from any country-specific sub-studies will be specified in separate analysis plans.

10.11. Data sharing

Not applicable.

11. ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, effectiveness, inferiority, futility or equivalence of different interventions with respect to the primary endpoints are possible, and if equivalence is demonstrated, determination of the optimal intervention may be based on secondary endpoints, such as all-cause mortality at 28 days.

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 are required.

11.2. Potential domain-specific adverse events

11.2.1. Convalescent Plasma

The following possible treatment-related adverse events should be reported in all patients in this domain, irrespective of intervention allocation. In addition, site staff are responsible for reporting all transfusion-related adverse events to their regional blood bank

- Severe allergic reaction or anaphylaxis
- Transfusion-associated Acute Lung Injury (TRALI)
- Transfusion-associated Circulatory Overload (TACO)
- Complications of transfusion not fitting into other transfusion reaction categories

Other SAEs should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see relevant core protocol documents).

11.3. Domain-specific consent issues

As noted in the background, and endorsed by the WHO, in the absence of evidence of effectiveness of specific treatments for COVID-19, the use of a no treatment control is both appropriate and ethical.

For patients who are not competent to consent, either prospective agreement or entry via waiver of-consent or some form of deferred consent can be applied, as required by an appropriate ethical review body.

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.

Clinicians are directed to not enrol an individual patient if the treating clinician believes that participation in this domain is not in the best interests of the patient.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the core protocol documents. This domain will receive additional domain-specific funding.

12.2. Funding of domain interventions and outcome measures

Regional blood banks will supply the convalescent plasma for the trial and arrange for distribution to participating hospitals via its routine blood product distribution system.

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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Domain-Specific Appendix: COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

COVID-19 Immunoglobulin Therapy Domain-Specific Appendix Version 1.0 dated 19 April 2020

Summary

In this domain of the REMAP-CAP trial, participants meeting the platform-entry criteria for REMAP-CAP admitted to participating intensive care units with microbiological testing confirmed COVID-19 infection will be randomized to receive one of two interventions:

- No immunoglobulin against COVID-19 (no placebo)
- Convalescent plasma

This domain will only enroll patients if the pandemic infection is proven (PISOP) stratum and be analyzed in the Pandemic Statistical Model as outlined from the Pandemic Appendix to Core (PAtC).

At this participating site the following interventions have been selected within this domain:

☐ No immunoglobulin against COVID-19 (no placebo)
☐ Convalescent plasma

REMAP-CAP: Immunoglobulin Therapy Domain Summary	
Interventions	• No immunoglobulin against COVID-19 (no placebo) • Convalescent plasma (up to 2 units within 48 hours)
Unit-of-analysis and Strata	The default unit-of-analysis for this domain will be the pandemic infection suspected or confirmed (PISOP) stratum. Analysis and Response Adaptive Randomization are applied by PISOP stratum.
Evaluable treatment-by-treatment Interactions	Treatment-treatment interactions will be evaluated between interventions in this domain and interventions in the Corticosteroid Domain and the COVID-19 Antiviral Therapy Domain. No other interactions will be evaluated with any other domain.
Nesting	None
Timing of Reveal	Randomization with Deferred Reveal at time of confirmation of infection by microbiological testing.
Inclusions	Inclusion criteria are the same as the Platform see Core Protocol Section 7.4.1, and • COVID-19 infection is confirmed by microbiological testing
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • More than 48 hours have elapsed since ICU admission • Patient has already received treatment with any non-trial prescribed antibody therapy (monoclonal antibody, hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this hospital admission • More than 14 days have elapsed since 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 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 previous history of transfusion-related acute lung injury will exclude a patient from receiving convalescent plasma • Known objection to receiving plasma products will exclude a patient from receiving any plasma components
Outcome measures	Primary REMAP endpoint: as defined in an operational document specified from the Pandemic Appendix to the Core Protocol Section 7.5.1. Secondary REMAP endpoints refer to Core Protocol Section 7.6.2 Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrolment): • All-cause mortality at 28 days • Serious adverse events (SAE) as defined in this appendix • Serious Adverse Events (SAE) as defined in Core Protocol Domain-specific exploratory outcomes

	• Percent of subjects who cleared SARS-CoV-2 infection (i.e. all samples (obtained at least in two time points after transfusion) tested negative for SARS-CoV-2 RNA, just in deeper respiratory sample, in all respiratory samples or just in blood) • Reduction in SARS-CoV-2 viral load (within the first 3 days; 4 days; 6 days; 9 days; 15 days and 28 days analyzed separately in blood and respiratory samples) • Change in SARS-CoV-2 neutralizing antibody levels (within the first 3 days; 4 days: 6 days; 9 days; 15 days and 28 days)

Domain-Specific Appendix: COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

COVID-19 Immunoglobulin Therapy Domain-Specific Appendix Version 2.2 dated 01 July 2020

Summary

In this domain of the REMAP-CAP trial, participants meeting the platform-entry criteria with microbiological testing confirmed SARS-CoV-2 infection will be randomized to receive one of two interventions:

- No immunoglobulin against SARS-CoV-2
- Convalescent plasma

This DSA applies to the following states and stratum:

<table>
<tr><td>Stratum</td><td colspan="3">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="3">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 colspan="2">Moderate State</td><td>Severe State</td><td>Severe State</td></tr>
<tr><td>Interventions specified in this DSA</td><td colspan="2">No immunoglobulin against SARS-CoV-2
Convalescent plasma</td><td>No immunoglobulin against SARS-CoV-2
Convalescent plasma</td><td>Not available</td></tr>
<tr><td>Interventions submitted for approval in this jurisdiction</td><td colspan="2">☐ No immunoglobulin against SARS-CoV-2
☐ Convalescent plasma</td><td>☐ No immunoglobulin against SARS-CoV-2
☐ Convalescent plasma</td><td>Not available</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>☐ No immunoglobulin against SARS-CoV-2
☐ Convalescent plasma</td><td>☐ No immunoglobulin against SARS-CoV-2
☐ Convalescent plasma</td><td>☐ No immunoglobulin against SARS-CoV-2
☐ Convalescent plasma</td><td>Not available</td></tr>
</table>

REMAP-CAP: Immunoglobulin Therapy Domain Summary	
Interventions	• No immunoglobulin against COVID-19 • Convalescent plasma (up to 2 units within 48 hours)
Unit-of-analysis and Strata and States	The default unit-of-analysis for this domain will be the pandemic infection suspected or confirmed (PISOP) stratum with SARS-CoV-2 infection strata applied. 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. Borrowing is permitted between states. Response Adaptive Randomization will be applied to using probabilities derived from the SARS-CoV-2 confirmed stratum.
Evaluable treatment-by-treatment Interactions	No interaction will be evaluated with any other domain.
Nesting	None
Timing of Reveal	Randomization with Deferred Reveal at time of confirmation of infection by microbiological testing.
Inclusions	Inclusion criteria are the same as those specified in the relevant core protocol documents, and • SARS-CoV-2 infection is confirmed by microbiological testing
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • If in ICU, more than 48 hours have elapsed since ICU admission • Patient has already received treatment with any non-trial prescribed antibody therapy (monoclonal antibody, hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this hospital admission • **Enrolment in a trial evaluating any antibody therapy directed against COVID-19, where the protocol of the trial requires continuation of the treatment assignment specified in that trial** • More than 14 days have elapsed since 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 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 previous history of transfusion-related acute lung injury will exclude a patient from receiving convalescent plasma • Known objection to receiving plasma products will exclude a patient from receiving any plasma components
Outcome measures	Primary REMAP endpoint: refer to the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol. Secondary REMAP endpoints refer to the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol

	Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrolment): • All-cause mortality at 28 days • Confirmed deep venous thrombosis • Confirmed pulmonary embolism • Confirmed ischemic stroke • Confirmed acute myocardial infarction • Other confirmed thrombotic events • Serious treatment-related adverse events (SAE) as defined in this appendix • Serious Adverse Events (SAE) as defined in Core Protocol Domain-specific exploratory outcomes • Nil

TABLE OF CONTENTS

1. ABBREVIATIONS

ADE	Antibody-dependent enhancement
CCP	Clinical Characterization Protocol
CRP	C-reactive protein
CVA	Cerebrovascular accident
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
DVT	Deep vein thrombosis
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
MERS-CoV	Middle East respiratory syndrome coronavirus
NHS	National Health Service of the United Kingdom
NHSBT	National Health Service Blood and Transplant
PAtC	Pandemic Appendix to the Core Protocol
PE	Pulmonary Embolism
PISOP	Pandemic Infection Suspected or Proven
PT	Prothrombin time
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS	Serious Acute Respiratory Syndrome
TACO	Transfusion-Associated Circulatory Overload
TRALI	Transfusion-related acute lung injury
TTI	Transfusion-Associated Circulatory Overload
WHO	World Health Organization

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While, all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see glossary, Section 1.2 Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models) and 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 Regions-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject of a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change overtime in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the relevant Core Protocol (either REMAP-CAP Core Protocol +/- Pandemic Appendix or REMAP-COVID Core Protocol), DSAs, RSAs, and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org).

3. COVID-19 IMMUNOGLOBULIN DOMAIN-SPECIFIC APPENDIX VERSION

The version of the COVID-19 Immunoglobulin Therapy Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the COVID-19 Immunoglobulin Therapy Domain-Specific Working Group (DSWG) on 19th April 2020

Version 2: Approved by the COVID-19 Immunoglobulin Therapy DSWG on 30 June 2020

Version 2.2: Approved by the Canadian members of the COVID-19 Immunoglobulin Therapy DSWG on 01 July 2020

4. COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN GOVERNANCE

4.1. Domain members

Chair:

Dr. Lise Estcourt*

Country Leads:

United Kingdom	Dr. Lise Estcourt[1]
	Dr. Manu Shankar-Hari[1]
Canada	Dr. Alexis Turgeon[2]
	Dr. Ryan Zarychanski[2]
USA	Dr. Bryan McVerry[3]
Australia	A/Prof. Zoe McQuilten[4]
New Zealand	Dr. Tom Hills[5]
	Dr. Colin McArthur[5]
Ireland	Prof. Alistair Nicol[6]

Members:

Dr. Donald Arnold[2]
Dr. Phillipe Bégin[2]
A/Prof. Scott Berry
Dr. Richard Charlewood[5]
Dr. Michaël Chassé[2]
A/Prof. Mark Coyne[6]
Prof. Jamie Cooper[4]
Dr. James Daly[4]

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Prof. Anthony Gordon[1]
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Dr. Heli Harvala-Simmonds[1]
Dr. Sheila MacLennan[1]
Dr. John Marshall[2]
Prof. David Menon[1]
Dr. Susan Morpeth[5]
Mr. Paul Mouncey
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Prof. Steve Webb[4]
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4.2. Contact Details

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5. COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The COVID-19 Immunoglobulin Therapy Domain-Specific Working Group (DSWG) have read the appendix and authorize it as the official COVID-19 Immunoglobulin Therapy Domain-Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair _____ Date 30 June 2020
Lise Estcourt

Country lead (Canada) _____ Date 01 July 2020
Alexis Turgeon

Country lead (Canada) _____ Date 01 July 2020
Ryan Zarychanski

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP platform to test the effectiveness of different strategies for immunoglobulin therapy for microbiological testing-confirmed SARS-CoV-2 infection in patients with acute illness due to suspected or proven COVID-19.

This is the version of the COVID-19 Immunoglobulin Therapy Domain that will apply in Canada and has the version number 2.2. It is anticipated that this domain may also enroll patients in other countries. However, because of differences in nature and supply of product, or timing of availability of product, it is anticipated that differences in the DSA will be necessary. Versions used in other countries, that are derived from this DSA, will be numbered sequentially with a new number after the decimal point (i.e. 1.1, 1.2 etc.) each applying to new countries. A major revision to the DSA will be allocated a new number before the decimal point, i.e. 2.0.

6.2. Domain-specific background

6.2.1. COVID-19 Infection

The first report of infection with SARS-CoV-2 (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 millions of reported cases across the globe, with hundreds of thousands of deaths, and documented sustained human-to-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/newsroom/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)). Due to previous experience with other 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 is to understand the effectiveness of COVID-19 treatments. Clinical guidance issued by the WHO indicates that unproven therapies should be administered preferably only within the setting of a clinical trial (https://www.who.int/docs/defaultsource/coronaviruse/clinical-management-of-novel-cov.pdf).

Globally, as of 20 June 2020 there are 8,666,697 confirmed cases, 460,066 deaths and 4,247,527 patients have recovered from SARS-CoV-2 illness (https://coronavirus.jhu.edu/map.html; Accessed on 20 June 2020). Estimates of the burden of critical illness among patients infected with COVID-19 vary and the corresponding case-fatality estimates are affected by factors such as health system capacity including the availability of diagnostic testing and critical care beds. Nevertheless, it is recognized that fatal critical illness, especially from severe respiratory failure from pneumonitis is high. In reports from China and from Italy (Grasselli et al., 2020, Huang et al., 2020, Remuzzi and Remuzzi, 2020), the proportion of confirmed COVID-19 cases requiring organ support in critical care units varies between 16% to 32% of all hospitalized SARS-CoV-2 illness. Although the overall case fatality rate is estimated as 5.7% (95% confidence intervals 5.5% – 5.9%) for COVID-19 disease for hospitalized patients (Baud et al., 2020), the mortality in critically ill patients with COVID-19 disease, especially those requiring mechanical ventilation, is much higher (Yang et al., 2020).

Interim guidance from the WHO for clinical care of infected patients focus upon supportive care, including organ support as needed, prevention of complications, and no specific anti-COVID-19 therapies. The WHO have recommended that any specific therapy targeted to COVID-19 infection should be provided only as part of a research protocol (https://www.who.int/publications/i/item/clinical-management-of-covid-19).

6.2.2. Convalescent Plasma

Convalescent plasma treatment, containing high titers of polyclonal antibody (Ab), has been used to treat severe viral pneumonia. Many studies have been poorly controlled but such series have shown decreased mortality in Spanish Influenza A (H1N1) infections in 1915-1917 (Luke et al., 2006, McGuire and Redden, 1918), Influenza A (H1N1)pdm09 infections in 2009/2010 (Hung et al., 2011, Ortiz et al., 2013) and of more relevance to this trial, SARS-CoV infections in 2003 (Cheng et al., 2005, Soo et al., 2004). A systematic review and meta-analysis performed identified 699 treated patients with SARS coronavirus infection or severe influenza and 568 untreated “controls” (Mair-Jenkins et al., 2015) found consistent reports of a reduction in mortality. Post hoc meta-analysis showed a statistically significant reduction in the pooled odds of mortality following treatment, compared with placebo or no therapy (odds ratio, 0.25; 95% CI:0.14–0.45) (Mair-Jenkins et al., 2015).

Several trials have shown that convalescent plasma had some efficacy in the treatment of SARS-CoV infection. Eight observational studies reported improved mortality after patients with SARS-CoV –

infection received various amounts of convalescent plasma (Mair-Jenkins et al., 2015). For example, a small retrospective case-comparison study (19 vs 21 patients) showed a 23% (95% CI: 6%-42%, p≤0.05) reduction in mortality after treatment with 200-400 ml of convalescent plasma, when compared with continuation of high-dose methylprednisolone (Soo et al., 2004). In a case series of 80 patients treated with 160-640 ml of convalescent plasma 12.5% died compared with the overall SARS-related mortality rate in Hong-Kong of 17% (Cheng et al., 2005). In this limited series, convalescent plasma given before 14 days after the onset of symptoms was associated with better outcome, however such post-hoc analyses are fraught with confounding factors but do suggest early treatment may be more efficacious.

Reports on the use of convalescent plasma to treat COVID-19 have emerged from the early stages of the pandemic in China (Duan et al., 2020, Shen et al., 2020, Zhang et al., 2020). The largest study showed that 10 patients hospitalized with COVID-19 each given 200ml of convalescent plasma with a neutralizing antibody titer of >1:640 described an improvement in clinical, laboratory and radiological parameters. However, this study was not adequately controlled or powered to allow robust conclusions (Duan et al., 2020).

Subsequently, the effectiveness of convalescent plasma has been assessed in an open-label, multicenter, randomized clinical trial in China comparing convalescent plasma with standard of care in 103 patients with 'severe' or 'life-threatening' COVID-19 (Li et al., 2020). There was a higher rate of nasopharyngeal SARS-CoV-2 PCR negativity at 72 hours in the convalescent plasma group (87.2% vs 37.5%, OR, 11.39 [95% CI, 3.91-33.18]; P < 0.001). In patients with 'severe' COVID-19, clinical improvement, defined as either hospital discharge or reduction of 2 points on a 6-point disease severity scale ranging from 6=death to 1=discharge, occurred in 91.3% (21/23) of the convalescent plasma group and 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; P = 0.03). However, this clinical improvement with convalescent plasma was not seen in patients with 'life-threatening' COVID-19. Overall, the secondary outcome of 28-day mortality was not significantly reduced with convalescent plasma treatment (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46]; P = 0.30).

6.2.2.1. *Adverse effects of convalescent plasma*

Minor side effects have been reported with convalescent plasma, such as fever or chills (Luke et al., 2006), or allergic transfusion reactions (Beigel et al., 2019). More significantly two reports of possible transfusion-related acute lung injury (TRALI) following convalescent plasma have been documented in one patient with Ebola disease and one patient with MERS-CoV, although no anti-HLA or anti-HNA antibodies were identified in donor plasma (Chun et al., 2016, Mora-Rillo et al., 2015). However, none of the 84 patients in the Ebola randomized controlled trial developed any serious adverse events due to the transfusion (Van Griensven et al., 2016). Convalescent plasma has now been given to more than 20,000 COVID-19 patients in the United States of America through an expanded access program (Joyner et al., 2020). In a convenience sample of 20,000 of these patients, mostly with 'severe' or 'life-threatening' COVID-19, the administration of convalescent plasma was generally safe with a low rate of serious adverse events. Specifically, transfusion reactions (n=89; <1%), thromboembolic or thrombotic events (n=87; <1%), and cardiac events (n=680, ~3%) were uncommon and the majority of thromboembolic/thrombotic (55/87) and cardiac events (562/680) were deemed to be unrelated to the convalescent plasma therapy.

6.2.2.2. *Antibody Dependent Enhancement*

Antibody-dependent enhancement (ADE) occurs when antibodies facilitate viral entry into host cells and enhance viral infection in these cells (Wan et al., 2019). Potential toxicity associated with

convalescent plasma remains a concern, and this is very relevant to COVID-19 patients who exhibit a spectrum of lung pathology from acute lung injury to acute respiratory disease syndrome and death. In SARS-CoV-associated disease, antibodies may mediate pathology if they target a different serotype of the virus (Wan et al., 2019, Wang et al., 2014). Furthermore, a novel mechanism for ADE where a neutralizing antibody binding to the surface protein of a coronavirus-like viral receptor triggers viral cell entry has been recently proposed. This ADE pathway was shown not only to be antibody dose dependent but also likely mediated by presence of non-neutralizing antibodies (Ricke and Malone, 2020). For these reasons, we plan to collect convalescent plasma at the earliest 28 days after recovery so that antibody response has matured in terms of titer and affinity.

There is currently no evidence of ADE occurring in the current epidemic, and a small trial of 10 patients in China with COVID-19 treated in a single infusion of 200ml of convalescent plasma showed neither pulmonary injury nor infection enhancement. The high levels of neutralizing antibodies (>1:640), timely transfusion (median time from onset of symptoms to hospital admission and CP transfusion was 6 days (IQR, 2.5–8.5 days) and 16.5 days (IQR 11.0–19.3 days), respectively, and appropriate plasma volume (200ml) were thought to contribute to the absence of side-effects (Duan et al., 2020).

6.2.2.3. *Collection of Convalescent Plasma*

Héma-Québec (HQ) and Canadian Blood Services (CBS) have been preparing to collect convalescent plasma from recovered COVID-19 infected patients. These patients are contacted by HQ or CBS to ask if they are willing to consider blood donation. Donors must have a history of COVID-19 infection documented by RT-PCR at time of infection or positive serology testing following infection. We are collecting convalescent plasma at least 14 days after complete resolution of symptoms prior to donation. Seropositivity of convalescent plasma will be evaluated with an ELISA test directed against the RBD of SARS-CoV-2 Spike protein or by a neutralization assay. Neutralization will be performed for each donation, before or after release of plasma. We will only use male plasma or plasma from female donors with no pregnancy history or with negative anti-HLA antibodies.

6.2.2.4. *Administration of convalescent plasma*

Administration of convalescent plasma is more likely to be beneficial early in the course of the disease (up to 10 to 14 days after onset of symptoms) (Chen et al., 2020).

6.2.2.5. *Need for a clinical trial*

Thus far, the available literature indicates that convalescent plasma has been used to treat thousands of patients with COVID-19 and that, in this setting, rates of serious adverse effects are low. There is a lack of high-quality evidence to determine whether convalescent plasma is an effective therapy for hospitalized patients with COVID-19 and crucial questions remain unanswered, including whether convalescent plasma reduces mortality in hospitalized patients and whether it improves outcomes in the critically unwell.

6.2.3. Intervention Strategy for this domain

It is intended that this domain of REMAP-CAP will evolve, taking into account evidence derived from other clinical trials, as well as availability of potentially effective immunoglobulin therapies. WHO guidance notes the flexibility associated with REMAP-CAP as a platform for the testing of multiple agents, including serial testing of additional interventions (https://apps.who.int/iris/bitstream/handle/10665/330680/WHO-HEO-RDBlueprint%28nCoV%29-2020.1-eng.pdf?ua=1).

At the commencement of this domain, a control group is included (i.e. some patients will not receive any immunoglobulin therapy that is intended to be active against COVID-19 infection). This is appropriate for two reasons. Firstly, there is relatively limited trial or clinical experience with the administration of immunoglobulin therapies and it is not reasonable to presume that such agents do not cause net harm. Secondly, designs that include only active interventions are not able to ascertain if any option is better or worse than no treatment. If, during the evolution of this domain, there is sufficient evidence of effectiveness of agents or clinical practice changes to include the routine use of such agents or both, the control intervention that specifies that no immunoglobulin therapy is administered will be abandoned. Although this domain will commence with a single immunoglobulin therapy, it is intended that additional agents can be added (allowing evaluation of several agents against a common control intervention) as well as allowing introduction of combinations of agents (to evaluate potential synergy). Any changes to the intervention structure of the domain will be specified using one or more amendments to this DSA with implementation occurring only after ethical approval has been obtained. The initial selection of immunoglobulin therapy to be evaluated is convalescent plasma. If at any stage evidence of harm or definitive evidence of absence of effectiveness in critically ill patients emerges for any intervention specified in this domain, the ITSC, as advised by the DSWG, may remove an intervention prior to declaration of a Platform Conclusion. If this occurs, presentation and publication of results that relate to that intervention will occur, so as to contribute additional weight of evidence available in the public domain.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of Immunoglobulin Therapy for patients who are eligible for the platform and who have microbiological testing-confirmed COVID-19.

We hypothesize that the probability of the occurrence of the primary end-point specified in the relevant core protocol documents will differ based on the immunoglobulin therapy intervention. The following interventions will be available:

- No immunoglobulin against SARS-CoV-2
- Convalescent plasma

Each participating site has the option to opt-in to two or more interventions to be included in the randomization schedule depending on local clinical preference, usual practice, acceptable practice, and the availability of the intervention at that site. As long as the ‘no immunoglobulin therapy for COVID-19’ intervention is retained in the platform it is strongly preferred that this intervention is always included by participating sites and is mandatory so long as there is only a single active intervention within the domain.

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial. Treatment allocation will be adaptive, as described in either the REMAP-CAP Core Protocol +/- Pandemic Appendix or the REMAP-COVID Core Protocol.

8.1. Population

The REMAP enrolls patients with severe pneumonia admitted to ICU and patients with acute illness due to suspected or proven COVID-19 admitted to hospital, including patients admitted to ICU).

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in either the REMAP-CAP Core Protocol +/- Pandemic Appendix or the REMAP-COVID Core Protocol. Patients eligible for REMAP-CAP may have conditions that exclude them from the COVID-19 Immunoglobulin Therapy Domain.

8.2.1. Domain inclusion criteria

Patients are eligible for this domain if:

- SARS-CoV-2 infection is confirmed by microbiological testing

8.2.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- If currently in ICU, 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)
- Patient has already received treatment with any non-trial prescribed antibody therapy (monoclonal antibody, hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this hospital admission
- **Enrolment in a trial evaluating any antibody therapy directed against COVID-19, where the protocol of the trial requires continuation of the assignment specified in that trial**
- More than 14 days have elapsed since hospital admission
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

8.2.3. Intervention exclusion criteria

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons.

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 who are not eligible for this domain 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/allergy to an agent specified as an intervention in this domain will exclude a patient from receiving that agent

- Known previous history of transfusion-related acute lung injury will exclude a patient from receiving convalescent plasma
- Known objection to receiving plasma products will exclude a patient from receiving any plasma components

8.3. Interventions

8.3.1. Immunoglobulin Therapy Interventions

Patients will be randomly assigned to receive one of the following open-label strategies. All interventions will be commenced immediately after allocation status is revealed.

- No immunoglobulin against COVID-19
- Convalescent plasma

If the domain evolves to comprise 3 or more interventions, it is required that all sites will participate in the 'No immunoglobulin against COVID-19' intervention, and each site has the option to opt-in to one or more of the remaining interventions based on local practice and availability of the intervention.

8.3.2. No immunoglobulin against SARS-CoV-2

Patients assigned to this intervention will not receive any preparation of immunoglobulin intended to neutralize SARS-CoV-2 during the index hospitalization. Administration of such a preparation is considered a protocol deviation.

8.3.3. Convalescent Plasma

8.3.3.1. *Dosing of convalescent plasma*

Patients assigned to receive plasma will receive at least one and not more than two adult units of ABO compatible convalescent plasma (total volume 550ml ± 150ml) within 48 hours of randomization. Volume of convalescent plasma administered will be recorded and where available the level of antibodies within each unit will be tested.

8.3.3.2. *Duration of administration of convalescent plasma*

ABO compatible convalescent plasma will be administered as early as possible within 48 hours of randomization depending on the availability of the product from Héma-Québec or Canadian Blood Services.

8.3.4. Discontinuation of study therapy

An immunoglobulin for SARS-CoV-2 infection should be discontinued if there is development of an SAE. Immunoglobulin therapy can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

8.4. Concomitant care

In patients who have received an allocation status in the COVID-19 Antiviral Domain, and have microbiological testing confirmed SARS-CoV-2 infection, continuation of antiviral agent will be as per the COVID-19 Antiviral Domain-Specific Appendix (Section 8.3). Additional agents intended to be

active against SARS-CoV-2 infection should not be administered, unless they have become standard of care during the trial or specified in another trial protocol. All 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 (occurring during the index hospitalization, censored at 90 days after enrollment) will be:

- All-cause mortality at 28 days
- Confirmed deep vein thrombosis
- Confirmed pulmonary embolus
- Confirmed ischemic cerebrovascular event
- Confirmed acute myocardial infarction
- Other confirmed thrombotic events
- Serious treatment-related adverse events (see section 11.2 of this appendix)
- Serious Adverse Events (SAE) as defined in core protocol documents and qualified in this appendix.

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 and any additional testing, which may differ between locations, is specified below.

Sites that are participating in this domain are encouraged to also participate in the Clinical Characterization Protocol (CCP) for patients with COVID-19 that has been established by the International Severe Acute Respiratory and Emerging Infectious Consortium (https://isaric.tghn.org/CCP/). This protocol specifies the collection of biological samples from patients with COVID-19. Samples collected in patients who are enrolled in the CCP may be made available to REMAP-CAP investigators to evaluate aspects of host or pathogen biology associated with assignment in this domain. Ethical approval at such sites and agreement from patients to undertake the CCP will be obtained separately.

9.2. Domain-specific data collection

Additional domain-specific data will be collected for the index hospitalization:

- Administration of immunoglobulin therapies
- Neutralizing antibody titer of trial immunoglobulin therapies (where available)
- Deep vein thrombosis
- Pulmonary embolism
- Ischemic cerebrovascular events
- Peak troponin
- Acute myocardial infarction (using fourth international definition)

Additional domain-specific data will be collected on all participants: Routinely collected data on neutrophil count, lymphocyte count, prothrombin time (PT), fibrinogen, CRP (if done for clinical reasons), D-Dimers (if done for clinical reasons) and troponins (if done for clinical reasons) at baseline.

9.3. Criteria for discontinuation

Refer to relevant core protocol documents for criteria for discontinuation of participation in the trial.

9.4. Blinding

9.4.1. Blinding

All interventions 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:

- Superiority of convalescent plasma compared to no immunoglobulin against SARS-CoV-2
- Futility of convalescent plasma compared to no immunoglobulin against SARS-CoV-2

Additional Platform Conclusions may be possible if further interventions are added to the domain.

In all other respects the stopping rules for this domain are those outlined in the core protocol documents.

10.2. Unit-of-analysis and strata

This domain is analyzed only in the pandemic statistical model and includes only patients who are SARS-CoV-2 infection confirmed. 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. Borrowing is permitted between states and strata. Response Adaptive Randomization will be applied in each illness severity state, using probabilities derived from the SARS-CoV-2 confirmed stratum.

The shock strata will not contribute to unit-of-analysis for this domain, as this strata is not applied in the Pandemic Statistical Model.

The influenza strata will not contribute to unit-of-analysis for this domain.

10.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal or Randomization with Deferred Reveal if confirmation of microbiological diagnosis is not known at the time of initial assessment of eligibility (see relevant core protocol documents)

10.4. Interactions with interventions in other domains

An a priori interaction with the Antibiotic Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the Macrolide Duration Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Influenza Antiviral Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the COVID-19 Antiviral Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Immune Modulation Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Corticosteroid Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Statin Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Vitamin C Domain is either not considered possible and will not be incorporated into the statistical model used to evaluate this domain in the pandemic statistical model or is not able to be evaluated for PINSNP patients as analysis occurs in different statistical models.

No interaction is evaluable between the Ventilation Domain and this domain.

10.5. Nesting of interventions

Nesting is not applicable to this domain

10.6. Threshold probability for superiority, effectiveness and inferiority

The threshold odds ratio delta for superiority, effectiveness and inferiority in this domain are those specified in the relevant core protocol documents

10.7. Threshold odds ratio delta for equivalence or futility

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 an active intervention.

10.8. Informative priors

This domain will launch with priors that are not informative for main effects. If new immunoglobulin agents are added to the domain, consideration will be given to the use of informative priors at the time of amendment of the DSA.

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. Data for post-trial sub-group analysis may not be available from all regions or for all patients in a region. The a priori patient sub-groups of interest are:

- Proven concomitant bacterial co-infection, defined as having isolation or detection of a known pathogen that causes pneumonia from blood, pleural fluid, or lower respiratory tract specimen.
- Receiving invasive mechanical ventilation at baseline
- Patients with undetectable virus at baseline (convalescent plasma intervention)
- Patients with different levels of neutralizing antibodies at baseline (convalescent plasma intervention)
- Dose of neutralizing antibodies received (convalescent plasma intervention, based on volume of transfusion and titer measurement, where available)
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

10.10. Domain-specific secondary and exploratory analyses

- Number of SAEs (excluding thrombotic events) from randomization until 72 hours after randomization, per day at risk; described by intervention.

- Number of thrombotic events from randomization up to the end of acute hospitalization, per day at risk. These will be analyzed using Poisson regression.

- Analyses of the data from any country-specific sub-studies will be specified in separate analysis plans.

10.11. Data sharing

Not applicable.

11.ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, effectiveness, inferiority, futility or equivalence of different interventions with respect to the primary endpoints are possible, and if equivalence is demonstrated, determination of the optimal intervention may be based on secondary endpoints, such as all-cause mortality at 28 days.

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 are required.

11.2. Potential domain-specific adverse events

11.2.1. Convalescent Plasma

For patients assigned to any intervention, occurrence of any of the following should be reported as a SAE:

- Serious allergic reaction or anaphylaxis

- Transfusion related acute lung injury (TRALI)

In addition, site staff are responsible for reporting all transfusion-related adverse events to their national or regional hemovigilance system.

Other SAEs should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see relevant core protocol documents).

11.3. Domain-specific consent issues

As noted in the background, and endorsed by the WHO, in the absence of evidence of effectiveness of specific treatments for COVID-19, the use of a no treatment control is both appropriate and ethical.

For patients who are not competent to consent, either prospective agreement or entry via waiver of-consent or some form of deferred consent can be applied, as required by an appropriate ethical review body.

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.

Clinicians are directed to not enrol an individual patient if the treating clinician believes that participation in this domain is not in the best interests of the patient.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the Core Protocol documents. This domain has received domain-specific funding from the Canadian Institutes of Health Research (CIHR)

12.2. Funding of domain interventions and outcome measures

Héma-Québec and Canadian Blood Services will supply the convalescent plasma for the trial and arrange for distribution to participating hospitals via its routine distribution system. This domain has received domain-specific funding from the Canadian Institutes of Health Research (CIHR)

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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Domain-Specific Appendix: COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

COVID-19 Immunoglobulin Therapy Domain-Specific Appendix Version 1.01 dated 01 June 2020

Summary

In this domain of the REMAP-CAP trial, participants meeting the platform-entry criteria for REMAP-CAP admitted to participating intensive care units with microbiological testing confirmed COVID-19 infection will be randomized to receive one of two interventions:

- No immunoglobulin against COVID-19 (no placebo)
- Convalescent plasma

This domain will only enroll patients if the pandemic infection is proven (PISOP) stratum and be analyzed in the Pandemic Statistical Model as outlined from the Pandemic Appendix to Core (PAtC).

At this participating site the following interventions have been selected within this domain:

☐ No immunoglobulin against COVID-19 (no placebo)
☐ Convalescent plasma

REMAP-CAP: Immunoglobulin Therapy Domain Summary	
Interventions	• No immunoglobulin against COVID-19 (no placebo) • Convalescent plasma (up to 2 units within 48 hours)
Unit-of-analysis and Strata	The default unit-of-analysis for this domain will be the pandemic infection suspected or confirmed (PISOP) stratum. Analysis and Response Adaptive Randomization are applied by PISOP stratum.
Evaluable treatment-by-treatment Interactions	Treatment-treatment interactions will be evaluated between interventions in this domain and interventions in the Corticosteroid Domain and the COVID-19 Antiviral Therapy Domain. No other interactions will be evaluated with any other domain.
Nesting	None
Timing of Reveal	Randomization with Deferred Reveal at time of confirmation of infection by microbiological testing.
Inclusions	Inclusion criteria are the same as the Platform see Core Protocol Section 7.4.1, and • COVID-19 infection is confirmed by microbiological testing
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • More than 48 hours have elapsed since ICU admission • Patient has already received treatment with any non-trial prescribed antibody therapy (monoclonal antibody, hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this hospital admission • More than 14 days have elapsed since 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 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 previous history of transfusion-related acute lung injury will exclude a patient from receiving convalescent plasma • Known objection to receiving plasma products will exclude a patient from receiving any plasma components
Outcome measures	Primary REMAP endpoint: as defined in an operational document specified from the Pandemic Appendix to the Core Protocol Section 7.5.1. Secondary REMAP endpoints refer to Core Protocol Section 7.6.2 Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrolment): • All-cause mortality at 28 days • Serious adverse events (SAE) as defined in this appendix • Serious Adverse Events (SAE) as defined in Core Protocol • Venous thromboembolic events at 90 days

	Domain-specific exploratory outcomes • Percent of subjects who cleared SARS-CoV-2 infection (i.e. all samples (obtained at least in two time points after transfusion) tested negative for SARS-CoV-2 RNA in all respiratory samples or just in blood) • Reduction in SARS-CoV-2 viral load (within the first 3 days; 4 days; 6 days; 9 days; 15 days and 28 days analyzed separately in blood and respiratory samples) • Change in SARS-CoV-2 neutralizing antibody levels (within the first 3 days; 4 days: 6 days; 9 days; 15 days and 28 days)

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1. ABBREVIATIONS

ADE	Antibody-dependent enhancement
CCP	Clinical Characterization Protocol
CRP	C-reactive protein
CVA	Cerebrovascular accident
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
DVT	Deep vein thrombosis
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
MERS-CoV	Middle East respiratory syndrome coronavirus
NHS	National Health Service of the United Kingdom
NHSBT	National Health Service Blood and Transplant
PAtC	Pandemic Appendix to the Core Protocol
PE	Pulmonary Embolism
PISOP	Pandemic Infection Suspected or Proven
PT	Prothrombin time
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS	Serious Acute Respiratory Syndrome
TACO	Transfusion-Associated Circulatory Overload
TRALI	Transfusion-related acute lung injury
TTI	Transfusion-Associated Circulatory Overload
WHO	World Health Organisation

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) and 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 Regions-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject of a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change overtime in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the Core Protocol, DSAs, RSAs, and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org).

3. COVID-19 IMMUNOGLOBULIN DOMAIN-SPECIFIC APPENDIX VERSION

The version of the COVID-19 Immunoglobulin Therapy Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the COVID-19 Immunoglobulin Therapy Domain-Specific Working Group (DSWG) on 19th April 2020

Version 1.01: Approved by the COVID-19 Immunoglobulin Therapy DSWG on 1st June 2020

4. COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN GOVERNANCE

4.1. Domain members

Chair:

Dr Lise Estcourt*

Co-chair:

Dr Manu Shankar-Hari*

Members:

Dr Jacinta Abraham
A/Prof Scott Berry
A/Prof Mark Coyne
Prof Anthony Gordon
Dr Heli Harvala-Simmonds
Prof Stephen Jolles
Dr Sheila MacLennan
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A/Prof Zoe McQuilten
*Prof David Menon
Mr Paul Mouncey
Prof Alistair Nichol
Dr Nicole Pridee
*Prof David Roberts
Prof Kathy Rowan
Dr Jon Silversides
Ms Helen Thomas
Prof Tim Walsh
Prof Steve Webb
Prof Erica Wood

*Members who are co-leading the COVID-19 Immunoglobulin Therapy Domain

4.2. Contact Details

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4.3. COVID-19 Immunoglobulin therapy DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The COVID-19 Immunoglobulin Therapy Domain-Specific Working Group (DSWG) have read the appendix and authorize it as the official COVID-19 Immunoglobulin Therapy Domain-Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair _____ Date 1st June 2020
Lise Estcourt

5. BACKGROUND AND RATIONALE

5.1. Domain definition

This is a domain within the REMAP-CAP to test the effectiveness of different strategies for immunoglobulin therapy for microbiological testing-confirmed COVID-19 infection in patients with concomitant severe pneumonia who are admitted to an Intensive Care Unit (ICU).

This is the version of the COVID-19 Immunoglobulin Therapy Domain that will apply in the United Kingdom and has the version number 1.0. It is anticipated that this domain may also enroll patients in other countries. However, because of differences in nature and supply of product, or timing of availability of product, it is anticipated that differences in the DSA will be necessary. Versions used in other countries, that are derived from this DSA, will be numbered sequentially with a new number after the decimal point (i.e. 1.1, 1.2 etc.) each applying to new countries. A major revision to the DSA will be allocated a new number before the decimal point, i.e. 2.0.

5.2. Domain-specific background

5.2.1. COVID-19 Infection

The first report of infection with COVID-19 occurred in Wuhan, China, in late 2019. Since that time, and as of the time of writing of this DSA, there have been hundreds of thousands of reported cases across the globe, with a range of severity, tens of thousands of deaths, and documented sustained

human-to-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/newsroom/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)). Due to previous experience with other 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. Clinical guidance issued by the WHO indicates that unproven therapies should be administered preferably only within the setting of a clinical trial (https://www.who.int/docs/defaultsource/coronaviruse/clinical-management-of-novel-cov.pdf).

Globally, as of 12th April 2020 there are 1,854,464 confirmed cases, 114,331 deaths and 435,074 patients have recovered from SARS-CoV-2 illness (https://coronavirus.jhu.edu/map.html; Accessed on 12th April 2020). Estimates of the burden of critical illness among patients infected with COVID-19 vary and the corresponding case-fatality estimates are unreliable and differ by resource availability in terms of testing and critical care beds. Nevertheless, it is recognized that fatal critical illness, especially from severe respiratory failure from pneumonitis is high. In reports from China and from Italy (Grasselli et al., 2020, Huang et al., 2020, Remuzzi and Remuzzi, 2020), the proportion of confirmed COVID-19 cases requiring organ support in critical care units varies between 16% to 32% of all hospitalized SARS-CoV-2 illness. Although the overall case fatality rate is estimated as 5.7% (95% confidence intervals 5.5% – 5.9%) for COVID-19 disease (Baud et al., 2020), the 28-day mortality in critically ill patients with COVID-19 disease is approximately 60%, and even higher in those requiring mechanical ventilation (Yang et al., 2020).

The corresponding figures in the United Kingdom are 84,279 confirmed cases and 10,612 deaths. In the UK, the critical care case-mix of COVID19 has been reported by the Intensive Care National Audit and Research Centre (ICNARC) (https://www.icnarc.org; Accessed on 12th April 2020). This report contains all confirmed COVID-19 cases reported to ICNARC up to midnight on 10th April 2020 from critical care units participating in the Case Mix Programme (all NHS adult, general intensive care and combined intensive care/high dependency units in England, Wales and Northern Ireland, plus some specialist and non-NHS critical care units). ICNARC has been notified of 4,960 admissions. Amongst these 4,960 admissions, the first 24-hour data to inform the case-mix characteristics such as age, sex, illness severity has been submitted to ICNARC for 4,292 admissions of 3,883 patients. Of the 3,883 patients, 59.0% of patients are mechanically ventilated within 24 hours of admission, 871 patients have died, 818 patients have been discharged alive from critical care. Importantly, 2,194 patients were last reported as still being in critical care. The predictions for all health care systems globally, including the UK, are that the demands on critical care requirements are likely to increase and any intervention that reduces this by accelerating illness resolution, ideally by reducing both mortality and by reducing critical care length of stay are essential.

Interim recommendations from the WHO for clinical care of infected patients focus upon supportive care, including organ support as needed, prevention of complications, and no specific anti-COVID-19 therapies. The WHO have recommended that any specific therapy targeted to COVID-19 infection should be provided only as part of a research protocol (https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf).

5.2.2. Convalescent Plasma

Convalescent plasma treatment, containing high titers of polyclonal antibody (Ab), has been used to treat severe viral pneumonia. Many studies have been poorly controlled but such series have shown decreased mortality in Spanish Influenza A (H1N1) infections in 1915-1917 (Luke et al., 2006, McGuire and Redden, 1918), Influenza A (H1N1)pdm09 infections in 2009/2010 (Hung et al., 2011, Ortiz et al., 2013) and more relevantly to this trial, SARS-CoV infections in 2003 (Cheng et al., 2005, Soo et al., 2004). A systematic review and meta-analysis performed identified 699 treated patients with SARS coronavirus infection and severe influenza and 568 untreated "controls" (Mair-Jenkins et al., 2015) found consistent reports of a reduction in mortality. Post hoc meta-analysis showed a statistically significant reduction in the pooled odds of mortality following treatment, compared with placebo or no therapy (odds ratio, 0.25; 95% CI:0.14–0.45) (Mair-Jenkins et al., 2015).

Several trials have shown that convalescent plasma had some efficacy in the treatment of SARS-CoV infected patients. Eight observational studies reported improved mortality after SARS-CoV – infected patients received various amounts of convalescent plasma (Mair-Jenkins et al., 2015). For example, a small retrospective case-comparison study (19 vs 21 patients) showed a case fatality rate reduction after convalescent plasma treatment of 23% (95% CI: 6%-42%, p≤0.05) (Soo et al., 2004). Each patient received 200 to 400 ml of convalescent plasma. In a case series of 80 patients treated with 160-640 ml of convalescent plasma 12.5% died compared with the overall SARS-related mortality rate in Hong-Kong of 17% (Cheng et al., 2005). In this limited series, convalescent plasma given before 14 days after the onset of symptoms was associated with better outcome, however such post-hoc analyses are fraught with confounding factors but do suggest early treatment may be more efficacious.

Convalescent plasma therapy had been given to at least 245 COVID-19 patients in China by the end of February 2020, and, according to a Chinese health official, 91 cases had shown improvement in clinical indicators and symptoms (http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm). There have been three published reports from China (Duan et al., 2020, Shen et al., 2020, Zhang et al., 2020), the largest study showed that 10 patients hospitalized with COVID-19 and given 200ml of convalescent plasma with a neutralizing antibody titer of >1:640 showed significant clinical and radiological improvement and commensurate reduction in C-reactive protein (CRP), liver function tests, viremia and oro-pharyngeal viral load and increases in lymphocyte count (Duan et al., 2020).

5.2.2.1. *Adverse effects of convalescent plasma*

Minor side effects have been reported with convalescent plasma, such as fever or chills (Luke et al., 2006), or allergic transfusion reactions (Beigel et al., 2019). More significantly two reports of possible transfusion-related acute lung injury (TRALI) following convalescent plasma have been documented in one patient with Ebola disease and one patient with MERS-CoV, although no anti-HLA or anti-HNA antibodies were identified in donor plasma (Chun et al., 2016, Mora-Rillo et al., 2015). However, none of the 84 patients in the Ebola randomized controlled trial developed any serious adverse events due to the transfusion (Van Griensven et al., 2016b).

5.2.2.2. *Antibody Dependent Enhancement*

Antibody-dependent enhancement (ADE) occurs when antibodies facilitate viral entry into host cells and enhance viral infection in these cells (Wan et al., 2019). Potential toxicity associated with convalescent plasma remains a concern, and this is very relevant to COVID-19 patients who exhibit a spectrum of lung pathology from acute lung injury to acute respiratory disease syndrome and death.

In SARS-CoV-associated disease, antibodies may mediate pathology if they target a different serotype of the virus (Wan et al., 2019, Wang et al., 2014). Furthermore, a novel mechanism for ADE where a neutralizing antibody binding to the surface protein of a coronavirus-like viral receptor triggers viral cell entry has been recently proposed. This ADE pathway was shown not only to be antibody dose dependent but also likely mediated by presence of non-neutralizing antibodies (Ricke and Malone, 2020). For these reasons, we plan to collect convalescent plasma at the earliest 28 days after recovery so that antibody response has matured in terms of titer and affinity.

There is currently no evidence of ADE occurring in the current epidemic, and a small trial of 10 patients in China with COVID-19 treated in a single infusion of 200ml of convalescent plasma showed neither pulmonary injury nor infection enhancement. The high levels of neutralizing antibodies (>1:640), timely transfusion (median time from onset of symptoms to hospital admission and CP transfusion was 6 days (IQR, 2.5–8.5 days) and 16.5 days (IQR 11.0–19.3 days), respectively, and appropriate plasma volume (200ml) were thought to contribute to the absence of side-effects (Duan et al., 2020).

5.2.2.3. *Collection of Convalescent Plasma*

NHS Blood and Transplant (NHSBT) has been preparing to collect convalescent plasma from recovered COVID-19 infected patients since this was requested by NHS England in mid-February. These patients are contacted to ask if they are willing to consider blood donation. We are collecting convalescent plasma at least 28 days after their recovery from the infection to maximize the quality and quantity of neutralizing antibodies present in their donations. In addition to the usual donor and donation screening, the first 1,000 donations will be tested for SARS-CoV-2 RNA, SARS-CoV-2 RNA testing will be stopped if there is no evidence of RNA in any of these donations. Neutralizing antibody levels will also be determined in each donation using microneutralization (TCID50) or pseudovirus particle assays or both. However, if an adequate correlation between neutralizing antibody titre and Elisa antibody reactivity is demonstrated, this can replace the test for neutralising antibodies. Only donations containing high levels of neutralizing antibodies will be offered for clinical use (the cut-off level to be defined during the first two weeks of collections; 1:160 previously used for SARS-CoV-1 (Cheng et al., 2005) and MERS-CoV (Arabi et al., 2015)). We will only use male plasma or plasma from female donors who have been tested and are eligible to donate apheresis platelets (Epstein et al., 2020) to reduce the risk of TRALI. Treatment with convalescent plasma with low levels of antibody has been shown to be ineffective in Ebola (Van Griensven et al., 2016a, Van Griensven et al., 2016b).

The Scottish National Blood Transfusion Service (SNBTS), Welsh Blood Service (WBS), and Northern Ireland Blood Transfusion Service (NIBTS) are instituting similar convalescent plasma production policies and they will supply convalescent plasma to hospitals in the devolved nations. There is a UK-wide collaboration to ensure production of convalescent plasma is consistent across all devolved nations. Any British Overseas Territories will also collaborate with the UK Blood Services to ensure a consistent product is produced.

The Irish Blood Transfusion Service will collect convalescent plasma at least 14 days after donors have recovered from infection, donors have to be nasopharyngeal swab negative prior to donation. The component will otherwise be similar to the component produced in the UK. Samples will be kept to ensure the component is consistent with the UK component.

The other blood services do not plan to perform SARS-CoV-2 RNA testing if there is no evidence of RNA in any of the initial 1000 donations tested by NHSBT.

5.2.2.4. *Administration of convalescent plasma*

Administration of convalescent plasma is more likely to be beneficial early in the course of the disease (up to 10 to 14 days after onset of symptoms) (Chen et al., 2020b).

5.2.2.5. *Need for a clinical trial*

Although there is evidence that convalescent plasma can have beneficial effects in patients with severe respiratory viral infections the majority of the evidence is of low quality. Two randomized trials, one of convalescent plasma and one of anti-influenza hyperimmune intravenous immunoglobulin showed no benefits of convalescent plasma (Beigel et al., 2019, Davey et al., 2019). We are therefore uncertain whether convalescent plasma will be effective for COVID-19 patients and a RCT is required to assess the benefits of convalescent plasma.

5.2.3. Intervention Strategy for this domain

It is intended that this domain of REMAP-CAP will evolve, taking into account evidence derived from other clinical trials, as well as availability of potentially effective immunoglobulin therapies. WHO guidance notes the flexibility associated with REMAP-CAP as a platform for the testing of multiple agents, including serial testing of additional interventions (https://apps.who.int/iris/bitstream/handle/10665/330680/WHO-HEO-RDBlueprint%28nCoV%29-2020.1-eng.pdf?ua=1).

At the commencement of this domain, a control group is included (i.e. some patients will not receive any immunoglobulin therapy that is intended to be active against COVID-19 infection). This is appropriate for two reasons. Firstly, there is relatively limited trial or clinical experience with the administration of immunoglobulin therapies in patients who are critically ill and it is not reasonable to presume that such agents do not cause net harm. Secondly, designs that include only active interventions are not able to ascertain if any option is better or worse than no treatment. If, during the evolution of this domain, there is sufficient evidence of effectiveness of agents or clinical practice changes to include the routine use of such agents or both, the control intervention that specifies that no immunoglobulin therapy is administered will be abandoned. Although this domain will commence with a single immunoglobulin therapy, it is intended that additional agents can be added (allowing evaluation of several agents against a common control intervention) as well as allowing introduction of combinations of agents (to evaluate potential synergy). Any changes to the intervention structure of the domain will be specified using one or more amendments to this DSA with implementation occurring only after ethical approval has been obtained. The initial selection of immunoglobulin therapy to be evaluated is convalescent plasma. If at any stage evidence of harm or definitive evidence of absence of effectiveness in critically ill patients emerges for any intervention specified in this domain, the ITSC, as advised by the DSWG, may remove an intervention prior to declaration of a Platform Conclusion. If this occurs, presentation and publication of results that relate to that intervention will occur, so as to contribute additional weight of evidence available in the public domain.

6. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of Immunoglobulin Therapy for patients with severe CAP who have microbiological testing-confirmed COVID-19.

We hypothesize that the primary end-point specified from the PAtC will differ based on the immunoglobulin therapy intervention. The following interventions will be available:

- No immunoglobulin against COVID-19 (no placebo)
- Convalescent plasma

We hypothesize that the treatment effect of different immunoglobulin strategies is different depending on allocation status in the Corticosteroid Domain. This is a treatment-by-treatment interaction between the interventions in the COVID-19 Immunoglobulin Therapy Domain and the Corticosteroid Domain.

We hypothesize that the treatment effect of different immunoglobulin strategies is different depending on allocation status in the COVID-19 Antiviral Therapy Domain. This is a treatment-by-treatment interaction between the interventions in the COVID-19 Immunoglobulin Therapy Domain and the COVID-19 Antiviral Therapy Domain.

Each participating site has the option to opt-in to two or more interventions to be included in the randomization schedule depending on local clinical preference, usual practice, acceptable practice, and the availability of the intervention at that site. As long as the 'no immunoglobulin therapy for COVID-19' intervention is retained in the platform it is strongly preferred that this intervention is always included by participating sites and is mandatory so long as there is only a single active intervention within the domain.

7. TRIAL DESIGN

This domain will be conducted as part of a REMAP trial (see Core Protocol Section 7). Treatment allocation will be adaptive, as described in the Core Protocol Section 7.5.2 and from the PAtC.

7.1. Population

The REMAP enrolls patients with severe pneumonia admitted to ICU (see Core Protocol Section 7.3).

7.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria (see Core Protocol Section 7.4 and PAtC). Patients eligible for REMAP may have conditions that exclude them from the COVID-19 Immunoglobulin Therapy Domain.

7.2.1. Domain inclusion criteria

Patients are eligible for this domain if:

- COVID-19 infection is confirmed by microbiological testing

7.2.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- More than 48 hours has elapsed since ICU admission

- Patient has already received treatment with any non-trial prescribed antibody therapy (monoclonal antibody, hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this hospital admission
- More than 14 days have elapsed since hospital admission
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

7.2.3. Intervention exclusion criteria

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons.

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 who are not eligible for this domain 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/allergy to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
- Known previous history of transfusion-related acute lung injury will exclude a patient from receiving convalescent plasma
- Known objection to receiving plasma products will exclude a patient from receiving any plasma components

7.3. Interventions

7.3.1. Immunoglobulin Therapy Interventions

Patients will be randomly assigned to receive one of the following open-label strategies. All interventions will be commenced immediately after allocation status is revealed.

- No immunoglobulin against COVID-19 (no placebo)
- Convalescent plasma

7.3.2. No immunoglobulin against COVID-19 (no placebo)

Patients assigned to this intervention will not receive any preparation of immunoglobulin intended to neutralize COVID-19 during the index hospitalization. Administration of such a preparation is considered a protocol deviation.

7.3.3. Convalescent Plasma

7.3.3.1. *Dosing of convalescent plasma*

Patients assigned to receive plasma will receive at least one and not more than two adult units of ABO compatible convalescent plasma (total volume 550ml ± 150ml) within 48 hours of randomization. Volume of convalescent plasma administered and the level of antibodies within each unit will be tested.

7.3.3.2. *Duration of administration of convalescent plasma*

Those receiving plasma will receive a unit of ABO compatible convalescent plasma on the first day of the study. If the patient has no serious adverse reactions to the transfusion the second unit of convalescent plasma will be given. There must be a minimum of 12 hours between transfusions to allow appropriate assessment of adverse reactions to the initial transfusion. Both transfusions should be given within 48 hours from randomization.

7.4. Concomitant care

Additional agents intended to be active against SARS-CoV-2 infection should not be administered, unless they have become standard of care during the trial. In patients who have received an allocation status in the COVID-19 Antiviral Domain, and have microbiological testing confirmed SARS-CoV-2 infection, continuation of antiviral agent will be as per the COVID-19 Antiviral Domain-Specific Appendix (Section 8.3). All treatment that is not specified by assignment within the platform will be determined by the treating clinician.

7.5. Endpoints

7.5.1. Primary endpoint

The primary endpoint for this domain is the primary outcome specified in an operational document from within the options specified in the PAtC.

7.5.2. Secondary endpoints

All secondary endpoints as specified from the PAtC 7.5.2.

The domain-specific secondary outcome measures (occurring during the index hospitalization, censored at 90 days after enrollment) will be:

- All-cause mortality at 28 days
- Serious treatment-related adverse events (see table 1 section 10.1 of this appendix)
- Serious Adverse Events (SAE) as defined in Core Protocol
- Venous thromboembolic events at 90 days

Domain-specific exploratory outcomes

- Proportion of subjects who cleared SARS-CoV-2 infection (i.e. all samples, obtained for at least two time points after transfusion) tested negative for SARS-CoV-2 RNA, just in lower respiratory sample, in all respiratory tract samples or just in blood)
- Reduction in SARS-CoV-2 viral load (within the first 3 days; 4 days; 6 days; 9 days; 15 days and 28 days analyzed separately in blood and respiratory tract samples)
- Change in SARS-CoV-2 neutralizing antibody levels (within the first 3 days; 4 days; 6 days; 9 days; 15 days and 28 days)

8. TRIAL CONDUCT

8.1. Domain-specific data collection

8.1.1. Additional testing for all participants

A group and screen sample must be processed locally, so that ABO compatible convalescent plasma can be administered.

Samples to be taken on Study Day 1 prior to administration of convalescent plasma to assess the level of:

1) Antibodies and neutralizing antibodies detectable prior to treatment on Day 1 (serum 6ml)
2) Testing for virus detectable on an oropharyngeal or nasopharyngeal swab prior to treatment on Study Day 1

These samples must be sent to the central testing laboratory (see laboratory protocol).

8.1.2. Additional testing sub-study for convalescent plasma

There will be additional testing as specified in this protocol for a sub-group of sites.

Please see Appendix 1 for schedule of sampling. Sites will opt-in to the additional testing sub-study. We aim for at least 100 participants in each study intervention to be included in the sub-study (maximum 200 participants per study intervention). Full details are included in the Laboratory SOP.

COVID-19 is characterized by cytokine excess (Chen et al., 2020a). Administration of convalescent plasma will be associated with changes in cytokine profile, which may be the causal mechanism for treatment effects via immunomodulation (Shankar-Hari and Rubenfeld, 2019, Shankar-Hari et al., 2011). Antibody dependent potentiation is an adverse event with convalescent plasma, which requires monitoring (Liu et al., 2019).

8.1.2.1. *Proposed work*

The following biological work to assess adverse effects and to explain treatment response will be done at pre-defined time points at baseline and at predefined time points post convalescent plasma administration (Appendix 1).

- A multiplexable Th1 / Th2 (including IL-10) cytokine profile (Chen et al., 2020a).
- D-dimer and other laboratory markers of disease severity
- Whole blood transcriptomic alterations (Blanco-Melo et al., 2020)
- Flow cytometric analyses to define the immune status of participants
- Genotype by SNP array
- Neutralizing and other anti-viral antibody assays.
- Viral PCR in respiratory and blood samples (Wölfel et al., 2020)
- Sequencing of SARS-CoV-2 from respiratory and blood samples

8.1.3. 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. If sites that are participating in this domain are not participating in the additional sample collection sub-study (section 8.1.2) they are encouraged to also participate in the Clinical Characterization Protocol (CCP) for patients with COVID-19 that has been established by the International Severe Acute Respiratory and Emerging Infectious Consortium (https://isaric.tghn.org/CCP/). This protocol specifies the collection of biological samples from patients with COVID-19. Samples collected in patients who are enrolled in the CCP may be made available to REMAP-CAP investigators to evaluate aspects of host or pathogen biology associated with assignment in this domain. Ethical approval at such sites and agreement from patients to undertake the CCP will be obtained separately.

8.1.4. Clinical data collection on all participants

Additional domain-specific data will be collected on all participants:

- Routinely collected data on neutrophil count, lymphocyte count, prothrombin time (PT), fibrinogen, CRP (if done for clinical reasons) at baseline
- SARS-CoV-2 viral load at baseline (in blood and respiratory samples)
- SARS-CoV-2 neutralizing antibody levels at baseline
- Serious treatment-related serious adverse events within 24 hours of the treatment, similar serious adverse events reported in both arms unrelated to transfusion in the first 72 hours of the study
- Transfusion-transmitted infection occurring at any time during the study
- Serious clinically diagnosed arterial (e.g. myocardial infarction (MI), cerebrovascular accident (CVA), mesenteric arterial thrombosis) or venous thrombotic events (e.g. deep vein thrombosis (DVT), pulmonary embolism (PE), portal or mesenteric venous thrombosis, or cortical venous sinus thrombosis) up to day 90

8.1.5. Clinical Data collection on participants within the intensive sampling sub-set

- Routinely collected data on neutrophil count, lymphocyte count, PT, fibrinogen, CRP (if done for clinical reasons) on days 2, 3, 4, 6, 9, 15, 28
- SARS-CoV-2 viral load at day 2, 3, 4, 6, 9, 15 and 28 (in blood and respiratory samples)
- SARS-CoV-2 neutralizing antibody levels at day 2, 3, 4, 6, 9, 15 and 28

Blood and respiratory samples will only be collected during inpatient admission, results will be censored at hospital discharge. Blood samples will be taken by fresh venipuncture if there is no indwelling cannula.

8.2. Criteria for discontinuation

Refer to Core Protocol Section 8.7 for criteria for discontinuation of participation in the REMAP-CAP trial.

8.3. Blinding

8.3.1. Blinding

All interventions will be administered on an open-label basis.

8.3.2. Unblinding

Not relevant.

9. STATISTICAL CONSIDERATIONS

9.1. Domain-specific stopping rules

If a Platform Conclusion of equivalence in the primary endpoint is demonstrated the DSMB and the ITSC may consider continuation of randomization if clinically relevant differences in secondary endpoints have not been demonstrated and it is considered plausible that clinically relevant differences in one or more secondary endpoints may be capable of being demonstrated. In all other respects the stopping rules for this domain are those outlined in the Core Protocol Sections 7.8.6 to 7.8.9.

9.2. Unit-of-analysis and strata

The default unit-of-analysis, for both analysis of treatment effect and the Response Adaptive Randomization, will be the SARS-CoV-2 infection confirmed stratum, as specified from the PAtC.

The shock strata will not contribute to unit-of-analysis for this domain, as this strata is not applied in the Pandemic Statistical Model.

The influenza strata will not contribute to unit-of-analysis for this domain.

9.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal or Randomization with Deferred Reveal if confirmation of microbiological diagnosis is not known at the time of initial assessment of eligibility (see section 7.8.3.6 in Core Protocol)

9.4. Interactions with interventions in other domains

An a priori interaction with the Antibiotic Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the Macrolide Duration Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Antiviral Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the COVID-19 Antiviral Domain is considered possible and will be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Immune Modulation Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Corticosteroid Domain is considered possible and will be incorporated into the statistical models used to analyze this domain.

No interaction is evaluable between the Ventilation Domain and this domain.

9.5. Nesting of interventions

Nesting is not applicable to this domain

9.6. Threshold probability for superiority and inferiority

The threshold odds ratio delta for superiority and inferiority in this domain are those specified as the default threshold from the PAtC.

9.7. Threshold odds ratio delta for equivalence

The threshold odds ratio delta for equivalence in this domain is that specified from the PAtC (Section 7.8.8).

9.8. Informative priors

This domain will launch with priors that are not informative for main effects. If new immunoglobulin agents are added to the domain, consideration will be given to the use of informative priors at the time of amendment of the DSA.

9.9. Post-trial Sub-groups

Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The a priori patient sub-groups of interest are:

- Proven concomitant bacterial co-infection, defined as having isolation or detection of a known pathogen that causes pneumonia from blood, pleural fluid, or lower respiratory tract specimen.
- Receiving invasive mechanical ventilation at baseline
- Patients with undetectable virus at baseline (convalescent plasma intervention)
- Patients with different levels of neutralizing antibodies at baseline (convalescent plasma intervention)
- Dose of neutralizing antibodies received (based on volume of transfusion and titer measurement)

- All remaining potentially evaluable treatment-by-treatment interactions with other domains

9.10. Domain-specific secondary and exploratory analyses

- All-cause mortality during the first 28 study days will be analyzed using a Kaplan-Meier estimate of survival and analyzed using Cox proportional hazards regression with adjustment for the stratification factors.

- Number of SAEs (excluding thrombotic events) from randomization until 72 hours after randomization, per day at risk; described by intervention.

- Number of thrombotic events from randomization up to the end of study day 90, per day at risk. These will be analyzed using Poisson regression.

- Analyses of the data from the sub-study (exploratory analyses) will be specified in a separate analysis plan.

10.ETHICAL CONSIDERATIONS

10.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, inferiority, or equivalence of different interventions with respect to the primary endpoint is possible, and if equivalence is demonstrated, determination of the optimal intervention may be based on secondary endpoints, such as all-cause mortality at 28 days.

The DSMB should take into account the public health, as well as clinical significance, of the analyses of this domain and are empowered to discuss results with relevant international and national public health authorities, with rapid dissemination of results to the larger community being the goal.

10.2. Potential domain-specific adverse events

10.2.1. Convalescent Plasma

All reportable SAEs listed in this section should be reported to REMAP-CAP in all patients in this domain, irrespective of intervention allocation. In addition, site staff are responsible for reporting all transfusion-related adverse events to their national or regional hemovigilance system (SHOT/SABRE in the UK) according to standard procedures. In Europe this is as required under the regulations of the EU Blood Directive (see section 10.1.1).

Adverse Reactions that are known to be related to transfusion are summarised in the table below together with information on whether they require reporting to the national or regional hemovigilance organisation as well as reporting as SARs:

Table 1: Serious Adverse Reactions and Events (see Appendix 2 for more detailed description)

Reactions	**Timing**	**Needs to be reported to SHOT/SABRE or other national or regional hemovigilance organisation** Call your hospital blood bank to let them know it needs to be reported – they will report to the hemovigilance system and inform you of any other tests that need to be performed	**Study Classification** Complete REMAP-CAP SAE form for ***all*** events
Fever >2°C rise or >39°C, needing hospital admission or medical intervention	**Within 24 hours of a transfusion and thought to be related**	**Yes**	**SAR**
	Within first 72 hours of study. Not related to transfusion	**No**	**SAE**
Severe allergic reaction or anaphylaxis (rash, angioedema, bronchospasm, hypotension)	**Within 24 hours of a transfusion and thought to be related**	**Yes**	**SAR**
	Within first 72 hours of study. Not related to transfusion	**No**	**SAE**
Hypotension, leading to shock (e.g. acidemia, impairment of vital organ function) without allergic or inflammatory symptoms. Urgent medical intervention required	**Within 24 hours of a transfusion and thought to be related**	**Yes**	**SAR**
	Within first 72 hours of study. Not related to transfusion	**No**	**SAE**
	Within 24 hours of a transfusion	**Yes**	**SAR**

Acute serious haemolytic reaction	**Within first 72 hours of study. Not related to transfusion**	**No**	**SAE**
Acute lung injury	**Within 24 hours of a transfusion**	**Yes**	**SAR**
	Within first 72 hours of study. Not related to transfusion	**No**	**SAE**
Circulatory overload	**Within 24 hours of a transfusion**	**Yes**	**SAR**
	Within first 72 hours of study. Not related to transfusion	**No**	**SAE**
Transfusion transmitted infection (TTI) (viral, bacterial or fungal)	**During entire study**	**Yes**	**SAR**
ADE of infection	**Within first 72 hours of study**	**Yes**	**SAR**
Clinically diagnosed arterial thromboembolism (e.g. CVA, MI)	**During first 90 days**	**No**	**SAE**

Information from hemovigilance systems (like SABRE/SHOT) will be used by the primary trials team in addition to the trials SAE data. A data-sharing agreement will be set up with SHOT to facilitate this.

Other SAEs should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see Core protocol Section 8.13).

10.3. Domain-specific consent issues

As noted in the background, and endorsed by the WHO, in the absence of evidence of effectiveness of specific treatments for COVID-19, the use of a no treatment control is both appropriate and ethical.

For patients who are not competent to consent, either prospective agreement or entry via waiver of-consent or some form of deferred consent can be applied, as required by an appropriate ethical review body.

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.

Clinicians are directed to not enrol an individual patient if the treating clinician believes that participation in this domain is not in the best interests of the patient.

11.GOVERNANCE ISSUES

11.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. This domain will receive any additional domain-specific funding. Initial funding is being provided by NHS Blood and Transplant to enable the domain to start. Further additional funding will be obtained during the life-time of the domain.

11.2. Funding of domain interventions and outcome measures

NHS Blood and Transplant will supply the convalescent plasma for the trial and arrange for distribution to participating sites via its routine distribution system.

11.3. Domain-specific declarations of interest

All investigators involved in REMAP-CAP maintain a registry of interests on the REMAP-CAP website. These are updated periodically and publicly accessible on the study website.

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13.APPENDIX 1

For sites that have agreed to participate in the intensive testing sub-study the testing regimen is:

Enrolment / Treatment

	Week 1							Week 2							Week 3							Week 4						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Blood (EDTA) 2ml	*			*																								
Blood (EDTA) 4ml	*	*	*	*		*			*			(*)			*													*
Blood (serum) 6ml	*	*	*	*		*			*			(*)			*													*
PAXgene 2.5ml	*								*																			
Nasopharyngeal ***or*** Oropharyngeal swab	*	*	*	*		*			*			(*)			*													*
Samples taken from admission up to hospital discharge. Samples must be taken prior to first and second units of plasma (Days 1 and 2). Follow-up samples at Day 3, Day 4, Day 6, Day 9, Day 15 and Day 28 are recommended. Samples can be taken +/- 12 hours of the defined time within the sampling protocol. Additional samples on Day 12 can be submitted.																												

14.APPENDIX 2

Type of SAE	Diagnostic criteria	Where should cases should be reported
Febrile Acute Transfusion Reaction **Report within 24 hours of a transfusion**	**Severe** A rise in temperature of 2°C or more, and/or rigors, chills, or fever 39°C or over, or other inflammatory symptoms/signs such as myalgia or nausea which precipitate stopping	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number

Febrile Acute Reaction **Report within first 72 hours of the trial**	the transfusion, prompt medical review AND/OR directly results in, or prolongs hospital stay	Must be reported on the REMAP-CAP trial SAE form
Allergic Acute Transfusion Reaction **(Report within 24 hours of a transfusion)**	**Severe** Bronchospasm, stridor, angioedema or circulatory problems which require urgent medical intervention AND/OR, directly result in or prolong hospital stay, or Anaphylaxis (severe, life-threatening, generalized or systemic hypersensitivity reaction with rapidly developing airway AND/OR breathing AND/OR circulation problems, usually associated with skin and mucosal changes)	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Allergic Acute Reaction **(Report within first 72 hours of the trial)**		Must be reported on the REMAP-CAP trial SAE form
Hypotensive Acute Transfusion Reaction **(Report within 24 hours of a transfusion)**	**Severe** Hypotension, as previously defined, leading to shock (e.g. acidemia, impairment of vital organ function) without allergic or inflammatory symptoms. Urgent medical intervention required	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Hypotensive Reaction **(Report within first 72 hours of the trial)**		Must be reported on the REMAP-CAP trial SAE form
Acute Hemolytic Transfusion Reaction (HTR) **(Report within 24 hours of a transfusion)**	Acute HTRs are defined as fever and other symptoms/signs of hemolysis within 24 hours of transfusion; confirmed by fall of Hb AND one or more of the following: • Rise in LDH • Rise in bilirubin • Positive DAT • Positive crossmatch	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number

<table>
<tr><td>Acute hemolytic reaction
(Report within first 72 hours of the trial)</td><td>Defined as fever and other symptoms/signs of hemolysis confirmed by fall of Hb AND one or more of the following:
• Rise in LDH
• Rise in bilirubin
• Positive DAT
• Positive crossmatch</td><td>Must be reported on the REMAP-CAP trial SAE form</td></tr>
<tr><td>Transfusion-Associated Circulatory Overload (TACO)
(Report within 12 hours of a transfusion)</td><td rowspan="2">* Required criteria (A and/or B)
A. Acute or worsening respiratory compromise and/or
B. Evidence of acute or worsening pulmonary edema
based on:
• clinical physical examination, and/or
• radiographic chest imaging and/or other noninvasive assessment of cardiac function

Additional criteria
C. Evidence for cardiovascular system changes not
explained by the patient’s underlying medical
condition, including development of tachycardia,
hypertension, jugular venous distension, enlarged cardiac silhouette and/or peripheral edema
D. Evidence of fluid overload including any of the following:</td><td>Patients classified with TACO should have:
at least one required criterion* with onset during or up to 24 hours after transfusion
Must be reported on the REMAP-CAP trial SAE form
AND
Must be reported to the hospital blood bank with details of the patient’s trial number</td></tr>
<tr><td>Circulatory overload</td><td>Must be reported on the REMAP-CAP trial SAE form</td></tr>
</table>

	a positive fluid balance; clinical improvement following diuresis **E.** Supportive result of a relevant biomarker, e.g. an increase of B-type natriuretic peptide levels (BNP) or N terminal-pro brain natriuretic peptide) NT-pro BNP to greater than 1.5 times baseline value **A total of 3 or more criteria** i.e. *A and/or B, and total of at least 3 (A to E) Acute or worsening respiratory compromise	
Transfusion-associated dyspnea	Respiratory distress within 24 hours of transfusion that does not meet the criteria of TRALI, TACO or allergic reaction. Respiratory distress in such cases should not be explained by the patient's underlying condition	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Transfusion-Related Acute Lung Injury (TRALI)	Acute dyspnea with hypoxia and bilateral pulmonary infiltrates during or within **six** hours of transfusion, not due to circulatory overload or other likely causes	Suspected TRALI should be reported – further investigations are required to confirm cases Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number

Acute lung injury	**Timing** Within 1 week of a known clinical insult or new or worsening respiratory symptoms **Chest imaging** Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules **Origin of edema** Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present **Oxygenation** Mild 200 mm Hg < PaO2/FIO2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H2Oc Moderate 100 mm Hg < PaO2/FIO2 ≤ 200 mm Hg with PEEP ≥ 5 cm H2O Severe PaO2/FIO2 ≤ 100 mm Hg with PEEP ≥ 5 cm H2O	Must be reported on the REMAP-CAP trial SAE form
Transfusion-Transmitted Infections (TTI)	Include as a TTI if, following investigation the recipient had evidence of infection post-transfusion, and there was no evidence of infection prior to transfusion, and no evidence of an alternative source of infection	Suspected TTI should be reported – requires further investigations to confirm the diagnosis Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number

Uncommon and new Complications of Transfusion not fitting into any of the other categories	Pathological reaction or adverse effect in temporal association with transfusion which cannot be attributed to already defined side effects and with no risk factor other than transfusion and do not fit under any of the other reportable categories. Including cases of antibody dependent enhancement of infection (ADE)	Suspected ADE should be reported Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
These reactions will be followed up by the national hemovigilance services. (UK hemovigilance system) has agreed to collect detailed information on these patients and we will share data based on the trial number of the participant		

Domain-Specific Appendix:

COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

COVID-19 Immunoglobulin Therapy Domain-Specific Appendix Version 1.0 dated 19 April 2020

TABLE OF CONTENTS

1. ABBREVIATIONS

ADE	Antibody-dependent enhancement
CCP	Clinical Characterization Protocol
CRP	C-reactive protein
CVA	Cerebrovascular accident
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
DVT	Deep vein thrombosis
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
MERS-CoV	Middle East respiratory syndrome coronavirus
NHS	National Health Service of the United Kingdom
NHSBT	National Health Service Blood and Transplant
PAtC	Pandemic Appendix to the Core Protocol
PE	Pulmonary Embolism
PISOP	Pandemic Infection Suspected or Proven
PT	Prothrombin time
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS	Serious Acute Respiratory Syndrome
TACO	Transfusion-Associated Circulatory Overload
TRALI	Transfusion-related acute lung injury
TTI	Transfusion-Associated Circulatory Overload
WHO	World Health Organisation

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) and 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 Regions-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject of a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change overtime in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the Core Protocol, DSAs, RSAs, and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org).

3. COVID-19 IMMUNOGLOBULIN DOMAIN-SPECIFIC APPENDIX VERSION

The version of the COVID-19 Immunoglobulin Therapy Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the COVID-19 Immunoglobulin Therapy Domain-Specific Working Group (DSWG) on 19th April 2020

4. COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN GOVERNANCE

4.1. Domain members

Chair:

Dr Lise Estcourt*

Co-chair:

Dr Manu Shankar-Hari*

Members:

A/Prof Scott Berry
A/Prof Mark Coyne
Prof Anthony Gordon
Dr Heli Harvala-Simmonds
Dr Sheila MacLennan
Dr Colin McArthur
A/Prof Zoe McQuilten
*Prof David Menon
Mr Paul Mouncey
Prof Alistair Nichol
Dr Nicole Pridee
*Prof David Roberts
Prof Kathy Rowan
Ms Helen Thomas
Prof Tim Walsh
Prof Steve Webb
Prof Erica Wood

*Members who are co-leading the COVID-19 Immunoglobulin Therapy Domain

4.2. Contact Details

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4.3. COVID-19 Immunoglobulin therapy DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The COVID-19 Immunoglobulin Therapy Domain-Specific Working Group (DSWG) have read the appendix and authorize it as the official COVID-19 Immunoglobulin Therapy Domain-Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair  Date 19th April 2020
Lise Estcourt

5. BACKGROUND AND RATIONALE

5.1. Domain definition

This is a domain within the REMAP-CAP to test the effectiveness of different strategies for immunoglobulin therapy for microbiological testing-confirmed COVID-19 infection in patients with concomitant severe pneumonia who are admitted to an Intensive Care Unit (ICU).

This is the version of the COVID-19 Immunoglobulin Therapy Domain that will apply in the United Kingdom and has the version number 1.0. It is anticipated that this domain may also enroll patients in other countries. However, because of differences in nature and supply of product, or timing of availability of product, it is anticipated that differences in the DSA will be necessary. Versions used in other countries, that are derived from this DSA, will be numbered sequentially with a new number after the decimal point (i.e. 1.1, 1.2 etc.) each applying to new countries. A major revision to the DSA will be allocated a new number before the decimal point, i.e. 2.0.

5.2. Domain-specific background

5.2.1. COVID-19 Infection

The first report of infection with COVID-19 occurred in Wuhan, China, in late 2019. Since that time, and as of the time of writing of this DSA, there have been hundreds of thousands of reported cases across the globe, with a range of severity, tens of thousands of deaths, and documented sustained human-to-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/newsroom/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)). Due to previous experience with other 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. Clinical guidance issued by the WHO indicates that unproven therapies should be administered preferably only within the setting of a clinical trial (https://www.who.int/docs/defaultsource/coronaviruse/clinical-management-of-novel-cov.pdf).

Globally, as of 12th April 2020 there are 1,854,464 confirmed cases, 114,331 deaths and 435,074 patients have recovered from SARS-CoV-2 illness (https://coronavirus.jhu.edu/map.html; Accessed on 12th April 2020). Estimates of the burden of critical illness among patients infected with COVID-19 vary and the corresponding case-fatality estimates are unreliable and differ by resource availability in terms of testing and critical care beds. Nevertheless, it is recognized that fatal critical illness, especially from severe respiratory failure from pneumonitis is high. In reports from China and from Italy (Grasselli et al., 2020, Huang et al., 2020, Remuzzi and Remuzzi, 2020), the proportion of confirmed COVID-19 cases requiring organ support in critical care units varies between 16% to 32% of all hospitalized SARS-CoV-2 illness. Although the overall case fatality rate is estimated as 5.7% (95% confidence intervals 5.5% – 5.9%) for COVID-19 disease (Baud et al., 2020), the 28-day mortality in critically ill patients with COVID-19 disease is approximately 60%, and even higher in those requiring mechanical ventilation (Yang et al., 2020).

The corresponding figures in the United Kingdom are 84,279 confirmed cases and 10,612 deaths. In the UK, the critical care case-mix of COVID19 has been reported by the Intensive Care National Audit and Research Centre (ICNARC) (https://www.icnarc.org; Accessed on 12th April 2020). This report contains all confirmed COVID-19 cases reported to ICNARC up to midnight on 10th April 2020 from critical care units participating in the Case Mix Programme (all NHS adult, general intensive care and combined intensive care/high dependency units in England, Wales and Northern Ireland, plus some specialist and non-NHS critical care units). ICNARC has been notified of 4,960 admissions. Amongst these 4,960 admissions, the first 24-hour data to inform the case-mix characteristics such as age, sex, illness severity has been submitted to ICNARC for 4,292 admissions of 3,883 patients. Of the 3,883 patients, 59.0% of patients are mechanically ventilated within 24 hours of admission, 871 patients have died, 818 patients have been discharged alive from critical care. Importantly, 2,194 patients were last reported as still being in critical care. The predictions for all health care systems globally, including the UK, are that the demands on critical care requirements are likely to increase and any intervention that reduces this by accelerating illness resolution, ideally by reducing both mortality and by reducing critical care length of stay are essential.

Interim recommendations from the WHO for clinical care of infected patients focus upon supportive care, including organ support as needed, prevention of complications, and no specific anti-COVID-19 therapies. The WHO have recommended that any specific therapy targeted to COVID-19 infection should be provided only as part of a research protocol (https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf).

5.2.2. Convalescent Plasma

Convalescent plasma treatment, containing high titers of polyclonal antibody (Ab), has been used to treat severe viral pneumonia. Many studies have been poorly controlled but such series have shown decreased mortality in Spanish Influenza A (H1N1) infections in 1915-1917 (Luke et al., 2006, McGuire and Redden, 1918), Influenza A (H1N1)pdm09 infections in 2009/2010 (Hung et al., 2011,

Ortiz et al., 2013) and more relevantly to this trial, SARS-CoV infections in 2003 (Cheng et al., 2005, Soo et al., 2004). A systematic review and meta-analysis performed identified 699 treated patients with SARS coronavirus infection and severe influenza and 568 untreated "controls" (Mair-Jenkins et al., 2015) found consistent reports of a reduction in mortality. Post hoc meta-analysis showed a statistically significant reduction in the pooled odds of mortality following treatment, compared with placebo or no therapy (odds ratio, 0.25; 95% CI:0.14–0.45) (Mair-Jenkins et al., 2015).

Several trials have shown that convalescent plasma had some efficacy in the treatment of SARS-CoV infected patients. Eight observational studies reported improved mortality after SARS-CoV – infected patients received various amounts of convalescent plasma (Mair-Jenkins et al., 2015). For example, a small retrospective case-comparison study (19 vs 21 patients) showed a case fatality rate reduction after convalescent plasma treatment of 23% (95% CI: 6%-42%, p≤0.05) (Soo et al., 2004). Each patient received 200 to 400 ml of convalescent plasma. In a case series of 80 patients treated with 160-640 ml of convalescent plasma 12.5% died compared with the overall SARS-related mortality rate in Hong-Kong of 17% (Cheng et al., 2005). In this limited series, convalescent plasma given before 14 days after the onset of symptoms was associated with better outcome, however such post-hoc analyses are fraught with confounding factors but do suggest early treatment may be more efficacious.

Convalescent plasma therapy had been given to at least 245 COVID-19 patients in China by the end of February 2020, and, according to a Chinese health official, 91 cases had shown improvement in clinical indicators and symptoms (http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm). There have been three published reports from China (Duan et al., 2020, Shen et al., 2020, Zhang et al., 2020), the largest study showed that 10 patients hospitalized with COVID-19 and given 200ml of convalescent plasma with a neutralizing antibody titer of >1:640 showed significant clinical and radiological improvement and commensurate reduction in C-reactive protein (CRP), liver function tests, viremia and oro-pharyngeal viral load and increases in lymphocyte count (Duan et al., 2020).

5.2.2.1. *Adverse effects of convalescent plasma*

Minor side effects have been reported with convalescent plasma, such as fever or chills (Luke et al., 2006), or allergic transfusion reactions (Beigel et al., 2019). More significantly two reports of possible transfusion-related acute lung injury (TRALI) following convalescent plasma have been documented in one patient with Ebola disease and one patient with MERS-CoV, although no anti-HLA or anti-HNA antibodies were identified in donor plasma (Chun et al., 2016, Mora-Rillo et al., 2015). However, none of the 84 patients in the Ebola randomized controlled trial developed any serious adverse events due to the transfusion (Van Griensven et al., 2016b).

5.2.2.2. *Antibody Dependent Enhancement*

Antibody-dependent enhancement (ADE) occurs when antibodies facilitate viral entry into host cells and enhance viral infection in these cells (Wan et al., 2019). Potential toxicity associated with convalescent plasma remains a concern, and this is very relevant to COVID-19 patients who exhibit a spectrum of lung pathology from acute lung injury to acute respiratory disease syndrome and death. In SARS-CoV-associated disease, antibodies may mediate pathology if they target a different serotype of the virus (Wan et al., 2019, Wang et al., 2014). Furthermore, a novel mechanism for ADE where a neutralizing antibody binding to the surface protein of a coronavirus-like viral receptor triggers viral cell entry has been recently proposed. This ADE pathway was shown not only to be antibody dose dependent but also likely mediated by presence of non-neutralizing antibodies (Ricke

and Malone, 2020). For these reasons, we plan to collect convalescent plasma at the earliest 28 days after recovery so that antibody response has matured in terms of titer and affinity.

There is currently no evidence of ADE occurring in the current epidemic, and a small trial of 10 patients in China with COVID-19 treated in a single infusion of 200ml of convalescent plasma showed neither pulmonary injury nor infection enhancement. The high levels of neutralizing antibodies (>1:640), timely transfusion (median time from onset of symptoms to hospital admission and CP transfusion was 6 days (IQR, 2.5–8.5 days) and 16.5 days (IQR 11.0–19.3 days), respectively, and appropriate plasma volume (200ml) were thought to contribute to the absence of side-effects (Duan et al., 2020).

5.2.2.3. *Collection of Convalescent Plasma*

NHS Blood and Transplant (NHSBT) has been preparing to collect convalescent plasma from recovered COVID-19 infected patients since this was requested by NHS England in mid-February. These patients are contacted by Public Health England to ask if they are willing to consider blood donation. We are collecting convalescent plasma at least 28 days after their recovery from the infection to maximize the quality and quantity of neutralizing antibodies present in their donations. In addition to the usual donor and donation screening, all donations will be tested for SARS-CoV-2 RNA. Neutralizing antibody levels will also be determined in each donation using TCDI50 and pseudovirus particle assays. Only RNA-negative donations containing high levels of neutralizing antibodies will be offered for clinical use (the cut-off level to be defined during the first two weeks of collections; 1:160 previously used for SARS-CoV-1 (Cheng et al., 2005) and MERS-CoV (Arabi et al., 2015)). We will only use male plasma or plasma from female donors who have been tested and are eligible to donate apheresis platelets (Epstein et al., 2020) to reduce the risk of TRALI. Treatment with convalescent plasma with low levels of antibody has been shown to be ineffective in Ebola (Van Griensven et al., 2016a, Van Griensven et al., 2016b).

5.2.2.4. *Administration of convalescent plasma*

Administration of convalescent plasma is more likely to be beneficial early in the course of the disease (up to 10 to 14 days after onset of symptoms) (Chen et al., 2020b).

5.2.2.5. *Need for a clinical trial*

Although there is evidence that convalescent plasma can have beneficial effects in patients with severe respiratory viral infections the majority of the evidence is of low quality. Two randomized trials, one of convalescent plasma and one of anti-influenza hyperimmune intravenous immunoglobulin showed no benefits of convalescent plasma (Beigel et al., 2019, Davey et al., 2019). We are therefore uncertain whether convalescent plasma will be effective for COVID-19 patients and a RCT is required to assess the benefits of convalescent plasma.

5.2.3. Intervention Strategy for this domain

It is intended that this domain of REMAP-CAP will evolve, taking into account evidence derived from other clinical trials, as well as availability of potentially effective immunoglobulin therapies. WHO guidance notes the flexibility associated with REMAP-CAP as a platform for the testing of multiple agents, including serial testing of additional interventions (https://apps.who.int/iris/bitstream/handle/10665/330680/WHO-HEO-RDBlueprint%28nCoV%29-2020.1-eng.pdf?ua=1).

At the commencement of this domain, a control group is included (i.e. some patients will not receive any immunoglobulin therapy that is intended to be active against COVID-19 infection). This is

appropriate for two reasons. Firstly, there is relatively limited trial or clinical experience with the administration of immunoglobulin therapies in patients who are critically ill and it is not reasonable to presume that such agents do not cause net harm. Secondly, designs that include only active interventions are not able to ascertain if any option is better or worse than no treatment. If, during the evolution of this domain, there is sufficient evidence of effectiveness of agents or clinical practice changes to include the routine use of such agents or both, the control intervention that specifies that no immunoglobulin therapy is administered will be abandoned. Although this domain will commence with a single immunoglobulin therapy, it is intended that additional agents can be added (allowing evaluation of several agents against a common control intervention) as well as allowing introduction of combinations of agents (to evaluate potential synergy). Any changes to the intervention structure of the domain will be specified using one or more amendments to this DSA with implementation occurring only after ethical approval has been obtained. The initial selection of immunoglobulin therapy to be evaluated is convalescent plasma. If at any stage evidence of harm or definitive evidence of absence of effectiveness in critically ill patients emerges for any intervention specified in this domain, the ITSC, as advised by the DSWG, may remove an intervention prior to declaration of a Platform Conclusion. If this occurs, presentation and publication of results that relate to that intervention will occur, so as to contribute additional weight of evidence available in the public domain.

6. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of Immunoglobulin Therapy for patients with severe CAP who have microbiological testing-confirmed COVID-19.

We hypothesize that the primary end-point specified from the PAtC will differ based on the immunoglobulin therapy intervention. The following interventions will be available:

- No immunoglobulin against COVID-19 (no placebo)
- Convalescent plasma

We hypothesize that the treatment effect of different immunoglobulin strategies is different depending on allocation status in the Corticosteroid Domain. This is a treatment-by-treatment interaction between the interventions in the COVID-19 Immunoglobulin Therapy Domain and the Corticosteroid Domain.

We hypothesize that the treatment effect of different immunoglobulin strategies is different depending on allocation status in the COVID-19 Antiviral Therapy Domain. This is a treatment-by-treatment interaction between the interventions in the COVID-19 Immunoglobulin Therapy Domain and the COVID-19 Antiviral Therapy Domain.

Each participating site has the option to opt-in to two or more interventions to be included in the randomization schedule depending on local clinical preference, usual practice, acceptable practice, and the availability of the intervention at that site. As long as the ‘no immunoglobulin therapy for COVID-19’ intervention is retained in the platform it is strongly preferred that this intervention is always included by participating sites and is mandatory so long as there is only a single active intervention within the domain.

7. TRIAL DESIGN

This domain will be conducted as part of a REMAP trial (see Core Protocol Section 7). Treatment allocation will be adaptive, as described in the Core Protocol Section 7.5.2 and from the PAtC.

7.1. Population

The REMAP enrolls patients with severe pneumonia admitted to ICU (see Core Protocol Section 7.3).

7.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria (see Core Protocol Section 7.4 and PAtC). Patients eligible for REMAP may have conditions that exclude them from the COVID-19 Immunoglobulin Therapy Domain.

7.2.1. Domain inclusion criteria

Patients are eligible for this domain if:

- COVID-19 infection is confirmed by microbiological testing

7.2.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- More than 48 hours has elapsed since ICU admission
- Patient has already received treatment with any non-trial prescribed antibody therapy (monoclonal antibody, hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this hospital admission
- More than 14 days have elapsed since hospital admission
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

7.2.3. Intervention exclusion criteria

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons.

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 who are not eligible for this domain 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/allergy to an agent specified as an intervention in this domain will exclude a patient from receiving that agent

- Known previous history of transfusion-related acute lung injury will exclude a patient from receiving convalescent plasma
- Known objection to receiving plasma products will exclude a patient from receiving any plasma components

7.3. Interventions

7.3.1. Immunoglobulin Therapy Interventions

Patients will be randomly assigned to receive one of the following open-label strategies. All interventions will be commenced immediately after allocation status is revealed.

- No immunoglobulin against COVID-19 (no placebo)
- Convalescent plasma

7.3.2. No immunoglobulin against COVID-19 (no placebo)

Patients assigned to this intervention will not receive any preparation of immunoglobulin intended to neutralize COVID-19 during the index hospitalization. Administration of such a preparation is considered a protocol deviation.

7.3.3. Convalescent Plasma

7.3.3.1. *Dosing of convalescent plasma*

Patients assigned to receive plasma will receive at least one and not more than two adult units of ABO compatible convalescent plasma (total volume 550ml ± 150ml) within 48 hours of randomization. Volume of convalescent plasma administered and the level of antibodies within each unit will be tested.

7.3.3.2. *Duration of administration of convalescent plasma*

Those receiving plasma will receive a unit of ABO compatible convalescent plasma on the first day of the study. If the patient has no serious adverse reactions to the transfusion the second unit of convalescent plasma will be given. There must be a minimum of 12 hours between transfusions to allow appropriate assessment of adverse reactions to the initial transfusion. Both transfusions should be given within 48 hours from randomization.

7.4. Concomitant care

Additional agents intended to be active against SARS-CoV-2 infection should not be administered, unless they have become standard of care during the trial. In patients who have received an allocation status in the COVID-19 Antiviral Domain, and have microbiological testing confirmed SARS-CoV-2 infection, continuation of antiviral agent will be as per the COVID-19 Antiviral Domain-Specific Appendix (Section 8.3). All treatment that is not specified by assignment within the platform will be determined by the treating clinician.

7.5. Endpoints

7.5.1. Primary endpoint

The primary endpoint for this domain is the primary outcome specified in an operational document from within the options specified in the PAtC.

7.5.2. Secondary endpoints

All secondary endpoints as specified from the PAtC 7.5.2.

The domain-specific secondary outcome measures (occurring during the index hospitalization, censored at 90 days after enrollment) will be:

- All-cause mortality at 28 days
- Serious treatment-related adverse events (see table 1 section 10.1 of this appendix)
- Serious Adverse Events (SAE) as defined in Core Protocol

Domain-specific exploratory outcomes

- Proportion of subjects who cleared SARS-CoV-2 infection (i.e. all samples, obtained for at least two time points after transfusion) tested negative for SARS-CoV-2 RNA, just in lower respiratory sample, in all respiratory tract samples or just in blood)
- Reduction in SARS-CoV-2 viral load (within the first 3 days; 4 days; 6 days; 9 days; 15 days and 28 days analyzed separately in blood and respiratory tract samples)
- Change in SARS-CoV-2 neutralizing antibody levels (within the first 3 days; 4 days; 6 days; 9 days; 15 days and 28 days)

8. TRIAL CONDUCT

8.1. Domain-specific data collection

8.1.1. Additional testing for all participants

A group and screen sample must be processed locally, so that ABO compatible convalescent plasma can be administered.

Samples to be taken on Study Day 1 prior to administration of convalescent plasma to assess the level of:

3) Antibodies and neutralizing antibodies detectable prior to treatment on Day 1 (serum 6ml)
4) Testing for virus detectable on a lower respiratory tract aspirate of the patient if they are intubated, or an oropharyngeal or nasopharyngeal swab if the patient is not intubated prior to treatment on Study Day 1

These samples must be sent to the central testing laboratory (see laboratory protocol).

8.1.2. Additional testing sub-study for convalescent plasma

There will be additional testing as specified in this protocol for a sub-group of sites.

Please see Appendix 1 for schedule of sampling. Sites will opt-in to the additional testing sub-study. We aim for at least 100 participants in each study intervention to be included in the sub-study (maximum 200 participants per study intervention). Full details are included in the Laboratory SOP.

COVID-19 is characterized by cytokine excess (Chen et al., 2020a). Administration of convalescent plasma will be associated with changes in cytokine profile, which may be the causal mechanism for treatment effects via immunomodulation (Shankar-Hari and Rubenfeld, 2019, Shankar-Hari et al., 2011). Antibody dependent potentiation is an adverse event with convalescent plasma, which requires monitoring (Liu et al., 2019).

8.1.2.1. *Proposed work*

The following biological work to assess adverse effects and to explain treatment response will be done at pre-defined time points at baseline and at predefined time points post convalescent plasma administration (Appendix 1).

- A multiplexable Th1 / Th2 (including IL-10) cytokine profile (Chen et al., 2020a).
- D-dimer and other laboratory markers of disease severity
- Whole blood transcriptomic alterations (Blanco-Melo et al., 2020)
- Flow cytometric analyses to define the immune status of participants
- Genotype by SNP array
- Neutralizing and other anti-viral antibody assays.
- Viral PCR in respiratory and blood samples (Wölfel et al., 2020)
- Sequencing of SARS-CoV-2 from respiratory and blood samples

8.1.3. 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. If sites that are participating in this domain are not participating in the additional sample collection sub-study (section 8.1.2) they are encouraged to also participate in the Clinical Characterization Protocol (CCP) for patients with COVID-19 that has been established by the International Severe Acute Respiratory and Emerging Infectious Consortium (https://isaric.tghn.org/CCP/). This protocol specifies the collection of biological samples from patients with COVID-19. Samples collected in patients who are enrolled in the CCP may be made available to REMAP-CAP investigators to evaluate aspects of host or pathogen biology associated with assignment in this domain. Ethical approval at such sites and agreement from patients to undertake the CCP will be obtained separately.

8.1.4. Clinical data collection on all participants

Additional domain-specific data will be collected on all participants:

- Routinely collected data on neutrophil count, lymphocyte count, prothrombin time (PT), fibrinogen, CRP (if done for clinical reasons) at baseline

- SARS-CoV-2 viral load at baseline (in blood and respiratory samples)
- SARS-CoV-2 neutralizing antibody levels at baseline
- Serious treatment-related serious adverse events within 24 hours of the treatment, similar serious adverse events reported in both arms unrelated to transfusion in the first 72 hours of the study
- Transfusion-transmitted infection occurring at any time during the study
- Serious clinically diagnosed arterial (e.g. myocardial infarction (MI), cerebrovascular accident (CVA), mesenteric arterial thrombosis) or venous thrombotic events (e.g. deep vein thrombosis (DVT), pulmonary embolism (PE), portal or mesenteric venous thrombosis, or cortical venous sinus thrombosis) up to day 90

8.1.5. Clinical Data collection on participants within the intensive sampling sub-set

- Routinely collected data on neutrophil count, lymphocyte count, PT, fibrinogen, CRP (if done for clinical reasons) on days 2, 3, 4, 6, 9, 15, 28
- SARS-CoV-2 viral load at day 2, 3, 4, 6, 9, 15 and 28 (in blood and respiratory samples)
- SARS-CoV-2 neutralizing antibody levels at day 2, 3, 4, 6, 9, 15 and 28

Blood and respiratory samples will only be collected during inpatient admission, results will be censored at hospital discharge. Blood samples will be taken by fresh venipuncture if there is no indwelling cannula.

8.2. Criteria for discontinuation

Refer to Core Protocol Section 8.7 for criteria for discontinuation of participation in the REMAP-CAP trial.

8.3. Blinding

8.3.1. Blinding

All interventions will be administered on an open-label basis.

8.3.2. Unblinding

Not relevant.

9. STATISTICAL CONSIDERATIONS

9.1. Domain-specific stopping rules

If a Platform Conclusion of equivalence in the primary endpoint is demonstrated the DSMB and the ITSC may consider continuation of randomization if clinically relevant differences in secondary endpoints have not been demonstrated and it is considered plausible that clinically relevant

differences in one or more secondary endpoints may be capable of being demonstrated. In all other respects the stopping rules for this domain are those outlined in the Core Protocol Sections 7.8.6 to 7.8.9.

9.2. Unit-of-analysis and strata

The default unit-of-analysis, for both analysis of treatment effect and the Response Adaptive Randomization, will be the SARS-CoV-2 infection confirmed stratum, as specified from the PAtC.

The shock strata will not contribute to unit-of-analysis for this domain, as this strata is not applied in the Pandemic Statistical Model.

The influenza strata will not contribute to unit-of-analysis for this domain.

9.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal or Randomization with Deferred Reveal if confirmation of microbiological diagnosis is not known at the time of initial assessment of eligibility (see section 7.8.3.6 in Core Protocol)

9.4. Interactions with interventions in other domains

An a priori interaction with the Antibiotic Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the Macrolide Duration Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Antiviral Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the COVID-19 Antiviral Domain is considered possible and will be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Immune Modulation Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Corticosteroid Domain is considered possible and will be incorporated into the statistical models used to analyze this domain.

No interaction is evaluable between the Ventilation Domain and this domain.

9.5. Nesting of interventions

Nesting is not applicable to this domain

9.6. Threshold probability for superiority and inferiority

The threshold odds ratio delta for superiority and inferiority in this domain are those specified as the default threshold from the PAtC.

9.7. Threshold odds ratio delta for equivalence

The threshold odds ratio delta for equivalence in this domain is that specified from the PAtC (Section 7.8.8).

9.8. Informative priors

This domain will launch with priors that are not informative for main effects. If new immunoglobulin agents are added to the domain, consideration will be given to the use of informative priors at the time of amendment of the DSA.

9.9. Post-trial Sub-groups

Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The a priori patient sub-groups of interest are:

- Proven concomitant bacterial co-infection, defined as having isolation or detection of a known pathogen that causes pneumonia from blood, pleural fluid, or lower respiratory tract specimen.
- Receiving invasive mechanical ventilation at baseline
- Patients with undetectable virus at baseline (convalescent plasma intervention)
- Patients with different levels of neutralizing antibodies at baseline (convalescent plasma intervention)
- Dose of neutralizing antibodies received (based on volume of transfusion and titer measurement)
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

9.10. Domain-specific secondary and exploratory analyses

- All-cause mortality during the first 28 study days will be analyzed using a Kaplan-Meier estimate of survival and analyzed using Cox proportional hazards regression with adjustment for the stratification factors.

- Number of SAEs (excluding thrombotic events) from randomization until 72 hours after randomization, per day at risk; described by intervention.

- Number of thrombotic events from randomization up to the end of study day 90, per day at risk. These will be analyzed using Poisson regression.

- Analyses of the data from the sub-study (exploratory analyses) will be specified in a separate analysis plan.

10.ETHICAL CONSIDERATIONS

10.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, inferiority, or equivalence of different interventions with respect to the primary endpoint is possible, and if equivalence is demonstrated, determination of the optimal intervention may be based on secondary endpoints, such as all-cause mortality at 28 days.

The DSMB should take into account the public health, as well as clinical significance, of the analyses of this domain and are empowered to discuss results with relevant international and national public health authorities, with rapid dissemination of results to the larger community being the goal.

10.2. Potential domain-specific adverse events

10.2.1. Convalescent Plasma

All reportable SAEs listed in this section should be reported to REMAP-CAP in all patients in this domain, irrespective of intervention allocation. In addition, site staff are responsible for reporting all transfusion-related adverse events to their national or regional hemovigilance system (SHOT/SABRE in the UK) according to standard procedures. In Europe this is as required under the regulations of the EU Blood Directive (see section 10.1.1).

Adverse Reactions that are known to be related to transfusion are summarised in the table below together with information on whether they require reporting to the national or regional hemovigilance organisation as well as reporting as SARs:

Table 1: Serious Adverse Reactions and Events (see Appendix 2 for more detailed description)

Reactions	**Timing**	**Needs to be reported to SHOT/SABRE or other national or regional hemovigilance organisation** Call your hospital blood bank to let them know it needs to be reported – they will report to the hemovigilance system and inform you of any other tests that need to be performed	**Study Classification** Complete REMAP-CAP SAE form for ***all*** events
Fever >2°C rise or >39°C, needing	**Within 24 hours of a transfusion and**	**Yes**	**SAR**

hospital admission or medical intervention	**thought to be related**		
	Within first 72 hours of study. Not related to transfusion	**No**	**SAE**
Severe allergic reaction or anaphylaxis (rash, angioedema, bronchospasm, hypotension)	**Within 24 hours of a transfusion and thought to be related**	**Yes**	**SAR**
	Within first 72 hours of study. Not related to transfusion	**No**	**SAE**
Hypotension, leading to shock (e.g. acidemia, impairment of vital organ function) without allergic or inflammatory symptoms. Urgent medical intervention required	**Within 24 hours of a transfusion and thought to be related**	**Yes**	**SAR**
	Within first 72 hours of study. Not related to transfusion	**No**	**SAE**
Acute serious haemolytic reaction	**Within 24 hours of a transfusion**	**Yes**	**SAR**
	Within first 72 hours of study. Not related to transfusion	**No**	**SAE**
Acute lung injury	**Within 24 hours of a transfusion**	**Yes**	**SAR**
	Within first 72 hours of study. Not related to transfusion	**No**	**SAE**
Circulatory overload	**Within 24 hours of a transfusion**	**Yes**	**SAR**
	Within first 72 hours of study. Not related to transfusion	**No**	**SAE**

Transfusion transmitted infection (TTI) (viral, bacterial or fungal)	**During entire study**	**Yes**	**SAR**
ADE of infection	**Within first 72 hours of study**	**Yes**	**SAR**
Clinically diagnosed venous thromboembolism (e.g. PE, DVT)	**During first 90 days**	**No**	**SAE**
Clinically diagnosed arterial thromboembolism (e.g. CVA, MI)	**During first 90 days**	**No**	**SAE**

Information from hemovigilance systems (like SABRE/SHOT) will be used by the primary trials team in addition to the trials SAE data. A data-sharing agreement will be set up with SHOT to facilitate this.

Other SAEs should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see Core protocol Section 8.13).

10.3. Domain-specific consent issues

As noted in the background, and endorsed by the WHO, in the absence of evidence of effectiveness of specific treatments for COVID-19, the use of a no treatment control is both appropriate and ethical.

For patients who are not competent to consent, either prospective agreement or entry via waiver of-consent or some form of deferred consent can be applied, as required by an appropriate ethical review body.

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.

Clinicians are directed to not enrol an individual patient if the treating clinician believes that participation in this domain is not in the best interests of the patient.

11.GOVERNANCE ISSUES

11.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. This domain will receive any additional domain-specific funding. Initial funding is being provided by NHS Blood

and Transplant to enable the domain to start. Further additional funding will be obtained during the life-time of the domain.

11.2. Funding of domain interventions and outcome measures

NHS Blood and Transplant will supply the convalescent plasma for the trial and arrange for distribution to participating sites via its routine distribution system.

11.3. Domain-specific declarations of interest

All investigators involved in REMAP-CAP maintain a registry of interests on the REMAP-CAP website. These are updated periodically and publicly accessible on the study website.

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13.APPENDIX 1

For sites that have agreed to participate in the intensive testing sub-study the testing regimen is:

Enrolment / Treatment

	Week 1							Week 2							Week 3							Week 4						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Blood (EDTA) 2ml	*			*																								
Blood (EDTA) 4ml	*	*	*	*		*			*			(*)			*													*
Blood (serum) 6ml	*	*	*	*		*			*			(*)			*													*
PAXgene 2.5ml	*								*																			
Nasopharyngeal ***or*** Oropharyngeal swab	*	*	*	*		*			*			(*)			*													*
Tracheal aspirate *(if ventilated)*	*	*	*	*		*			*			(*)			*													*
Samples taken from admission up to hospital discharge. Samples must be taken prior to first and second units of plasma (Days 1 and 2). Follow-up samples at Day 3, Day 4, Day 6, Day 9, Day 15 and Day 28 are recommended. Samples can be taken +/- 12 hours of the defined time within the sampling protocol. Additional samples on Day 12 can be submitted.																												

14.APPENDIX 2

Type of SAE	Diagnostic criteria	Where should cases should be reported
Febrile Acute Transfusion Reaction **Report within 24 hours of a transfusion**	**Severe** A rise in temperature of 2°C or more, and/or rigors, chills, or fever 39°C or over, or other inflammatory symptoms/signs such as myalgia or nausea which precipitate stopping the transfusion, prompt medical review AND/OR directly results in, or prolongs hospital stay	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Febrile Acute Reaction **Report within first 72 hours of the trial**		Must be reported on the REMAP-CAP trial SAE form
Allergic Acute Transfusion Reaction **(Report within 24 hours of a transfusion)**	**Severe** Bronchospasm, stridor, angioedema or circulatory problems which require urgent medical intervention AND/OR, directly result in or prolong hospital stay, or Anaphylaxis (severe, life-threatening, generalized or systemic hypersensitivity reaction with rapidly developing airway AND/OR breathing AND/OR circulation problems, usually associated with skin and mucosal changes)	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Allergic Acute Reaction **(Report within first 72 hours of the trial)**		Must be reported on the REMAP-CAP trial SAE form
Hypotensive Acute Transfusion Reaction **(Report within 24 hours of a transfusion)**	**Severe** Hypotension, as previously defined, leading to shock (e.g. acidemia, impairment of vital organ function) without allergic or inflammatory symptoms. Urgent medical intervention required	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Hypotensive Reaction **(Report within first 72 hours of the trial)**		Must be reported on the REMAP-CAP trial SAE form

Acute Hemolytic Transfusion Reaction (HTR) **(Report within 24 hours of a transfusion)**	Acute HTRs are defined as fever and other symptoms/signs of hemolysis within 24 hours of transfusion; confirmed by fall of Hb AND one or more of the following: • Rise in LDH • Rise in bilirubin • Positive DAT • Positive crossmatch	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Acute hemolytic reaction **(Report within first 72 hours of the trial)**	Defined as fever and other symptoms/signs of hemolysis confirmed by fall of Hb AND one or more of the following: • Rise in LDH • Rise in bilirubin • Positive DAT • Positive crossmatch	Must be reported on the REMAP-CAP trial SAE form
Transfusion-Associated Circulatory Overload (TACO) **(Report within 12 hours of a transfusion)**	*** Required criteria (A and/or B)** **A.** Acute or worsening respiratory compromise and/or **B.** Evidence of acute or worsening pulmonary edema based on: • clinical physical examination, and/or • radiographic chest imaging and/or other noninvasive assessment of cardiac function	Patients classified with TACO should have: **at least one required criterion*** with onset during or up to 24 hours after transfusion Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Circulatory overload	**Additional criteria** **C.** Evidence for cardiovascular system changes not explained by the patient's underlying medical	Must be reported on the REMAP-CAP trial SAE form

	condition, including development of tachycardia, hypertension, jugular venous distension, enlarged cardiac silhouette and/or peripheral edema **D.** Evidence of fluid overload including any of the following: a positive fluid balance; clinical improvement following diuresis **E.** Supportive result of a relevant biomarker, e.g. an increase of B-type natriuretic peptide levels (BNP) or N terminal-pro brain natriuretic peptide) NT-pro BNP to greater than 1.5 times baseline value **A total of 3 or more criteria** i.e. *A and/or B, and total of at least 3 (A to E) Acute or worsening respiratory compromise	
Transfusion-associated dyspnea	Respiratory distress within 24 hours of transfusion that does not meet the criteria of TRALI, TACO or allergic reaction. Respiratory distress in such cases should not be explained by the patient's underlying condition	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Transfusion-Related Acute Lung Injury (TRALI)	Acute dyspnea with hypoxia and bilateral pulmonary	Suspected TRALI should be reported – further investigations are required to confirm cases

	infiltrates during or within **six** hours of transfusion, not due to circulatory overload or other likely causes	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Acute lung injury	**Timing** Within 1 week of a known clinical insult or new or worsening respiratory symptoms **Chest imaging** Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules **Origin of edema** Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present **Oxygenation** Mild 200 mm Hg < PaO2/FIO2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H2Oc Moderate 100 mm Hg < PaO2/FIO2 ≤ 200 mm Hg with PEEP ≥ 5 cm H2O Severe PaO2/FIO2 ≤ 100 mm Hg with PEEP ≥ 5 cm H2O	Must be reported on the REMAP-CAP trial SAE form
Transfusion-Transmitted Infections (TTI)	Include as a TTI if, following investigation the recipient had evidence of infection post-transfusion, and there was no evidence of infection prior to transfusion, and no	Suspected TTI should be reported – requires further investigations to confirm the diagnosis

	evidence of an alternative source of infection	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Uncommon and new Complications of Transfusion not fitting into any of the other categories	Pathological reaction or adverse effect in temporal association with transfusion which cannot be attributed to already defined side effects and with no risk factor other than transfusion and do not fit under any of the other reportable categories. Including cases of antibody dependent enhancement of infection (ADE)	Suspected ADE should be reported Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
These reactions will be followed up by the national hemovigilance services. (UK hemovigilance system) has agreed to collect detailed information on these patients and we will share data based on the trial number of the participant		

Statistical Analysis Plan

for the Immunoglobulin Domain

for Patients with COVID-19 Pandemic Infection Suspected Or Proven (PISOP)

TABLE OF CONTENTS

1. COVID-19 IMMUNOGLOBULIN DOMAIN SAP VERSION

The version is in this document's header and on the cover page.

1.1. Version History

Version 1.1: Finalized on 23 Feb, 2021.

2. SAP AUTHORS

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3. INTRODUCTION

This statistical plan for the first analysis of the immunoglobulin domain in the pandemic stratum of the REMAP-CAP trial is an appendix to the Pandemic Appendix to Core (PAtC) Statistical Analysis Plan (SAP). This document synthesizes that information and describes the details of the statistical analysis for the unblinding of the immunoglobulin domain, within the pandemic stratum of REMAP-CAP. This plan details the statistical analyses in the original REMAP-CAP core SAP and the pandemic stratum SAP applied to the analysis of immunoglobulin domain. The plan here is completely prespecified for the imminent unblinding of the results for immunoglobulin domain within the pandemic infection suspected or proven (PISOP) (COVID-19) stratum.

Enrollment in the COVID-19 Immunoglobulin Domain started on 5th May, 2020. The domain was halted in the PISOP stratum following a statistical trigger for futility met in the severe COVID-19 stratum. The REMAP-CAP ITSC decided on 7th January 2021 to stop the severe state of the Immunoglobulin domain of REMAP-CAP within the PISOP stratum and report the results for these interventions in the domain. Enrollment to the severe state of the Immunoglobulin domain was halted on 11th January 2021. Enrollment to the moderate state of the Immunoglobulin domain was halted on 18th January 2021 following the press release of results from the RECOVERY trial of no evidence of benefit (https://www.recoverytrial.net/news/statement-from-the-recovery-trial-chief-investigators-15-january-2021-recovery-trial-closes-recruitment-to-convalescent-plasma-treatment-for-patients-hospitalised-with-covid-19).

REMAP-CAP explores multiple treatment domains by randomizing patients within multiple domains. The adaptive platform trial was designed to have modular results for individual interventions or full domains announced upon reaching a platform conclusion. For this domain, there have been two interim analyses conducted and domain closure was based on both *internal and external results*; hence the results for the convalescent plasma intervention will be unblinded and made public. This document prespecifies the analysis plan for this unblinding.

The authors of this document are blinded to the data and results in the REMAP-CAP trial other than those already publicly disclosed or simultaneously unblinded for subsequent reporting.

4. DESIGN CONSIDERATIONS

REMAP-CAP is designed with Bayesian analyses as the primary analysis method for the trial. There is one overarching Bayesian model, prespecified in the SAP, driving all adaptations, platform conclusions, and result summaries. That primary statistical analysis model will be used to report the results for the immunoglobulin domain within the severe and moderate states of the PISOP stratum. At the time of concluding enrollment the Convalescent Plasma domain, there were less than 100 participants enrolled in the moderate state. Given this limited sample size, the primary focus of this SAP is reporting results for the severe state of the Immunoglobulin domain. Descriptive and model summaries may be presented for the moderate state to facilitate future systematic reviews by others.

The decision to use a Bayesian analysis in REMAP-CAP was driven in part by the uncertainty of the extent of the pandemic. The sample size could be small, or large, and there may be unexpected external events, such as other trial results, that alter the design of REMAP-CAP. Given the expected evolution of the design, and uncertain sample size, the Bayesian approach is more appropriate.

REMAP-CAP defines several statistical triggers within the trial, that at any analysis of the trial would result in public disclosure and a declaration of a platform conclusion. The following internal statistical triggers were defined for the severe state of the immunoglobulin domain:

1. **Domain Superiority**. If convalescent plasma is deemed to have at least a 99% posterior probability of being superior to no immunoglobulin against SARS-CoV-2, then superiority would be declared for convalescent plasma.
2. **Intervention Futility**. If convalescent plasma is deemed to have a less than 5% probability of at least a 20% odds ratio improvement compared to the control, then futility would be declared.

The 99% threshold for efficacy was selected to have good properties for potential outbreak sample sizes. For example, the type I error rate of any conclusion of efficacy for a single intervention 'A' vs. control is less than 2.5% for approximately less than 1000 patients on intervention 'A' with multiple interim analyses (see main and pandemic SAP).

5. UNBLINDING

REMAP-CAP has multiple domains to which patients can be randomized and multiple interventions within domains. At the unblinding of the COVID-19 Immunoglobulin domain, other domains to which the patients have been randomized will remain blinded for this analysis. In this analysis plan there are analyses conducted by the Statistical Analysis Committee (SAC) using additional randomizations and also unblinding of other randomizations. The SAC is unblinded to all interventions/domains in their function for REMAP-CAP. This SAP also includes analyses that are conducted with knowledge of only unblinded interventions and domains. At this time, that includes the COVID-19 antiviral domain, the COVID-19 corticosteroid domain, and the IL-6ra and control interventions in the Immune Modulation Therapy domain. Finally, the SAP includes other analyses that are conducted with only knowledge of the convalescent plasma/control allocation status for patients. These may be conducted by investigators who are blinded to other information about other interventions and domains. All of these analyses are identified below.

6. INTERVENTIONS

There are three assignments within the convalescent plasma domain. These are

P1. No immunoglobulin against COVID-19 (control or standard of care (SOC) arm)

P2. Convalescent plasma at randomization

P3. Delayed Convalescent plasma. This assignment has the following definitions: (a) Delayed convalescent plasma infusion for subjects who fail to demonstrate clinical improvement within 96 hours of admission; (b) Delayed convalescent plasma infusion as a rescue therapy for moderately ill hospitalized patients who require transfer initiation of ICU level organ support as defined by the Core Protocol care after 48 hours of hospitalization; (c) Severely ill patients requiring ICU-level organ support at the time of admission will be randomized to receive: Delayed convalescent plasma infusion for subjects who fail to demonstrate clinical improvement within 96 hours of admission.)

For the primary analysis completed by the SAC, all treatment arms will be modeled, but only analysis results for convalescent plasma relative to no immunoglobulin against SARS-CoV-2 (control) will be reported. For all secondary analyses completed by blinded investigators, convalescent plasma will be compared to the no immunoglobulin against SARS-CoV-2 intervention (control; P1). Delayed convalescent plasma (P3) will be treated as a separate arm in all analyses.

Some models in this SAP will estimate and report the interaction effects of convalescent plasma with the unblinded domains at the time of finalizing SAP. This includes the interactions between convalescent plasma and fixed-dose corticosteroids; convalescent plasma and pooled antiviral domain interventions (hydroxychloroquine (HCQ), lopinavir/ritonavir, and lopinavir/ritonavir + HCQ).

7. DISEASE STATES

There are two disease states in the PAtC, which are **moderate** and **severe**. The immunoglobulin domain has randomized patients in moderate and severe state(s). The majority of patients are in the severe state, with less than 10% of the randomizations occurring in the moderate state. The main focus of the reporting of the Immunoglobulin domain is the severe state, however summaries/results for the moderate state may be reported where appropriate.

8. ANALYSIS POPULATIONS

1. REMAP-CAP COVID-19 severe and moderate state intent-to-treat (ITT): This population consists of all PISOP patients randomized within at least one domain. This population includes patients in the severe and/or moderate states. This is the analysis population for the analyses performed by the unblinded SAC.
2. Unblinded ITT: This population consists of all PISOP patients in the severe state randomized within the immunoglobulin domain or any of the previously reported interventions and domains within the PISOP stratum (Corticosteroid domain, Antiviral domain, and IL-6ra/control interventions within the Immune Modulation Therapy domain). This is the default population for secondary analyses.
3. Convalescent plasma specific severe state ITT: This population consists of only patients in the severe state randomized to convalescent plasma or control in the Immunoglobulin domain within the PISOP stratum.
4. Convalescent plasma specific per protocol: This consists of the patients in the Convalescent plasma specific severe state ITT population who have been treated as per protocol. In this domain that is defined as '*patients assigned to receive plasma will receive at least one and not more than two adult units of ABO compatible convalescent plasma (total volume 550ml ¬± 150ml) within 48 hours of randomization*' for the convalescent plasma intervention. In this domain, that is defined as '*patients assigned to receive no plasma will not receive convalescent plasma at any time after randomization*' for the control intervention.
5. Convalescent plasma specific moderate state ITT: This population consists of all patients within the PISOP stratum in the moderate state randomized to convalescent plasma or control in the Immunoglobulin domain within the PISOP stratum.

9. ENDPOINTS

The following endpoints will be analyzed, graphically displayed, and summarized through descriptive statistics.

1. **Organ-Support Free-Days** (OSFD)
    a. An ordinal endpoint with mortality as the worst outcome. The primary endpoint for the REMAP-CAP PISOP stratum. The organs considered are cardiovascular (vasopressor/inotrope support) and respiratory (ventilation support). See Appendix A for a detailed description.

2. **In-Hospital Mortality**
    a. A dichotomous endpoint of in-hospital death where the death component corresponds to a –1 on the OSFD endpoint.
3. **Mortality**
    a. This is a time-to-event endpoint through 90-days.
    b. Any patient currently in the hospital or transferred on organ support to an alternative care facility will be censored at their last known status alive.
    c. Any patient successfully discharged from hospital, alive, without organ support, will be imputed as a 90-day “no mortality” event if 90-day mortality data is not yet recorded.
4. **Progression to intubation and mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or death**
    a. A dichotomous endpoint of whether a patient progresses to intubation and mechanical ventilation, ECMO or death in hospital.
    b. This endpoint will only be analyzed for subjects that are not on intubation, mechanical ventilation, or ECMO at baseline.
5. **Cardiovascular Support-Free Days**
    a. An ordinal outcome of number of days free of cardiovascular support. This is the exact calculation of OSFD, with Vasopressor/Inotropes as the only organ support category. In-hospital death is considered a –1.
6. **Respiratory Support-Free Days**
    a. An ordinal outcome of number of days free of respiratory support. This is the exact calculation of OSFD, with respiratory support as the only organ support category. In-hospital death is considered a –1.
    b. Qualifying types of respiratory support include high-flow nasal cannula (HFNC), non-invasive respiratory support (NIV) and invasive mechanical ventilation (IMV).
7. **Length of ICU stay**
    a. A time-to-event endpoint of leaving the ICU alive. If a patient is known to leave the ICU and return to the ICU within 14-days that intervening time will be ignored.
    b. This variable will be truncated at 90-days: all deaths in ICU will be considered 90-days with no liberation of ICU.
    c. Patients still in the ICU at data snapshot will be considered censored.
8. **Length of hospital stay**
    a. A time-to-event endpoint of leaving the hospital alive. If a patient is known to leave and return to the hospital within 14-days that intervening time will be ignored.

b. This variable will be truncated at 90-days and all deaths in-hospital will be considered 90-days with no events.

c. Patients still in the hospital at data snapshot will be considered censored.

9. **At least one serious adverse event (SAE)**

a. A dichotomous endpoint of SAE.

10. **The World Health Organization (WHO) 8-point ordinal scale measured at day 14.**

a. A modified WHO ordinal scale will be used:

0 + 1 + 2 = No longer hospitalized
3 = Hospitalized, no oxygen therapy
4 = Oxygen by mask or nasal prongs
5 = Non-invasive ventilation or high-flow oxygen
6 = Intubation and mechanical ventilation
7 = Ventilation + additional organ support: vasopressors, renal replacement therapy (RRT), ECMO
8 = Death

11. **Domain Specific endpoints**

1. All-cause mortality at 28 days

a. This is a time-to-event endpoint through 28-days.

b. Any patient currently in the hospital or transferred on organ support to an alternative care facility will be censored at their last known status alive.

c. Any patient successfully discharged from hospital, alive, without organ support, will be imputed as a 28-day "no mortality" event if 28-day mortality data is not yet recorded.

2. Serious treatment-related adverse events

a. A dichotomous outcome endpoint of any treatment-related adverse event

b. This endpoint will be summarized descriptively. Treatment-related adverse events are defined according to each participating site's national or regional hemovigilance system definitions (such as SHOT/SABRE in the UK) summarized in Table-1 in section 10.1 of the Immunoglobulin COVID-19 DSA.

3. Venous thromboembolic events at 90 days

a. A dichotomous endpoint of any venous thromboembolic event through 90 days.

4. All thrombotic events at 90 days

a. A dichotomous outcome endpoint of any thrombotic event

Thrombotic events will consist of:

i. Confirmed deep vein thrombosis
ii. Confirmed pulmonary embolus
iii. Confirmed ischemic cerebrovascular event

iv. Confirmed acute myocardial infarction

v. Other confirmed thrombotic events

10. GRAPHICAL DATA SUMMARIES

1. All ordinal endpoints will be plotted using stacked cumulative bar plots and cumulative probability plots.
2. All time-to-event endpoints will be plotted using Kaplan-Meier plots. Positive clinical event outcomes will be plotted as the cumulative rate of event, and negative events will be plotted as the cumulative rate of event-free.

11. DESCRIPTIVE STATISTICS

1. Ordinal endpoints will be summarized by the cumulative frequency of each outcome. The 25th, 50th, and 75th percentiles will be summarized.
2. Dichotomous endpoints will be summarized by the number and proportion in each category.
3. Time-to-event outcomes will summarize the 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles from the Kaplan-Meier estimates, as available.
4. All thromboembolic and thrombotic endpoints will be summarized by the number and proportion in each category

12. BASELINE CHARACTERISTICS

The following demographics will be summarized across arms. More may be added as baseline summaries.
Age, sex, BMI, ethnicity, APACHE II score (measured from hospital admission to randomization), SARS CoV-2 PCR status reassessed at randomization, SARS CoV-2 antibody status reassessed at randomization, preexisting conditions, baseline use of high-frequency nasal oxygenation, non-invasive ventilation, invasive mechanical ventilation, ECMO, vasopressors/inotropes, renal replacement therapy, dose of convalescent plasma received (estimated as a function of donor plasma antibody titer and volume of plasma infused) and miscellaneous physiological values and inflammatory biomarker laboratory values.

13. COMPLIANCE

The compliance to convalescent plasma use will be summarized descriptively as the fraction of use, for each randomized arm.

14. ANALYTIC APPROACH

Each inferential analysis will be done using a Bayesian model. Some default frequentist methods are used for exploration and description. A summary of the analysis methods is provided below.

14.1. Primary Analysis of Primary Endpoint

The **primary analysis model** is a Bayesian cumulative logistic model for the ordinal primary endpoint. The model is described below.

The primary endpoint for the PISOP strata has 24 possible, ordered outcomes. Let the outcome for a patient by labeled as Y_i, with possible values, –1 (death), 0, 1, …, 21, 22. The outcome of 22 for the severe state (never received organ support) is not possible. Hence there are 23 possible outcomes for the severe state. A cumulative logistic model is specified. The model is structured so that an odds-ratio >1 implies patient benefit. The full details of the model including both severe and moderate states are in the Current State of The Statistical Model, Version 3.0. The full details of the model including the severe state only are in the Current State of The Statistical Model, Version 2.3. The model has factors that are estimated within each state for:

- Each level of the ordinal endpoint
- Each Global site, nested within country
- Age; ≤39, 40-49, 50-59, 60-69, 70-79, 80+
- Sex
- Time; 2-week buckets of time working backwards from the last enrolled patient, with the most recent bucket being 4 weeks.
- For each domain an effect for being randomized to the domain
- For each domain an effect for being ineligible for the domain
- An effect for each intervention within each domain
- Pre-specified interactions in the model between domains, as stated within this SAP. Region-specific DSAs differed in whether an interaction between CP and antiviral as well as CP and corticosteroid would be included in the primary efficacy analysis, but these interactions are no longer planned.

The primary/secondary analyses for convalescent plasma use the following rules:

- The high-dose 7-day hydrocortisone arm will be combined with the 7-day hydrocortisone arm (fixed-duration). They were originally nested, which allows their pooling, and there were very few patients randomized to the high-dose 7-day hydrocortisone arm.
- All interactions between the shock-based steroid arm and other domains will be removed from the model (assumed to be zero).
- All sites within a country that have <5 patients randomized will have their results combined into a single site within that country.
- If there is an outcome in the ordinal scale that did not occur in the data, then that outcome will be combined to a single outcome with a neighboring outcome (the worse outcome). This is done for model stability. For example, if the outcome 11 never occurred a combined outcome of 10 & 11 will be modeled for the analysis.

In addition to the rules above, analyses run by the ITSC analysis committee will use the following conventions:

- The two IL-6 receptor agonists, Tocilizumab and Sarilumab, will be combined into a single pooled IL-6ra intervention and compared to control. This convention is used because the

investigator analysis team is unblinded to the efficacy of IL-6ra interventions compared to control but remains blinded to the comparative effectiveness of Tocilizumab compared to Sarilumab.

In addition to the rules above, sensitivity analyses run by the ITSC analysis committee that include additional interactions between convalescent plasma and the unblinded domains (antivirals/steroids/IL-6ra interventions) use the following conventions:

- The two IL-6 receptor agonists, Tocilizumab and Sarilumab, will be combined into a single pooled IL-6ra arm for intervention and interaction effects.
- All antivirals in the COVID-19 Antiviral Domain will be combined into a single pooled antiviral arm.
- A standard normal prior (N(0,1)) will be used on each interaction term for interactions involving convalescent plasma.

The analysis models will be referenced with certain model assumptions for sensitivity analyses. For example, the "time effects" in the model could be assumed to be 0.

14.1.1. Proportional odds assumption

The primary analysis model is based on an assumption of a proportional effect of treatment across the scale of the ordinal outcome. In order to assess the robustness of the results to this assumption, a dichotomous model is fit to every level of the ordinal outcome across the scale and the odds-ratio for each dichotomous break is presented. If the cumulative probabilities are less than 5% or greater than 95% for specific dichotomizations, these models may be ignored at the discretion of the statistician performing the analyses. No statistical test of proportional odds is conducted.

14.2. Analytic Approach for Secondary Dichotomous Endpoints

A Bayesian logistic regression model will be used for each dichotomous outcome. The model will always specify the "event" as the negative outcome, so that an odds-ratio >1 implies benefit to patients within each model. The model is the standard logistic link function model:

$$\log\left(\frac{\mathrm{rr}}{1-\mathrm{rr}}\right) = \mathrm{a} - [\mathrm{factors}]$$

References will be made to the factors in the model and their prior distribution. Many of these factors will be the same as the primary analysis model, with the same priors, as the parameters have similar interpretation. For example, all in-hospital mortality models should use the Beta prior distribution implied by the Dirichlet prior in the OSFD model. If not otherwise specified, the prior distribution for the main effect is $\mathrm{a} \sim \mathrm{N}(0, 1.82^2)$ (similar to a uniform prior on the probability scale).

14.3. Analytic Approach for Secondary Time-To-Event Endpoints

All inferential time-to-event analyses will be done using a Bayesian piecewise exponential model. The Bayesian time-to-event model is intended to mirror a Cox proportional hazards model, with the underlying hazard rate modeled with a piecewise exponential model. The underlying hazard will be modeled with a hazard rate for each 10-day period in the model. The prior distribution for each hazard rate is a gamma distribution with 1 day of exposure and a mean equal to the total exposure divided by the total number of events. This prior will have very little weight but will provide numerical stability to the model. Each factor is incorporated as a proportional hazard ratio through an additive linear model of the log-hazard. The default prior for each factor is a the same as for the

log-odds in the ordinal model. If other non-specified variables are added to the model, then a normal distribution with mean 0 and standard deviation 10 will be utilized.

14.4. Markov Chain Monte Carlo (MCMC) Model Stability

The Bayesian models have many parameters and there may be risk of poor model stability, including convergence of the MCMC and the mixing behavior. These instabilities may be based on sparse data on the outcome or covariates. The statisticians running the model may make changes that do not affect the overall outcome but provide reliable model diagnostics and scientific rigor. Any alterations will be noted.

14.5. Model Outputs

The standard model outputs for each treatment effect will be the mean, standard deviation, median, and 95% credible intervals (all credible intervals will range from equal-tailed percentiles, so 95% credible intervals will range from the 2.5^{th} percentile to the 97.5^{th} percentile). For the ordinal models, the odds-ratio will be summarized. For the dichotomous endpoints, the odds-ratio will be summarized. For the time-to-event models, the hazard ratio will be summarized.
For each inferential model, a posterior probability that convalescent plasma is superior to control will be provided. This posterior probability has been identified as the primary analysis metric between arms. A posterior probability greater than 99% of superiority has been identified as statistically significant in REMAP-CAP.

14.6. Exploratory Analyses

Exploratory analyses after unblinding will not be considered inferential and no p-values will be presented. Any post-hoc exploratory analyses will use the following methods:

1. Ordinal endpoints will be compared using a cumulative proportional odds model with summaries of the odds-ratio, with 95% confidence intervals and Wilcoxon test for robustness against a lack of proportional odds.
2. Time-to-Event analyses will utilize a Cox proportional hazards model, summarizing the hazard ratios and 95% confidence intervals.
3. Continuous endpoints will compare means with 95% confidence intervals based on two-sample t-test procedures.
4. Dichotomous proportions will be compared using logistic regressions summarizing the odds-ratio and 95% confidence intervals. Differences between proportions will be summarized using observed differences and normal approximations for the 95% credible intervals.

15. SPECIFIC PROSPECTIVE ANALYSES

There are 37* specific prospective analyses, summarized in the table and described in detail below.
The a priori patient subgroups of interest in this domain are:

- Receiving invasive mechanical ventilation at baseline
- Patients with undetectable virus at baseline (convalescent plasma intervention)

  - This will be considered as a dichotomous variable (baseline PCR positive versus negative), reassessed using samples collected at baseline by the trial team, post randomization.
- Patients with different levels of neutralizing antibodies at baseline (convalescent plasma intervention)
  - This will be considered as a dichotomous variable (baseline antibody positive versus negative), reassessed using samples collected at baseline by the trial team, post randomization.
- Dose of neutralizing antibodies received (convalescent plasma intervention, estimated as a function of donor plasma antibody titer and volume of plasma infused
  - This will be considered as a categorical variable with three pre-defined cut-off values (no units received with a Euroimmun ≥ 8, one unit received with a Euroimmun ≥ 8, two units received with a Euroimmun ≥ 8)
- Time from hospitalization to randomization into the trial (convalescent plasma intervention)
  - This will be considered as a categorical variable with three pre-defined cut-off values (up to 72 hours; 3 to 7 days; more than 7 days)
- Patients with known immunodeficiency (convalescent plasma intervention)
  - This will be considered as a dichotomous variable (patient has immunodeficiency (defined as on immunosuppressive drugs or underlying disease causing immune deficiency) versus those who do not)
- All potentially evaluable treatment-by-treatment interactions = all domains that have reached a conclusion (COVID-19 Antiviral Domain, Corticosteroid Domain, Anticoagulation Domain, IL-6ra/control).

The a priori patient sensitivity analyses of interest in this domain are:

- Per-protocol analysis of patients receiving the complete dose of convalescent plasma

Summary Table for COVID-19 Immunoglobulin Therapy Domain

#	Status	Population	Endpoint	Other
15.1	Primary	REMAP-CAP COVID-19 severe and moderate state ITT	OSFD	Includes all interventions and prespecified interactions
15.2	Primary	REMAP-CAP COVID-19 severe and moderate state ITT	In-Hospital Mortality	Includes all interventions and prespecified interactions
15.3	Sensitivity	REMAP-CAP COVID-19 severe and moderate state ITT	Dichotomized OSFD	A logistic regression will be run for each dichotomization of OSFDs as a robustness check.
15.4	Secondary	Unblinded ITT	OSFD	Includes all unblinded interventions and prespecified interactions

15.5	Secondary	Unblinded ITT	In-Hospital Mortality	Includes all unblinded interventions and prespecified interactions
15.6	Sensitivity	Unblinded ITT	OSFD	Remove site and time effects
15.7	Sensitivity	Unblinded ITT	In-Hospital Mortality	Remove site and time effects
15.8	Sensitivity	Unblinded ITT	OSFD	Includes additional interactions between unblinded domains/interventions
15.9	Sensitivity	Unblinded ITT	In-Hospital Mortality	Includes additional interactions between unblinded domains/interventions
15.10	Secondary	Convalescent plasma specific severe state ITT	OSFD	
15.11	Secondary	Convalescent plasma specific severe state ITT	In-Hospital Mortality	
15.12	Sensitivity	Convalescent plasma specific per protocol	OSFD	
15.13	Sensitivity	Convalescent plasma specific per protocol	In-Hospital Mortality	
15.14	Secondary	Unblinded ITT	90-day mortality	
15.15	Secondary	Unblinded ITT	28-day mortality	
15.16	Secondary	Unblinded ITT	Progression to intubation, ECMO, death	In patients not intubated at baseline
15.17	Secondary	Unblinded ITT	Cardiovascular support-free days	
15.18	Secondary	Unblinded ITT	Respiratory support-free days	
15.19	Secondary	Unblinded ITT	Length of ICU Stay	
15.20	Secondary	Unblinded ITT	Length of Hospital Stay	
15.21	Secondary	Unblinded ITT	WHO Scale at 14 days	
15.22	Primary Safety Analysis	Convalescent plasma specific severe state ITT	Serious adverse events per patient	Time effects are removed from the model
15.23	Secondary Safety Analysis	Convalescent plasma specific severe state ITT	Venous thromboembolic events at 90-days	Time effects are removed from the model
15.24	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by SARS CoV-2 PCR status reassessed at randomization
15.25	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by SARS CoV-2 PCR status reassessed at randomization
15.26	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by SARS CoV-2 antibody status reassessed at randomization
15.27	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by SARS CoV-2 antibody status reassessed at randomization
15.28	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by Convalescent plasma Dose administered
15.29	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by Convalescent plasma Dose administered

15.30	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by receiving invasive mechanical ventilation at baseline
15.31	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by receiving invasive mechanical ventilation at baseline
15.32	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by time from hospitalization to randomization
15.33	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by time from hospitalization to randomization
15.34	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by presence or absence of immunodeficiency
15.35	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by presence or absence of immunodeficiency
15.36	Graphical Summaries	Convalescent plasma specific severe state ITT	All endpoints	Including combinations across unblinded domains.
15.37	Graphical Summaries	Convalescent plasma specific moderate state ITT	All endpoints	Including combinations across unblinded domains.

* There is one additional subgroup defined in the DSA based on co-infection with bacterial pathogens that will not be pursued, due to the small numbers.

15.1. The primary analysis for the convalescent plasma intervention of the COVID-19 Immunoglobulin Domain

- Population: REMAP-CAP COVID-19 severe and moderate state ITT
- Endpoint: Organ Support-Free Days
- Model: Primary analysis ordinal model
- Factors: All interventions and prespecified interactions, age, sex, site, time
- Analysis: Conducted by the unblinded SAC

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for superiority. A 95% probability of an OR < 1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported for each state:

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control (OR>1)	
Convalescent plasma is futile compared to control (OR<1.2)	

The following will be reported for each state:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.2. The primary in-hospital mortality analysis for the convalescent plasma intervention of the COVID-19 Immunoglobulin Domain

- Population: REMAP-CAP COVID-19 severe and moderate state ITT
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: All interventions and prespecified interactions, age, sex, site, time
- Analysis: Conducted by the unblinded SAC

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for superiority. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported for each state:

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported for each state:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.3. A sensitivity analysis of REMAP-CAP COVID-19 severe and moderate state ITT

- Population: REMAP-CAP COVID-19 severe and moderate state ITT
- Endpoint: Dichotomized Organ-Support Free-Days
- Model: A logistic regression will be run for each dichotomization of OSFDs as a robustness check
- Factors: All interventions and prespecified interactions, age, sex, site, time, convalescent plasma and control interventions
- Analysis: Conducted by the unblinded SAC

The following odds-ratios will be reported for convalescent plasma in the severestate:

OSFD Dichotomization	Mean	SD	Median	95% Credible Interval
-1 vs ≥0				
≤0 vs ≥1				
≤1 vs ≥2				
≤2 vs ≥3				
≤3 vs ≥4				
≤4 vs ≥5				
≤5 vs ≥6				
≤6 vs ≥7				
≤7 vs ≥8				
≤8 vs ≥9				
≤9 vs ≥10				
≤10 vs ≥11				
≤11 vs ≥12				
≤12 vs ≥13				
≤13 vs ≥14				
≤14 vs ≥15				
≤15 vs ≥16				

≤16 vs ≥17				
≤17 vs ≥18				
≤18 vs ≥19				
≤19 vs ≥20				
≤20 vs 21				

15.4. A secondary analysis of OSFD restricted to the Unblinded ITT

- Population: Unblinded Domain ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, pooled IL-6ra) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				

Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.5. A secondary analysis of in-hospital mortality restricted to the Unblinded ITT

- Population: Unblinded Domain ITT
- Endpoint: In-hospital mortality
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, pooled IL-6ra) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.6. A sensitivity analysis of OSFD restricted to the Unblinded ITT population with site and time factors removed

- Population: Unblinded Domain ITT
- Endpoint: Organ support free days
- Model: Primary analysis ordinal model
- Factors: Age, sex, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, pooled IL-6ra) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Convalescent plasma				

15.7. A sensitivity analysis of in-hospital mortality restricted to the Unblinded ITT population with site and time factors removed

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary analysis dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, pooled IL-6ra) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

c. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Convalescent plasma				

15.8. A sensitivity analysis of OSFD with interactions between unblinded interventions

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, pooled IL-6ra) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions, additional unblinded interactions in the severe state (interaction between convalescent plasma and pooled antiviral interventions, interaction between convalescent plasma and fixed dose corticosteroids)
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

b. Odds ratio effects and posterior probabilities for the interaction terms between convalescent plasma and the Antiviral Domain / Corticosteroid Domain / Pooled IL-6ra interventions will be reported relative to an additive effect. Odds ratios > 1 indicate a synergistic effect, odds ratios =1 indicate an additive effect, and odds ratios < 1 indicate a sub-additive effect.

c. The prior distributions will be set to N(0,1) for the following interactions: convalescent plasma with fixed dose corticosteroid, convalescent plasma with pooled antiviral interventions, convalescent plasma with pooled IL-6ra interventions.

The following posterior probabilities will be reported for the severe state

Quantity of Interest	Posterior Probability
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	
Convalescent plasma*Fixed dose corticosteroid OR>1	

Convalescent plasma*antivirals OR>1	
Convalescent plasma*Pooled IL-6ra OR>1	

The following will be reported for the severe state:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				
Convalescent plasma*Fixed dose corticosteroid interaction				
Convalescent plasma*antivirals interaction				
Convalescent plasma*Pooled IL-6ra interactions				

15.9. A sensitivity analysis of In-Hospital Mortality with interactions between unblinded interventions

- Population: REMAP-CAP COVID-19 severe and moderate state ITT
- Endpoint: In-hospital mortality
- Model: Primary analysis dichotomous model with weaker priors for the interaction effects
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, pooled IL-6ra) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions, additional unblinded interactions in the severe state (interaction between convalescent plasma and pooled antiviral interventions, interaction between convalescent plasma and fixed dose corticosteroids)
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

b. Odds ratio effects and posterior probabilities for the interaction terms between convalescent plasma and the Antiviral Domain / Corticosteroid Domain / Pooled IL-6ra interventions will be reported relative to an additive effect. Odds ratios > 1 indicate a synergistic effect, odds ratios =1 indicate an additive effect, and odds ratios < 1 indicate a sub-additive effect.

c. The prior distributions will be set to N(0,1) for the following interactions: convalescent plasma with fixed dose corticosteroid, convalescent plasma with pooled antiviral interventions, convalescent plasma with pooled IL-6ra interventions.

The following posterior probabilities will be reported for the severe state

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	
Convalescent plasma*Fixed dose corticosteroid OR>1	

Convalescent plasma*antivirals OR>1	
Convalescent plasma*Pooled IL-6ra OR>1	

The following will be reported for the severe state:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				
Convalescent plasma*Fixed dose corticosteroid interaction				
Convalescent plasma*antivirals interaction				
Convalescent plasma*Pooled IL-6ra interactions				

15.10. A secondary analysis of OSFD restricted to the Convalescent Plasma Specific Severe State ITT

- Population: Convalescent plasma specific severe state ITT
- Endpoint: In-hospital mortality
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.11. A secondary analysis of in-hospital mortality restricted to the Unblinded ITT

- Population: Unblinded Domain ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.12. A sensitivity analysis of OSFD restricted to per protocol patients

- Population: Convalescent plasma specific per protocol
- Endpoint: OSFD
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.13. A sensitivity analysis of in-hospital mortality in per protocol patients

- Population: Convalescent plasma specific per protocol
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.14. A secondary analysis of 90-day mortality

- Population: Unblinded ITT
- Endpoint: 90-day mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.15. A secondary analysis of 28-day mortality

- Population: Unblinded ITT
- Endpoint: 28-day mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.16. A secondary analysis of progression to intubation, ECMO or death

- Population: Unblinded ITT not on MV or ECMO at baseline.
- Endpoint: Progression to MV, ECMO, or death
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.17. A secondary analysis of REMAP-CAP COVID-19 severe state ITT cardiovascular support free days

- Population: Unblinded ITT
- Endpoint: Vasopressor/Inotropes free days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.18. A secondary analysis of REMAP-CAP COVID-19 severe state ITT respiratory support free days

- Population: Unblinded ITT
- Endpoint: Respiratory support free days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.19. A secondary analysis of length of ICU stay

- Population: Unblinded ITT
- Endpoint: Length of ICU stay
- Model: Primary TTE model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.20. A secondary analysis of length of hospital stay

- Population: Unblinded ITT
- Endpoint: Hospital length of stay
- Model: Primary TTE model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.21. A secondary analysis of WHO scale at 14-days

- Population: Unblinded ITT
- Endpoint: Modified WHO Ordinal scale at 14-days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.22. A primary safety analysis for convalescent plasma

- Population: Convalescent plasma specific ITT
- Endpoint: Serious Adverse Events (SAE)
- Model: Primary dichotomous model
- Factors: Age, sex, site, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	

The following will be reported:

Odds-Ratio Parameter	**Mean**	**SD**	**Median**	**95% Credible Interval**
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Convalescent plasma				

15.23. A secondary safety analysis of venous thromboembolic events

- Population: Convalescent plasma specific ITT
- Endpoint: Venous thromboembolic events at 90-days
- Model: Primary dichotomous model
- Factors: Age, sex, site, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Convalescent plasma is superior to control	

The following will be reported:

Odds-Ratio Parameter	**Mean**	**SD**	**Median**	**95% Credible Interval**
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Convalescent plasma				

15.24. A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by SARS CoV-2 PCR Status subgroup

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with PCR status (positive versus negative), immune modulation interventions (control, pooled IL-6ra), corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in PCR positive patients	
Convalescent plasma is superior compared to control in PCR negative patients	
Convalescent plasma is futile compared to control in PCR positive patients	
Convalescent plasma is futile compared to control in PCR negative patients	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				

Convalescent plasma in PCR positive				
Convalescent plasma in PCR negative				

15.25. A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by SARS CoV-2 PCR Status subgroup

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with PCR status (positive versus negative), immune modulation interventions (control, pooled IL-6ra), corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in PCR positive patients	
Convalescent plasma is superior compared to control in PCR negative patients	
Convalescent plasma is futile compared to control in PCR positive patients	
Convalescent plasma is futile compared to control in PCR negative patients	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				

…				
Time Bucket k-1				
Convalescent plasma in PCR positive				
Convalescent plasma in PCR negative				

15.26. A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by SARS CoV-2 antibody Status subgroup

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with antibody status (positive vs negative), corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in PCR positive patients	
Convalescent plasma is superior compared to control in PCR negative patients	
Convalescent plasma is futile compared to control in PCR positive patients	
Convalescent plasma is futile compared to control in PCR negative patients	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				

Convalescent plasma in PCR positive				
Convalescent plasma in PCR negative				

15.27. A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by SARS CoV-2 antibody Status subgroup

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with antibody status (positive vs negative), corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in PCR positive patients	
Convalescent plasma is superior compared to control in PCR negative patients	
Convalescent plasma is futile compared to control in PCR positive patients	
Convalescent plasma is futile compared to control in PCR negative patients	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				

…				
Time Bucket k-1				
Convalescent plasma in PCR positive				
Convalescent plasma in PCR negative				

15.28. A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by convalescent plasma Dose administered subgroup

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with dose subgroup (low vs mid vs high), corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in the 'low' dose subgroup	
Convalescent plasma is futile in the 'low' dose subgroup	
Convalescent plasma is superior to control in the 'mid' dose subgroup	
Convalescent plasma is futile compared to control in the 'mid' dose subgroup	
Convalescent plasma is superior to control in the 'high' dose subgroup	
Convalescent plasma is futile compared to control in the 'high' dose subgroup	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				

Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in the ‘low’ dose subgroup				
Convalescent plasma in the ‘mid’ dose subgroup				
Convalescent plasma in the ‘high’ dose subgroup				

15.29. A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by convalescent plasma Dose administered subgroup

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with dose subgroup (low vs mid vs high), corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in the 'low' dose subgroup	
Convalescent plasma is futile in the 'low' dose subgroup	
Convalescent plasma is superior to control in the 'mid' dose subgroup	
Convalescent plasma is futile compared to control in the 'mid' dose subgroup	
Convalescent plasma is superior to control in the 'high' dose subgroup	
Convalescent plasma is futile compared to control in the 'high' dose subgroup	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				

Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in the ‘low’ dose subgroup				
Convalescent plasma in the ‘mid’ dose subgroup				
Convalescent plasma in the ‘high’ dose subgroup				

15.30. A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by receipt of mechanical ventilation at baseline subgroup

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with baseline mechanical ventilation status, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in patients receiving mechanical ventilation at baseline	
Convalescent plasma is superior compared to control in patients not receiving mechanical ventilation at baseline	
Convalescent plasma is futile compared to control in patients receiving mechanical ventilation at baseline	
Convalescent plasma is futile compared to control in patients not receiving mechanical ventilation at baseline	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				

Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients receiving mechanical ventilation at baseline				
Convalescent plasma in patients not receiving mechanical ventilation at baseline				

15.31. A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by receipt of mechanical ventilation at baseline subgroup

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with baseline mechanical ventilation status, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in patients receiving mechanical ventilation at baseline	
Convalescent plasma is superior compared to control in patients not receiving mechanical ventilation at baseline	
Convalescent plasma is futile compared to control in patients receiving mechanical ventilation at baseline	
Convalescent plasma is futile compared to control in patients not receiving mechanical ventilation at baseline	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				

Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients receiving mechanical ventilation at baseline				
Convalescent plasma in patients not receiving mechanical ventilation at baseline				

15.32. A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by time from hospitalization to randomization

- Population: Unblinded ITT
- Endpoint: OSFD
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with time from hospitalization to randomization subgroups, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

b. Time from hospitalization to randomization into the trial (convalescent plasma intervention) will be considered as a categorical variable with three pre-defined cut-off values (up to 72 hours; 3 to 7 days; more than 7 days). The reference group is the subgroup randomized <72 hours from hospitalization.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in patients randomized within 72 hours after hospitalization	
Convalescent plasma is superior compared to control in patients randomized 3-7 days after hospitalization	
Convalescent plasma is superior compared to control in patients randomized >7 days from hospitalization	
Convalescent plasma is futile compared to control in patients randomized within 72 hours after hospitalization	

Convalescent plasma is futile compared to control in patients randomized 3-7 days after hospitalization	
Convalescent plasma is futile compared to control in patients randomized >7 days after hospitalization	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients randomized <72 hours after hospitalization				
Convalescent plasma in patients randomized 3-7 days after hospitalization				
Convalescent plasma in patients randomized >7 days after hospitalization				
Randomization 3-7 days after hospitalization (relative to <72 hours subgroup)				
Randomization >7 days after hospitalization (relative to <72 hours subgroup)				

15.33. A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by time from hospitalization to randomization

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with time from hospitalization to randomization subgroups, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

b. Time from hospitalization to randomization into the trial (convalescent plasma intervention) will be considered as a categorical variable with three pre-defined cut-off values (up to 72 hours; 3 to 7 days; more than 7 days). The reference group is the subgroup randomized <72 hours from hospitalization.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Convalescent plasma is superior to control in patients randomized within 72 hours after hospitalization	
Convalescent plasma is superior compared to control in patients randomized 3-7 days after hospitalization	
Convalescent plasma is superior compared to control in patients randomized >7 days from hospitalization	
Convalescent plasma is futile compared to control in patients randomized within 72 hours after hospitalization	

Convalescent plasma is futile compared to control in patients randomized 3-7 days after hospitalization	
Convalescent plasma is futile compared to control in patients randomized >7 days after hospitalization	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients randomized <72 hours after hospitalization				
Convalescent plasma in patients randomized 3-7 days after hospitalization				
Convalescent plasma in patients randomized >7 days after hospitalization				
Randomization 3-7 days after hospitalization (relative to <72 hours subgroup)				
Randomization >7 days after hospitalization (relative to <72 hours subgroup)				

15.34. A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by immunodeficiency status

- Population: Unblinded ITT
- Endpoint: OSFD
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with immunodeficiency status, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

b. There will be two subgroups based on the patients known immunodeficiency (convalescent plasma intervention): patient has immunodeficiency versus those who do not.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in patients with immunodeficiency	
Convalescent plasma is superior compared to control in patients without immunodeficiency	
Convalescent plasma is futile compared to control in patients with immunodeficiency	
Convalescent plasma is futile compared to control in patients without immunodeficiency	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				

Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients with immunodeficiency				
Convalescent plasma in patients without immunodeficiency				
Immunodeficiency (relative to no immunodeficiency subgroup)				

15.35. A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by immunodeficiency status

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with immunodeficiency status, corticosteroid interventions (control, fixed-duration, shock-based), immune modulation interventions (control, pooled IL-6ra), and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

b. There will be two subgroups based on the patients known immunodeficiency (convalescent plasma intervention): patient has immunodeficiency versus those who do not.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in patients with immunodeficiency	
Convalescent plasma is superior compared to control in patients without immunodeficiency	
Convalescent plasma is futile compared to control in patients with immunodeficiency	
Convalescent plasma is futile compared to control in patients without immunodeficiency	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				

Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients with immunodeficiency				
Convalescent plasma in patients without immunodeficiency				
Immunodeficiency (relative to no immunodeficiency subgroup)				

15.36. Graphical summaries

The following graphical summaries will be provided for all endpoints:

- Population: Convalescent plasma specific ITT
- Endpoint: all endpoints
- Factors: Convalescent plasma and no immunoglobulin interventions
- Analysis: Conducted by the ITSC Analysis Center

The following additional graphical summaries will be provided for OSFD and in-hospital mortality:

- Population: Convalescent plasma specific ITT
- Endpoint: OSFD, in-hospital mortality
- Factors:
    - Convalescent plasma and no immunoglobulin interventions interacted with pooled fixed-dose corticosteroid
    - Convalescent plasma and no immunoglobulin interventions interacted with pooled antiviral domain (no antiviral control, HCQ, Kaletra, HCQ + Kaletra)
    - Convalescent plasma and no immunoglobulin interventions interacted with pooled IL-6ra interventions (no immune modulation therapy, pooled IL-6ra)
- Analysis: Conducted by the ITSC Analysis Center

Appendix A: Definition of organ support-free days

This outcome is an ordinal scale of integers from –1 to 22 for each state (Moderate or Severe) derived from a composite of the patient's vital status at the end of acute hospital admission and days spent receiving organ failure support while admitted to an ICU (including a repurposed ICU) during the 21 days (504 hours) after randomisation.

A patient enrolled in the Severe State while still in an Emergency Department is regarded as 'admitted to an ICU' and the time of commencement of organ failure support is the time of randomisation, as it is for all other patients in the Severe State.

Patents who survive to hospital discharge and are enrolled in one or more domains in the Moderate State and are enrolled in one or more domains in the Severe State have a primary end point value for each state, which may be different.

If deceased between first enrolment and ultimate hospital discharge, code OutcomeDay21 as -1

If not deceased, ModerateOutcomeDay21 = 21 – (the sum of the length of time in days and part-days between time of first commencement of organ failure support while admitted to an ICU and the time of last cessation of organ failure support during that ICU admission plus time between first commencement and last cessation of organ failure support during any and all subsequent readmissions to ICU, censored at the 504 hours after enrolment in the Moderate State)

- A patient who is enrolled in the Moderate State who never receives organ failure support while admitted to an ICU has an ModerateOutcomeDay21 = 22.
- A patient who is enrolled in the Moderate State in a ward location who commences organ failure support on the ward and is transferred to an ICU while receiving organ failure support has a commencement time of organ failure support corresponding to the time of ICU admission.

If not deceased, SevereOutcomeDay21 = 21 – (the sum of the length of time in days and part- days between time of enrolment and the time of last cessation of organ failure support during that ICU admission plus the lengths of time between first commencement and last cessation of organ failure support during any and all subsequent readmissions to ICU, censored at 504 hours after the time of enrolment

Decimals are rounded up or down to nearest whole day.

If transferred between hospitals before the last study day 21 and known to be alive at ultimate hospital discharge use all available information to calculate Outcome Day21 with an assumption that no subsequent organ failure support in an ICU was provided.

If transferred between hospitals before the last study day 21 and vital status at ultimate hospital discharge is not known, code as follows:

- If last known to be on a ward use all available information to calculate Outcome Day 21 with an assumption that the patient has not died prior to ultimate hospital discharge and that there were no subsequent ICU admissions.
- If last known to be in an ICU, code OutcomeDay21 as missing (999)

If a patient is discharged alive from the ultimate hospital before 504 hours from each enrolment, assume all subsequent time is alive and without provision of organ failure support in an ICU.

If the patient is alive at the end of one or both censoring time points, the hours will be calculated as above. If the patient dies after the end of one or both of the censoring time points and before hospital discharge, the value will be updated to -1

A patient who remains admitted to an acute hospital and is still alive at the end of study day 90 no further changes to coding will be made.

Statistical Analysis Plan

for the Immunoglobulin Domain

for Patients with COVID-19 Pandemic

Infection Suspected Or Proven (PISOP)

COVID-19 Immunoglobulin Domain SAP Version 1.0 dated 08 February 2021

TABLE OF CONTENTS

1. COVID-19 IMMUNOGLOBULIN DOMAIN SAP VERSION

The version is in this document's header and on the cover page.

1.1. Version History

Version 1: Finalized on 08 February, 2021.

2. SAP AUTHORS

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3. INTRODUCTION

This statistical plan for the first analysis of the immunoglobulin domain in the pandemic stratum of the REMAP-CAP trial is an appendix to the Pandemic Appendix to Core (PAtC) Statistical Analysis Plan (SAP). This document synthesizes that information and describes the details of the statistical analysis for the unblinding of the immunoglobulin domain, within the pandemic stratum of REMAP-CAP. This plan details the statistical analyses in the original REMAP-CAP core SAP and the pandemic stratum SAP applied to the analysis of immunoglobulin domain. The plan here is completely prespecified for the imminent unblinding of the results for immunoglobulin domain within the pandemic infection suspected or proven (PISOP) (COVID-19) stratum.

Enrollment in the COVID-19 Immunoglobulin Domain started on 5th May, 2020. The domain was halted in the PISOP stratum following a statistical trigger for futility met in the severe COVID-19 stratum. The REMAP-CAP ITSC decided on 7th January 2021 to stop the severe state of the Immunoglobulin domain of REMAP-CAP within the PISOP stratum and report the results for these interventions in the domain. Enrollment to the severe state of the Immunoglobulin domain was halted on 11th January 2021. Enrollment to the moderate state of the Immunoglobulin domain was halted on 18th January 2021 following the press release of results from the RECOVERY trial of no evidence of benefit (https://www.recoverytrial.net/news/statement-from-the-recovery-trial-chief-investigators-15-january-2021-recovery-trial-closes-recruitment-to-convalescent-plasma-treatment-for-patients-hospitalised-with-covid-19).

REMAP-CAP explores multiple treatment domains by randomizing patients within multiple domains. The adaptive platform trial was designed to have modular results for individual interventions or full domains announced upon reaching a platform conclusion. For this domain, there have been two interim analyses conducted and domain closure was based on both *internal and external results*; hence the results for the convalescent plasma intervention will be unblinded and made public. This document prespecifies the analysis plan for this unblinding.

The authors of this document are blinded to the data and results in the REMAP-CAP trial other than those already publicly disclosed or simultaneously unblinded for subsequent reporting.

4. DESIGN CONSIDERATIONS

REMAP-CAP is designed with Bayesian analyses as the primary analysis method for the trial. There is one overarching Bayesian model, prespecified in the SAP, driving all adaptations, platform conclusions, and result summaries. That primary statistical analysis model will be used to report the results for the immunoglobulin domain within the severe and moderate states of the PISOP stratum. At the time of concluding enrollment the Convalescent Plasma domain, there were less than 100 participants enrolled in the moderate state. Given this limited sample size, the primary focus of this SAP is reporting results for the severe state of the Immunoglobulin domain. Descriptive and model summaries may be presented for the moderate state to facilitate future systematic reviews by others.

The decision to use a Bayesian analysis in REMAP-CAP was driven in part by the uncertainty of the extent of the pandemic. The sample size could be small, or large, and there may be unexpected external events, such as other trial results, that alter the design of REMAP-CAP. Given the expected evolution of the design, and uncertain sample size, the Bayesian approach is more appropriate.

REMAP-CAP defines several statistical triggers within the trial, that at any analysis of the trial would result in public disclosure and a declaration of a platform conclusion. The following internal statistical triggers were defined for the severe state of the immunoglobulin domain:

3. **Domain Superiority**. If convalescent plasma is deemed to have at least a 99% posterior probability of being superior to no immunoglobulin against SARS-CoV-2, then superiority would be declared for convalescent plasma.
4. **Intervention Futility**. If convalescent plasma is deemed to have a less than 5% probability of at least a 20% odds ratio improvement compared to the control, then futility would be declared.

The 99% threshold for efficacy was selected to have good properties for potential outbreak sample sizes. For example, the type I error rate of any conclusion of efficacy for a single intervention 'A' vs. control is less than 2.5% for approximately less than 1000 patients on intervention 'A' with multiple interim analyses (see main and pandemic SAP).

5. UNBLINDING

REMAP-CAP has multiple domains to which patients can be randomized and multiple interventions within domains. At the unblinding of the COVID-19 Immunoglobulin domain, other domains to which the patients have been randomized will remain blinded for this analysis. In this analysis plan there are analyses conducted by the Statistical Analysis Committee (SAC) using additional randomizations and also unblinding of other randomizations. The SAC is unblinded to all interventions/domains in their function for REMAP-CAP. This SAP also includes analyses that are conducted with knowledge of only unblinded interventions and domains. At this time, that includes the COVID-19 antiviral domain, the COVID-19 corticosteroid domain, and the IL-6ra and control interventions in the Immune Modulation Therapy domain. Finally, the SAP includes other analyses that are conducted with only knowledge of the convalescent plasma/control allocation status for patients. These may be conducted by investigators who are blinded to other information about other interventions and domains. All of these analyses are identified below.

6. INTERVENTIONS

There are three assignments within the convalescent plasma domain. These are

P1. No immunoglobulin against COVID-19 (control or standard of care (SOC) arm)

P2. Convalescent plasma at randomization

P3. Delayed Convalescent plasma. This assignment has the following definitions: (a) Delayed convalescent plasma infusion for subjects who fail to demonstrate clinical improvement within 96 hours of admission; (b) Delayed convalescent plasma infusion as a rescue therapy for moderately ill hospitalized patients who require transfer initiation of ICU level organ support as defined by the Core Protocol care after 48 hours of hospitalization; (c) Severely ill patients requiring ICU-level organ support at the time of admission will be randomized to receive: Delayed convalescent plasma infusion for subjects who fail to demonstrate clinical improvement within 96 hours of admission.)

For the primary analysis completed by the SAC, all treatment arms will be modeled, but only analysis results for convalescent plasma relative to no immunoglobulin against SARS-CoV-2 (control) will be reported. For all secondary analyses completed by blinded investigators, convalescent plasma will be compared to the no immunoglobulin against SARS-CoV-2 intervention (control; P1). Delayed convalescent plasma (P3) will be treated as a separate arm in all analyses.

Some models in this SAP will estimate and report the interaction effects of convalescent plasma with the unblinded domains at the time of finalizing SAP. This includes the interactions between convalescent plasma and fixed-dose corticosteroids; convalescent plasma and pooled antiviral domain interventions (hydroxychloroquine (HCQ), lopinavir/ritonavir, and lopinavir/ritonavir + HCQ).

7. DISEASE STATES

There are two disease states in the PAtC, which are **moderate** and **severe**. The immunoglobulin domain has randomized patients in moderate and severe state(s). The majority of patients are in the severe state, with less than 10% of the randomizations occurring in the moderate state. The main focus of the reporting of the Immunoglobulin domain is the severe state, however summaries/results for the moderate state may be reported where appropriate.

8. ANALYSIS POPULATIONS

6. REMAP-CAP COVID-19 severe and moderate state intent-to-treat (ITT): This population consists of all PISOP patients randomized within at least one domain. This population includes patients in the severe and/or moderate states. This is the analysis population for the analyses performed by the unblinded SAC.
7. Unblinded ITT: This population consists of all PISOP patients in the severe state randomized within the immunoglobulin domain or any of the previously reported interventions and domains within the PISOP stratum (Corticosteroid domain, Antiviral domain, and IL-6ra/control interventions within the Immune Modulation Therapy domain). This is the default population for secondary analyses.
8. Convalescent plasma specific severe state ITT: This population consists of only patients in the severe state randomized to convalescent plasma or control in the Immunoglobulin domain within the PISOP stratum.
9. Convalescent plasma specific per protocol: This consists of the patients in the Convalescent plasma specific severe state ITT population who have been treated as per protocol. In this domain that is defined as '*patients assigned to receive plasma will receive at least one and not more than two adult units of ABO compatible convalescent plasma (total volume 550ml ¬± 150ml) within 48 hours of randomization*' for the convalescent plasma intervention. In this domain, that is defined as '*patients assigned to receive no plasma will not receive convalescent plasma at any time after randomization*' for the control intervention.
10. Convalescent plasma specific moderate state ITT: This population consists of all patients within the PISOP stratum in the moderate state randomized to convalescent plasma or control in the Immunoglobulin domain within the PISOP stratum.

9. ENDPOINTS

The following endpoints will be analyzed, graphically displayed, and summarized through descriptive statistics.

12. **Organ-Support Free-Days** (OSFD)
    a. An ordinal endpoint with mortality as the worst outcome. The primary endpoint for the REMAP-CAP PISOP stratum. The organs considered are cardiovascular (vasopressor/inotrope support) and respiratory (ventilation support). See Appendix A for a detailed description.

13. **In-Hospital Mortality**
    a. A dichotomous endpoint of in-hospital death where the death component corresponds to a –1 on the OSFD endpoint.
14. **Mortality**
    a. This is a time-to-event endpoint through 90-days.
    b. Any patient currently in the hospital or transferred on organ support to an alternative care facility will be censored at their last known status alive.
    c. Any patient successfully discharged from hospital, alive, without organ support, will be imputed as a 90-day "no mortality" event if 90-day mortality data is not yet recorded.
15. **Progression to intubation and mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or death**
    a. A dichotomous endpoint of whether a patient progresses to intubation and mechanical ventilation, ECMO or death in hospital.
    b. This endpoint will only be analyzed for subjects that are not on intubation, mechanical ventilation, or ECMO at baseline.
16. **Cardiovascular Support-Free Days**
    a. An ordinal outcome of number of days free of cardiovascular. This is the exact calculation of OSFD, with Vasopressor/Inotropes as the only organ support category. In-hospital death is considered a –1.
17. **Respiratory Support-Free Days**
    a. An ordinal outcome of number of days free of ventilation. This is the exact calculation of OSFD, with respiratory support as the only organ support category. In-hospital death is considered a –1.
    b. Qualifying types of respiratory support include high-flow nasal cannula (HFNC), non-invasive respiratory support (NIV) and invasive mechanical ventilation (IMV).
18. **Length of ICU stay**
    a. A time-to-event endpoint of leaving the ICU alive. If a patient is known to leave the ICU and return to the ICU within 14-days that intervening time will be ignored.
    b. This variable will be truncated at 90-days: all deaths in ICU will be considered 90-days with no liberation of ICU.
    c. Patients still in the ICU at data snapshot will be considered censored.
19. **Length of hospital stay**
    a. A time-to-event endpoint of leaving the hospital alive. If a patient is known to leave and return to the hospital within 14-days that intervening time will be ignored.

b. This variable will be truncated at 90-days and all deaths in-hospital will be considered 90-days with no events.

c. Patients still in the hospital at data snapshot will be considered censored.

20. **At least one serious adverse event (SAE)**

a. A dichotomous endpoint of SAE.

21. **The World Health Organization (WHO) 8-point ordinal scale measured at day 14.**

a. A modified WHO ordinal scale will be used:

0 + 1 + 2 = No longer hospitalized
3 = Hospitalized, no oxygen therapy
4 = Oxygen by mask or nasal prongs
5 = Non-invasive ventilation or high-flow oxygen
6 = Intubation and mechanical ventilation
7 = Ventilation + additional organ support: vasopressors, renal replacement therapy (RRT), ECMO
8 = Death

22. **Domain Specific endpoints**

5. All-cause mortality at 28 days

a. This is a time-to-event endpoint through 28-days.

b. Any patient currently in the hospital or transferred on organ support to an alternative care facility will be censored at their last known status alive.

c. Any patient successfully discharged from hospital, alive, without organ support, will be imputed as a 28-day "no mortality" event if 28-day mortality data is not yet recorded.

6. Serious treatment-related adverse events

a. A dichotomous outcome endpoint of any treatment-related adverse event

b. This endpoint will be summarized descriptively. Treatment-related adverse events are defined according to each participating site's national or regional hemovigilance system definitions (such as SHOT/SABRE in the UK) summarized in Table-1 in section 10.1 of the Immunoglobulin COVID-19 DSA.

7. Venous thromboembolic events at 90 days

a. A dichotomous endpoint of any venous thromboembolic event through 90 days.

8. All thrombotic events at 90 days

a. A dichotomous outcome endpoint of any thrombotic event

Thrombotic events will consist of:

i. Confirmed deep vein thrombosis
ii. Confirmed pulmonary embolus
iii. Confirmed ischemic cerebrovascular event

iv. Confirmed acute myocardial infarction

v. Other confirmed thrombotic events

10. GRAPHICAL DATA SUMMARIES

3. All ordinal endpoints will be plotted using stacked cumulative bar plots and cumulative probability plots.
4. All time-to-event endpoints will be plotted using Kaplan-Meier plots. Positive clinical event outcomes will be plotted as the cumulative rate of event, and negative events will be plotted as the cumulative rate of event-free.

11. DESCRIPTIVE STATISTICS

5. Ordinal endpoints will be summarized by the cumulative frequency of each outcome. The 25th, 50th, and 75th percentiles will be summarized.
6. Dichotomous endpoints will be summarized by the number and proportion in each category.
7. Time-to-event outcomes will summarize the 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles from the Kaplan-Meier estimates, as available.
8. All thromboembolic and thrombotic endpoints will be summarized by the number and proportion in each category

12. BASELINE CHARACTERISTICS

The following demographics will be summarized across arms. More may be added as baseline summaries.
Age, sex, BMI, ethnicity, APACHE II score (measured from hospital admission to randomization), SARS CoV-2 PCR status reassessed at randomization, SARS CoV-2 antibody status reassessed at randomization, preexisting conditions, baseline use of high-frequency nasal oxygenation, non-invasive ventilation, invasive mechanical ventilation, ECMO, vasopressors/inotropes, renal replacement therapy, dose of convalescent plasma received (estimated as a function of donor plasma antibody titer and volume of plasma infused) and miscellaneous physiological values and inflammatory biomarker laboratory values.

13. COMPLIANCE

The compliance to convalescent plasma use will be summarized descriptively as the fraction of use, for each randomized arm.

14. ANALYTIC APPROACH

Each inferential analysis will be done using a Bayesian model. Some default frequentist methods are used for exploration and description. A summary of the analysis methods is provided below.

14.1. Primary Analysis of Primary Endpoint

The **primary analysis model** is a Bayesian cumulative logistic model for the ordinal primary endpoint. The model is described below.

The primary endpoint for the PISOP strata has 24 possible, ordered outcomes. Let the outcome for a patient by labeled as Y_i, with possible values, –1 (death), 0, 1, …, 21, 22. The outcome of 22 for the severe state (never received organ support) is not possible. Hence there are 23 possible outcomes for the severe state. A cumulative logistic model is specified. The model is structured so that an odds-ratio >1 implies patient benefit. The full details of the model including both severe and moderate states are in the Current State of The Statistical Model, Version 3.0. The full details of the model including the severe state only are in the Current State of The Statistical Model, Version 2.3. The model has factors that are estimated within each state for:

- Each level of the ordinal endpoint
- Each Global site, nested within country
- Age; ≤39, 40-49, 50-59, 60-69, 70-79, 80+
- Sex
- Time; 2-week buckets of time working backwards from the last enrolled patient, with the most recent bucket being 4 weeks.
- For each domain an effect for being randomized to the domain
- For each domain an effect for being ineligible for the domain
- An effect for each intervention within each domain
- Pre-specified interactions in the model between domains

The primary/secondary analyses for convalescent plasma use the following rules:

- The high-dose 7-day hydrocortisone arm will be combined with the 7-day hydrocortisone arm (fixed-duration). They were originally nested, which allows their pooling, and there were very few patients randomized to the high-dose 7-day hydrocortisone arm.
- All interactions between the shock-based steroid arm and other domains will be removed from the model (assumed to be zero).
- All sites within a country that have <5 patients randomized will have their results combined into a single site within that country.
- If there is an outcome in the ordinal scale that did not occur in the data, then that outcome will be combined to a single outcome with a neighboring outcome (the worse outcome). This is done for model stability. For example, if the outcome 11 never occurred a combined outcome of 10 & 11 will be modeled for the analysis.

In addition to the rules above, sensitivity analyses run by the ITSC analysis committee that include additional interactions between convalescent plasma and antivirals/steroids use the following conventions:

- The two IL-6 receptor agonists, Tocilizumab and Sarilumab, will be combined into a single pooled IL-6ra arm.
- All antivirals in the COVID-19 Antiviral Domain will be combined into a single pooled antiviral arm.

- A standard normal prior (N(0,1)) will be used on each interaction term for interactions involving convalescent plasma.

The analysis models will be referenced with certain model assumptions for sensitivity analyses. For example, the "time effects" in the model could be assumed to be 0.

14.1.1. Proportional odds assumption

The primary analysis model is based on an assumption of a proportional effect of treatment across the scale of the ordinal outcome. In order to assess the robustness of the results to this assumption, a dichotomous model is fit to every level of the ordinal outcome across the scale and the odds-ratio for each dichotomous break is presented. If the cumulative probabilities are less than 5% or greater than 95% for specific dichotomizations, these models may be ignored at the discretion of the statistician performing the analyses. No statistical test of proportional odds is conducted.

14.2. Analytic Approach for Secondary Dichotomous Endpoints

A Bayesian logistic regression model will be used for each dichotomous outcome. The model will always specify the "event" as the negative outcome, so that an odds-ratio >1 implies benefit to patients within each model. The model is the standard logistic link function model:

$$\log\left(\frac{\mathrm{rr}}{1-\mathrm{rr}}\right) = \mathrm{a} - [\mathrm{factors}]$$

References will be made to the factors in the model and their prior distribution. Many of these factors will be the same as the primary analysis model, with the same priors, as the parameters have similar interpretation. For example, all in-hospital mortality models should use the Beta prior distribution implied by the Dirichlet prior in the OSFD model. If not otherwise specified, the prior distribution for the main effect is $\mathrm{a} \sim \mathrm{N}(0, 1.82^2)$ (similar to a uniform prior on the probability scale).

14.3. Analytic Approach for Secondary Time-To-Event Endpoints

All inferential time-to-event analyses will be done using a Bayesian piecewise exponential model. The Bayesian time-to-event model is intended to mirror a Cox proportional hazards model, with the underlying hazard rate modeled with a piecewise exponential model. The underlying hazard will be modeled with a hazard rate for each 10-day period in the model. The prior distribution for each hazard rate is a gamma distribution with 1 day of exposure and a mean equal to the total exposure divided by the total number of events. This prior will have very little weight but will provide numerical stability to the model. Each factor is incorporated as a proportional hazard ratio through an additive linear model of the log-hazard. The default prior for each factor is a the same as for the log-odds in the ordinal model. If other non-specified variables are added to the model, then a normal distribution with mean 0 and standard deviation 10 will be utilized.

14.4. Markov Chain Monte Carlo (MCMC) Model Stability

The Bayesian models have many parameters and there may be risk of poor model stability, including convergence of the MCMC and the mixing behavior. These instabilities may be based on sparse data on the outcome or covariates. The statisticians running the model may make changes that do not affect the overall outcome but provide reliable model diagnostics and scientific rigor. Any alterations will be noted.

14.5. Model Outputs

The standard model outputs for each treatment effect will be the mean, standard deviation, median, and 95% credible intervals (all credible intervals will range from equal-tailed percentiles, so 95% credible intervals will range from the 2.5th percentile to the 97.5th percentile). For the ordinal models, the odds-ratio will be summarized. For the dichotomous endpoints, the odds-ratio will be summarized. For the time-to-event models, the hazard ratio will be summarized.
For each inferential model, a posterior probability that convalescent plasma is superior to control will be provided. This posterior probability has been identified as the primary analysis metric between arms. A posterior probability greater than 99% of superiority has been identified as statistically significant in REMAP-CAP.

14.6. Exploratory Analyses

Exploratory analyses after unblinding will not be considered inferential and no p-values will be presented. Any post-hoc exploratory analyses will use the following methods:

5. Ordinal endpoints will be compared using a cumulative proportional odds model with summaries of the odds-ratio, with 95% confidence intervals and Wilcoxon test for robustness against a lack of proportional odds.
6. Time-to-Event analyses will utilize a Cox proportional hazards model, summarizing the hazard ratios and 95% confidence intervals.
7. Continuous endpoints will compare means with 95% confidence intervals based on two-sample t-test procedures.
8. Dichotomous proportions will be compared using logistic regressions summarizing the odds-ratio and 95% confidence intervals. Differences between proportions will be summarized using observed differences and normal approximations for the 95% credible intervals.

15. SPECIFIC PROSPECTIVE ANALYSES

There are 35 specific prospective analyses, summarized in the table and described in detail below.
The a priori patient subgroups of interest in this domain are:

- Proven concomitant bacterial co-infection, defined as having isolation or detection of a known pathogen that causes pneumonia from blood, pleural fluid, or lower respiratory tract specimen.
- Receiving invasive mechanical ventilation at baseline
- Patients with undetectable virus at baseline (convalescent plasma intervention)
    - This will be considered as a dichotomous variable (baseline PCR positive versus negative), reassessed using samples collected at baseline by the trial team, post randomization.
- Patients with different levels of neutralizing antibodies at baseline (convalescent plasma intervention)

  - This will be considered as a dichotomous variable (baseline antibody positive versus negative), reassessed using samples collected at baseline by the trial team, post randomization.
- Dose of neutralizing antibodies received (convalescent plasma intervention, estimated as a function of donor plasma antibody titer and volume of plasma infused
  - This will be considered as a categorical variable with three pre-defined cut-off values (no units received with a Euroimmun ≥ 8, one unit received with a Euroimmun ≥ 8, two units received with a Euroimmun ≥ 8)
- Time from hospitalization to randomization into the trial (convalescent plasma intervention)
  - This will be considered as a categorical variable with three pre-defined cut-off values (up to 72 hours; 3 to 7 days; more than 7 days)
- Patients with known immunodeficiency (convalescent plasma intervention)
  - This will be considered as a dichotomous variable (patient has immunodeficiency (defined as on immunosuppressive drugs or underlying disease causing immune deficiency) versus those who do not)
- All remaining potentially evaluable treatment-by-treatment interactions with other a priori defined domains (COVID-19 Antiviral Domain and the Corticosteroid Domain).

The a priori patient sensitivity analyses of interest in this domain are:

- Per-protocol analysis of patients receiving the complete dose of convalescent plasma

Summary Table for COVID-19 Immunoglobulin Therapy Domain

#	Status	Population	Endpoint	Other
15.1	Primary	REMAP-CAP COVID-19 severe and moderate state ITT	OSFD	Includes all interventions and prespecified interactions
15.2	Primary	REMAP-CAP COVID-19 severe and moderate state ITT	In-Hospital Mortality	Includes all interventions and prespecified interactions
15.3	Sensitivity	REMAP-CAP COVID-19 severe and moderate state ITT	Dichotomized OSFD	A logistic regression will be run for each dichotomization of OSFDs as a robustness check.
15.4	Secondary	Unblinded ITT	OSFD	Includes all unblinded interventions and prespecified interactions
15.5	Secondary	Unblinded ITT	In-Hospital Mortality	Includes all unblinded interventions and prespecified interactions
15.6	Sensitivity	Unblinded ITT	OSFD	Remove site and time effects
15.7	Sensitivity	Unblinded ITT	In-Hospital Mortality	Remove site and time effects
15.8	Sensitivity	Unblinded ITT	OSFD	Includes additional interactions between convalescent plasma and antivirals/corticosteroids interventions.

15.9	Sensitivity	Unblinded ITT	In-Hospital Mortality	Includes additional interactions between convalescent plasma and antivirals/corticosteroids interventions.
15.10	Secondary	Convalescent plasma specific severe state ITT	OSFD	
15.11	Secondary	Convalescent plasma specific severe state ITT	In-Hospital Mortality	
15.12	Sensitivity	Convalescent plasma specific per protocol	OSFD	
15.13	Sensitivity	Convalescent plasma specific per protocol	In-Hospital Mortality	
15.14	Secondary	Unblinded ITT	90-day mortality	
15.15	Secondary	Unblinded ITT	28-day mortality	
15.16	Secondary	Unblinded ITT	Progression to intubation, ECMO, death	In patients not intubated at baseline
15.17	Secondary	Unblinded ITT	Cardiovascular support-free days	
15.18	Secondary	Unblinded ITT	Respiratory support-free days	
15.19	Secondary	Unblinded ITT	Length of ICU Stay	
15.20	Secondary	Unblinded ITT	Length of Hospital Stay	
15.21	Secondary	Unblinded ITT	WHO Scale at 14 days	
15.22	Primary Safety Analysis	Convalescent plasma specific severe state ITT	Serious adverse events per patient	Time effects are removed from the model
15.23	Secondary Safety Analysis	Convalescent plasma specific severe state ITT	Venous thromboembolic events at 90-days	Time effects are removed from the model
15.24	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by SARS CoV-2 PCR status reassessed at randomization
15.25	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by SARS CoV-2 PCR status reassessed at randomization
15.26	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by SARS CoV-2 antibody status reassessed at randomization
15.27	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by SARS CoV-2 antibody status reassessed at randomization
15.28	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by Convalescent plasma Dose administered
15.29	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by Convalescent plasma Dose administered
15.30	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by bacterial co-infection status
15.31	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by bacterial co-infection status

15.32	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by receiving invasive mechanical ventilation at baseline
15.33	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by receiving invasive mechanical ventilation at baseline
15.34	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by time from hospitalization to randomization
15.35	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by time from hospitalization to randomization
15.36	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by presence or absence of immunodeficiency
15.37	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by presence or absence of immunodeficiency
15.38	Graphical Summaries	Convalescent plasma specific severe state ITT	All endpoints	Including combinations across unblinded domains.
15.39	Graphical Summaries	Convalescent plasma specific moderate state ITT	All endpoints	Including combinations across unblinded domains.

15.1. The primary analysis for the convalescent plasma intervention of the COVID-19 Immunoglobulin Domain

- Population: REMAP-CAP COVID-19 severe and moderate state ITT
- Endpoint: Organ Support-Free Days
- Model: Primary analysis ordinal model
- Factors: All interventions and prespecified interactions, age, sex, site, time
- Analysis: Conducted by the unblinded SAC

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for superiority. A 95% probability of an OR < 1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported for each state:

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control (OR>1)	
Convalescent plasma is futile compared to control (OR<1.2)	

The following will be reported for each state:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.2. The primary in-hospital mortality analysis for the convalescent plasma intervention of the COVID-19 Immunoglobulin Domain

- Population: REMAP-CAP COVID-19 severe and moderate state ITT
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: All interventions and prespecified interactions, age, sex, site, time
- Analysis: Conducted by the unblinded SAC

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for superiority. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported for each state:

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported for each state:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.3. A sensitivity analysis of REMAP-CAP COVID-19 severe and moderate state ITT

- Population: REMAP-CAP COVID-19 severe and moderate state ITT
- Endpoint: Dichotomized Organ-Support Free-Days
- Model: A logistic regression will be run for each dichotomization of OSFDs as a robustness check
- Factors: All interventions and prespecified interactions, age, sex, site, time, convalescent plasma and control interventions
- Analysis: Conducted by the unblinded SAC

The following odds-ratios will be reported for convalescent plasma in the severe state:

OSFD Dichotomization	Mean	SD	Median	95% Credible Interval
-1 vs ≥0				
≤0 vs ≥1				
≤1 vs ≥2				
≤2 vs ≥3				
≤3 vs ≥4				
≤4 vs ≥5				
≤5 vs ≥6				
≤6 vs ≥7				
≤7 vs ≥8				
≤8 vs ≥9				
≤9 vs ≥10				
≤10 vs ≥11				
≤11 vs ≥12				
≤12 vs ≥13				
≤13 vs ≥14				
≤14 vs ≥15				
≤15 vs ≥16				

≤16 vs ≥17				
≤17 vs ≥18				
≤18 vs ≥19				
≤19 vs ≥20				
≤20 vs 21				

15.4. A secondary analysis of OSFD restricted to the Unblinded ITT

- Population: Unblinded Domain ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, Tocilizumab, Sarilumab) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				

Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.5. A secondary analysis of in-hospital mortality restricted to the Unblinded ITT

- Population: Unblinded Domain ITT
- Endpoint: In-hospital mortality
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, Tocilizumab, Sarilumab) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

d. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.6. A sensitivity analysis of OSFD restricted to the Unblinded ITT population with site and time factors removed

- Population: Unblinded Domain ITT
- Endpoint: Organ support free days
- Model: Primary analysis ordinal model
- Factors: Age, sex, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, Tocilizumab, Sarilumab) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

e. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Convalescent plasma				

15.7. A sensitivity analysis of in-hospital mortality restricted to the Unblinded ITT population with site and time factors removed

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary analysis dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, Tocilizumab, Sarilumab) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

f. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Convalescent plasma				

15.8. A sensitivity analysis of OSFD with interactions between unblinded interventions

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, Tocilizumab, Sarilumab) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions, additional unblinded interactions in the severe state (interaction between convalescent plasma and pooled antiviral interventions, interaction between convalescent plasma and fixed dose corticosteroids)
- Analysis: Conducted by the unblinded SAC

Notes

d. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

e. Odds ratio effects and posterior probabilities for the interaction terms between convalescent plasma and the Antiviral Domain / Corticosteroid Domain interventions will be reported relative to an additive effect. Odds ratios > 1 indicate a synergistic effect, odds ratios =1 indicate an additive effect, and odds ratios < 1 indicate a sub-additive effect.

f. The prior distributions will be set to N(0,1) for the following interactions: convalescent plasma with fixed dose corticosteroid, convalescent plasma with pooled antiviral interventions.

The following posterior probabilities will be reported for the severe state

Quantity of Interest	Posterior Probability
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	
Convalescent plasma*Fixed dose corticosteroid OR>1	

Convalescent plasma*antivirals OR>1	

The following will be reported for the severe state:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				
Convalescent plasma*Fixed dose corticosteroid interaction				
Convalescent plasma*antivirals interaction				

15.9. A sensitivity analysis of In-Hospital Mortality with interactions between unblinded interventions

- Population: REMAP-CAP COVID-19 severe and moderate state ITT
- Endpoint: In-hospital mortality
- Model: Primary analysis dichotomous model with weaker priors for the interaction effects
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based), antiviral interventions (control, HCQ, Kaletra, Kaletra+HCQ), immune modulation interventions (control, Tocilizumab, Sarilumab) and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions, additional unblinded interactions in the severe state (interaction between convalescent plasma and pooled antiviral interventions, interaction between convalescent plasma and fixed dose corticosteroids)
- Analysis: Conducted by the unblinded SAC

Notes

d. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

e. Odds ratio effects and posterior probabilities for the interaction terms between convalescent plasma and the Antiviral Domain / Corticosteroid Domain interventions will be reported relative to an additive effect. Odds ratios > 1 indicate a synergistic effect, odds ratios =1 indicate an additive effect, and odds ratios < 1 indicate a sub-additive effect.

f. The prior distributions will be set to N(0,1) for the following interactions: convalescent plasma with fixed dose corticosteroid, convalescent plasma with pooled antiviral interventions.

The following posterior probabilities will be reported for the severe state

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	
Convalescent plasma*Fixed dose corticosteroid OR>1	

Convalescent plasma*antivirals OR>1	

The following will be reported for the severe state:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				
Convalescent plasma*Fixed dose corticosteroid interaction				
Convalescent plasma*antivirals interaction				

15.10. A secondary analysis of OSFD restricted to the Convalescent Plasma Specific Severe State ITT

- Population: Convalescent plasma specific severe state ITT
- Endpoint: In-hospital mortality
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.11. A secondary analysis of in-hospital mortality restricted to the Unblinded ITT

- Population: Unblinded Domain ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.12. A sensitivity analysis of OSFD restricted to per protocol patients

- Population: Convalescent plasma specific per protocol
- Endpoint: OSFD
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.13. A sensitivity analysis of in-hospital mortality in per protocol patients

- Population: Convalescent plasma specific per protocol
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.14. A secondary analysis of 90-day mortality

- Population: Unblinded ITT
- Endpoint: 90-day mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.15. A secondary analysis of 28-day mortality

- Population: Unblinded ITT
- Endpoint: 28-day mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.16. A secondary analysis of progression to intubation, ECMO or death

- Population: Unblinded ITT not on MV or ECMO at baseline.
- Endpoint: Progression to MV, ECMO, or death
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.17. A secondary analysis of REMAP-CAP COVID-19 severe state ITT cardiovascular support free days

- Population: Unblinded ITT

- Endpoint: Vasopressor/Inotropes free days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.18. A secondary analysis of REMAP-CAP COVID-19 severe state ITT respiratory support free days

- Population: Unblinded ITT
- Endpoint: Respiratory support free days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.19. A secondary analysis of length of ICU stay

- Population: Unblinded ITT
- Endpoint: Length of ICU stay
- Model: Primary TTE model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.20. A secondary analysis of length of hospital stay

- Population: Unblinded ITT
- Endpoint: Hospital length of stay
- Model: Primary TTE model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.21. A secondary analysis of WHO scale at 14-days

- Population: Unblinded ITT
- Endpoint: Modified WHO Ordinal scale at 14-days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	
Convalescent plasma is futile compared to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma				

15.22. A primary safety analysis for convalescent plasma

- Population: Convalescent plasma specific ITT
- Endpoint: Serious Adverse Events (SAE)
- Model: Primary dichotomous model
- Factors: Age, sex, site, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control	

The following will be reported:

Odds-Ratio Parameter	**Mean**	**SD**	**Median**	**95% Credible Interval**
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Convalescent plasma				

15.23. A secondary safety analysis of venous thromboembolic events

- Population: Convalescent plasma specific ITT
- Endpoint: Venous thromboembolic events at 90-days
- Model: Primary dichotomous model
- Factors: Age, sex, site, convalescent plasma and control interventions, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Convalescent plasma is superior to control	

The following will be reported:

Odds-Ratio Parameter	**Mean**	**SD**	**Median**	**95% Credible Interval**
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Convalescent plasma				

15.24. A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by SARS CoV-2 PCR Status subgroup

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with PCR status (positive versus negative), corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in PCR positive patients	
Convalescent plasma is superior compared to control in PCR negative patients	
Convalescent plasma is futile compared to control in PCR positive patients	
Convalescent plasma is futile compared to control in PCR negative patients	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				

Convalescent plasma in PCR positive				
Convalescent plasma in PCR negative				

15.25. A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by SARS CoV-2 PCR Status subgroup

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with PCR status (positive versus negative), corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in PCR positive patients	
Convalescent plasma is superior compared to control in PCR negative patients	
Convalescent plasma is futile compared to control in PCR positive patients	
Convalescent plasma is futile compared to control in PCR negative patients	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				

…				
Time Bucket k-1				
Convalescent plasma in PCR positive				
Convalescent plasma in PCR negative				

15.26. A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by SARS CoV-2 antibody Status subgroup

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with antibody status (positive vs negative) , corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in PCR positive patients	
Convalescent plasma is superior compared to control in PCR negative patients	
Convalescent plasma is futile compared to control in PCR positive patients	
Convalescent plasma is futile compared to control in PCR negative patients	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				

Convalescent plasma in PCR positive				
Convalescent plasma in PCR negative				

15.27. A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by SARS CoV-2 antibody Status subgroup

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with antibody status (positive vs negative) , corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in PCR positive patients	
Convalescent plasma is superior compared to control in PCR negative patients	
Convalescent plasma is futile compared to control in PCR positive patients	
Convalescent plasma is futile compared to control in PCR negative patients	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				

…				
Time Bucket k-1				
Convalescent plasma in PCR positive				
Convalescent plasma in PCR negative				

15.28. A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by convalescent plasma Dose administered subgroup

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with dose subgroup (low vs mid vs high) , corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in the 'low' dose subgroup	
Convalescent plasma is futile in the 'low' dose subgroup	
Convalescent plasma is superior to control in the 'mid' dose subgroup	
Convalescent plasma is futile compared to control in the 'mid' dose subgroup	
Convalescent plasma is superior to control in the 'high' dose subgroup	
Convalescent plasma is futile compared to control in the 'high' dose subgroup	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				

Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in the ‘low’ dose subgroup				
Convalescent plasma in the ‘mid’ dose subgroup				
Convalescent plasma in the ‘high’ dose subgroup				

15.29. A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by convalescent plasma Dose administered subgroup

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with dose subgroup (low vs mid vs high) , corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in the 'low' dose subgroup	
Convalescent plasma is futile in the 'low' dose subgroup	
Convalescent plasma is superior to control in the 'mid' dose subgroup	
Convalescent plasma is futile compared to control in the 'mid' dose subgroup	
Convalescent plasma is superior to control in the 'high' dose subgroup	
Convalescent plasma is futile compared to control in the 'high' dose subgroup	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				

Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in the ‘low’ dose subgroup				
Convalescent plasma in the ‘mid’ dose subgroup				
Convalescent plasma in the ‘high’ dose subgroup				

15.30. A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by bacterial co-infection status subgroup

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with bacterial co-infection status (positive vs negative) , corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in bacterial co-infection positive patients	
Convalescent plasma is superior compared to control in bacterial co-infection negative patients	
Convalescent plasma is futile compared to control in bacterial co-infection positive patients	
Convalescent plasma is futile compared to control in bacterial co-infection negative patients	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				

Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in bacterial co-infection positive				
Convalescent plasma in bacterial co-infection negative				

15.31. A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by bacterial co-infection Status subgroup

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with bacterial co-infection status (positive vs negative) , corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in bacterial co-infection positive patients	
Convalescent plasma is superior compared to control in bacterial co-infection negative patients	
Convalescent plasma is futile compared to control in bacterial co-infection positive patients	
Convalescent plasma is futile compared to control in bacterial co-infection negative patients	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				

Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in bacterial co-infection positive				
Convalescent plasma in bacterial co-infection negative				

15.32. A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by receipt of mechanical ventilation at baseline subgroup

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with baseline mechanical ventilation status, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in patients receiving mechanical ventilation at baseline	
Convalescent plasma is superior compared to control in patients not receiving mechanical ventilation at baseline	
Convalescent plasma is futile compared to control in patients receiving mechanical ventilation at baseline	
Convalescent plasma is futile compared to control in patients not receiving mechanical ventilation at baseline	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				

Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients receiving mechanical ventilation at baseline				
Convalescent plasma in patients not receiving mechanical ventilation at baseline				

15.33. A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by receipt of mechanical ventilation at baseline subgroup

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with baseline mechanical ventilation status, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

b. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in patients receiving mechanical ventilation at baseline	
Convalescent plasma is superior compared to control in patients not receiving mechanical ventilation at baseline	
Convalescent plasma is futile compared to control in patients receiving mechanical ventilation at baseline	
Convalescent plasma is futile compared to control in patients not receiving mechanical ventilation at baseline	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				

Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients receiving mechanical ventilation at baseline				
Convalescent plasma in patients not receiving mechanical ventilation at baseline				

15.34. A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by time from hospitalization to randomization

- Population: Unblinded ITT
- Endpoint: OSFD
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with time from hospitalization to randomization subgroups, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

c. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

d. Time from hospitalization to randomization into the trial (convalescent plasma intervention) will be considered as a categorical variable with three pre-defined cut-off values (up to 72 hours; 3 to 7 days; more than 7 days). The reference group is the subgroup randomized <72 hours from hospitalization.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Convalescent plasma is superior to control in patients randomized within 72 hours after hospitalization	
Convalescent plasma is superior compared to control in patients randomized 3-7 days after hospitalization	
Convalescent plasma is superior compared to control in patients randomized >7 days from hospitalization	
Convalescent plasma is futile compared to control in patients randomized within 72 hours after hospitalization	
Convalescent plasma is futile compared to control in patients randomized 3-7 days after hospitalization	

Convalescent plasma is futile compared to control in patients randomized >7 days after hospitalization	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients randomized <72 hours after hospitalization				
Convalescent plasma in patients randomized 3-7 days after hospitalization				
Convalescent plasma in patients randomized >7 days after hospitalization				
Randomization 3-7 days after hospitalization (relative to <72 hours subgroup)				
Randomization >7 days after hospitalization (relative to <72 hours subgroup)				

15.35. A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by time from hospitalization to randomization

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with time from hospitalization to randomization subgroups, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

c. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

d. Time from hospitalization to randomization into the trial (convalescent plasma intervention) will be considered as a categorical variable with three pre-defined cut-off values (up to 72 hours; 3 to 7 days; more than 7 days). The reference group is the subgroup randomized <72 hours from hospitalization.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Convalescent plasma is superior to control in patients randomized within 72 hours after hospitalization	
Convalescent plasma is superior compared to control in patients randomized 3-7 days after hospitalization	
Convalescent plasma is superior compared to control in patients randomized >7 days from hospitalization	
Convalescent plasma is futile compared to control in patients randomized within 72 hours after hospitalization	

Convalescent plasma is futile compared to control in patients randomized 3-7 days after hospitalization	
Convalescent plasma is futile compared to control in patients randomized >7 days after hospitalization	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients randomized <72 hours after hospitalization				
Convalescent plasma in patients randomized 3-7 days after hospitalization				
Convalescent plasma in patients randomized >7 days after hospitalization				
Randomization 3-7 days after hospitalization (relative to <72 hours subgroup)				
Randomization >7 days after hospitalization (relative to <72 hours subgroup)				

15.36. A subgroup analysis of OSFD restricted to the Unblinded ITT with differential treatment effects by immunodeficiency status

- Population: Unblinded ITT
- Endpoint: OSFD
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with immunodeficiency status, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

c. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

d. There will be two subgroups based on the patients known immunodeficiency (convalescent plasma intervention): patient has immunodeficiency versus those who do not.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in patients with immunodeficiency	
Convalescent plasma is superior compared to control in patients without immunodeficiency	
Convalescent plasma is futile compared to control in patients with immunodeficiency	
Convalescent plasma is futile compared to control in patients without immunodeficiency	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				

Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients with immunodeficiency				
Convalescent plasma in patients without immunodeficiency				
Immunodeficiency (relative to no immunodeficiency subgroup)				

15.37. A subgroup analysis of in-hospital mortality restricted to the Unblinded ITT with differential treatment effects by immunodeficiency status

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, convalescent plasma and control interventions interacted with immunodeficiency status, corticosteroid interventions (control, fixed-duration, shock-based) and antiviral interventions (HCQ, Kaletra, Kaletra+HCQ), and prespecified interactions between corticosteroids/antivirals/IL-6ra interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

c. Convalescent plasma will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A <5% probability of an OR>1.2 will be used as a statistical trigger for futility.

d. There will be two subgroups based on the patients known immunodeficiency (convalescent plasma intervention): patient has immunodeficiency versus those who do not.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Convalescent plasma is superior to control in patients with immunodeficiency	
Convalescent plasma is superior compared to control in patients without immunodeficiency	
Convalescent plasma is futile compared to control in patients with immunodeficiency	
Convalescent plasma is futile compared to control in patients without immunodeficiency	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				

Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Convalescent plasma in patients with immunodeficiency				
Convalescent plasma in patients without immunodeficiency				
Immunodeficiency (relative to no immunodeficiency subgroup)				

15.38. Graphical summaries

The following graphical summaries will be provided for all endpoints:

- Population: Convalescent plasma specific ITT
- Endpoint: all endpoints
- Factors: Convalescent plasma and no immunoglobulin interventions
- Analysis: Conducted by the ITSC Analysis Center

The following additional graphical summaries will be provided for OSFD and in-hospital mortality:

- Population: Convalescent plasma specific ITT
- Endpoint: OSFD, in-hospital mortality
- Factors:
    - Convalescent plasma and no immunoglobulin interventions interacted with pooled fixed-dose corticosteroid
    - Convalescent plasma and no immunoglobulin interventions interacted with pooled antiviral domain (no antiviral control, HCQ, Kaletra, HCQ + Kaletra)
- Analysis: Conducted by the ITSC Analysis Center

16. Appendix A: Definition of organ support-free days

This outcome is an ordinal scale of integers from –1 to 22 for each state (Moderate or Severe) derived from a composite of the patient's vital status at the end of acute hospital admission and days spent receiving organ failure support while admitted to an ICU (including a repurposed ICU) during the 21 days (504 hours) after randomisation.

A patient enrolled in the Severe State while still in an Emergency Department is regarded as 'admitted to an ICU' and the time of commencement of organ failure support is the time of randomisation, as it is for all other patients in the Severe State.

Patents who survive to hospital discharge and are enrolled in one or more domains in the Moderate State and are enrolled in one or more domains in the Severe State have a primary end point value for each state, which may be different.

If deceased between first enrolment and ultimate hospital discharge, code OutcomeDay21 as -1

If not deceased, ModerateOutcomeDay21 = 21 – (the sum of the length of time in days and part-days between time of first commencement of organ failure support while admitted to an ICU and the time of last cessation of organ failure support during that ICU admission plus time between first commencement and last cessation of organ failure support during any and all subsequent readmissions to ICU, censored at the 504 hours after enrolment in the Moderate State)

- A patient who is enrolled in the Moderate State who never receives organ failure support while admitted to an ICU has an ModerateOutcomeDay21 = 22.
- A patient who is enrolled in the Moderate State in a ward location who commences organ failure support on the ward and is transferred to an ICU while receiving organ failure support has a commencement time of organ failure support corresponding to the time of ICU admission.

If not deceased, SevereOutcomeDay21 = 21 – (the sum of the length of time in days and part- days between time of enrolment and the time of last cessation of organ failure support during that ICU admission plus the lengths of time between first commencement and last cessation of organ failure support during any and all subsequent readmissions to ICU, censored at 504 hours after the time of enrolment

Decimals are rounded up or down to nearest whole day.

If transferred between hospitals before the last study day 21 and known to be alive at ultimate hospital discharge use all available information to calculate Outcome Day21 with an assumption that no subsequent organ failure support in an ICU was provided.

If transferred between hospitals before the last study day 21 and vital status at ultimate hospital discharge is not known, code as follows:

- If last known to be on a ward use all available information to calculate Outcome Day 21 with an assumption that the patient has not died prior to ultimate hospital discharge and that there were no subsequent ICU admissions.
- If last known to be in an ICU, code OutcomeDay21 as missing (999)

If a patient is discharged alive from the ultimate hospital before 504 hours from each enrolment, assume all subsequent time is alive and without provision of organ failure support in an ICU.

If the patient is alive at the end of one or both censoring time points, the hours will be calculated as above. If the patient dies after the end of one or both of the censoring time points and before hospital discharge, the value will be updated to -1

A patient who remains admitted to an acute hospital and is still alive at the end of study day 90 no further changes to coding will be made.

Appendix to Core Protocol:

STATISTICAL ANALYSIS APPENDIX

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

REMAP-CAP Statistical Analysis Appendix Version 3 dated 24 August 2019

TABLE OF CONTENTS

1. ABBREVIATIONS

CAP	Community-Acquired Pneumonia
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
ITT	Intention To Treat
MCMC	Markov Chain Monte Carlo
mITT	Modified Intention To Treat
NDLM	Normal Dynamic Linear Model
P:F ratio	Ratio of Partial Pressure of Oxygen in Arterial Blood and Fraction of Inspired Oxygen Concentration
PP	Per Protocol
RAR	Response Adaptive Randomization
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia
SAC	Statistical Analysis Committee

2. STATISTICAL ANALYSIS APPENDIX PROTOCOL VERSION

The version of the Statistical Analysis Appendix is indicated in this document's header and on the cover page.

2.1. *Version History*

Version 1: Approved by the International Trial Steering Committee (ITSC) on 7 November 2016

Version 1.1: Approved by the ITSC on 12 April 2017

Version 2: Approved by the ITSC on 12 December 2017

Version 3: Approved by the ITSC on 24 August 2019

3. INTRODUCTION

This trial design is built as a process – with the possibility of multiple interventions within multiple domains and multiple patient groups being investigated. The trial design is built prospectively to be flexible. These flexible aspects are designed and planned and are part of the protocol. In this report, we describe the details of the prospective statistical design. In contrast to many clinical trial designs, where there is a single intervention or a small number of interventions, this REMAP is designed generically so that it may incorporate a flexible number of interventions, with the possibility of these numbers evolving as the science evolves. This statistical analysis plan describes the statistical design in the most general way possible, and thus applies for all imaginable trial design states. The current trial design state is described a separate document, Current Statistical Modeling.

Similar interventions are grouped within *domains*. Each patient is randomized to a single intervention from each domain. This set of randomized interventions across the domains is the patient's *regimen*. Patients are also grouped into *strata* and into disease *states*. The efficacy of the interventions may vary by strata. Optimal interventions will be identified by strata. Some interventions may only be administered to patients in certain disease states. The specific domains, interventions, strata, and states being investigated in REMAP are allowed to evolve throughout the perpetual nature of this trial. These evolutionary aspects are described. The adaptations in the design are controlled by a statistical model. This statistical model is described in the section entitled "Statistical Modeling" (Section 5). The modeling can expand and contract to accommodate the

number of domains, interventions, strata, and states being evaluated at any time. The section entitled "Trial adaptation and stopping criteria and guidelines for interventions" (Section 9) describes the adaptations in this REMAP. These include the timing of adaptive analyses, the Response Adaptive Randomization (RAR), and the requirements for declaration of superiority, inferiority, or equivalence of interventions. A separate document, The Current Statistical Modeling document, describes the current domains, interventions, strata, states and specifies the current statistical modeling. Another separate document, the Simulations Appendix, presents a range of simulation-based operating characteristics based on the current state of the trial. This includes simulating from various assumptions of treatment effects and observing the behavior of the trial design: for example, the number of patients assigned to each intervention and the probability of declaring interventions superior, inferior, or equivalent by strata.

4. STRUCTURE OF TRIAL

4.1. *Primary Endpoint*

The primary endpoint for the trial is all-cause mortality at 90 days. This is considered as a dichotomous endpoint where outcomes will be failure (mortality within 90 days of enrollment) or success (not a failure). We label the outcome for a patient as Y, where Y=1 is defined as a failure (death within 90 days) and Y=0 is a patient success.

4.2. *Domains*

For the purposes of REMAP, a domain defines a specific set of competing treatments within a common clinical mode. Each domain has a set of mutually exclusive and exhaustive interventions. Every eligible patient will be randomized to one and only one of the available interventions from each domain.

We label the domains as d = 1, 2,…, D. A specific domain may also be referred to by a letter: A, B, C, …. Interventions within a domain are labeled with a subscript index, j. Therefore, d_j refers to intervention j within domain d. There are j = 1, …, J_d interventions in each domain d. It is expected that the number of domains, and the number of interventions within each domain will expand or contract as the trial progresses.

4.3. *Regimens*

Every patient will be randomized to a set of interventions, exactly one from each domain. The set of interventions are referred to as a regimen. All possible combinations define the set of available arms in the trial. We label a regimen as *r*. As an example, assuming 4 domains denoted as domain A, B, C, and D, a regimen would be:

$$r = (A_a, B_b, C_c, D_d).$$

4.4. *Strata*

There are multiple covariates within this REMAP to describe patients' baseline characteristics, but some of these covariates are treated as possibly prognostic in that the treatment effect may vary across these covariates. We label these select covariates as prospectively defined strata and the treatment effect of an intervention is modeled as possibly varying across the strata.

Within each stratum, patients will be grouped in a dichotomous manner. If a strata is defined as an ordinal-type variable, then dichotomous indicator variables according to the desired contrasts will be defined. Therefore, let $x_1, \ldots, x_K$ be the set of K dichotomous indicator variables that define the different strata. The number of unique strata (or sub-groups) is 2^K. We label the dichotomous groups in each stratum as g=1,2. For example, the trial will begin with a single stratum – shock. Therefore, shock is strata x_1. Within this stratum, patients will either not be in shock (g = 1) or will be in shock (g = 2).

The number of strata may be expanded, or the existing strata may be modified as the trial progresses. The description here is expandable when strata are defined by a dichotomous structure.

4.5. *State*

A state is a clinical condition of a patient that may change during the course of their treatment. The different states within the REMAP are used to define possible eligibility of the patient for different domains at different times in the trial and as a covariate of analysis within the statistical model to adjust for disease severity. A state is a set of mutually exclusive categories, defined by characteristics of a patient, and states are dynamic in that they can change for a single patient, at different time-points, during the patient's participation in the REMAP.

The number of state variables and the number of states within the REMAP may be varied, depending on the impact of the number of states on statistical power, as determined by simulations. The *a priori* defined states that are used may be changed during the life of the REMAP as knowledge is accumulated.

The states are modeled as additive covariates within the statistical model. We label the different states as s=1,…,S.

4.6. *Randomization*

Randomization assignments are performed for patients at baseline. Randomization is performed separately by strata in that the randomization probabilities to the interventions may vary depending on the group membership of the patient within the strata. Patients are randomized to a full regimen, and not to individual interventions within the domains. Section 9.6 describes the response adaptive randomization allocation procedure.

However, there may be domains where the therapy is specific to a certain disease state. Some patients will not be in disease states that require the interventions from a particular domain. For example, a domain may be specific to a more severe disease state. Initially the patient may not be in that severe disease state but could transition to that disease state. Randomization at baseline will assign an intervention in each domain regardless of disease state. However, the domains may differ in the timing of when the randomization assignment is revealed. Some domains will employ an *immediate* reveal at baseline. For these immediate reveal domains the randomization will be treated in an intent-to-treat fashion for the primary analysis in that all patients will be included in the analysis of that domain. Some domains may employ *deferred reveal*, in which the randomization assignment is revealed based on an initial eligibility criterion at the time of randomization but the information to assess that eligibility criterion only becomes known after some time. These domains will be treated analogously to the immediate reveal domains for analysis. Finally, some domains will employ *delayed reveal*, in which the randomization is revealed only for patients in the disease states, or who progress to the disease states, that require that domain. The revealing of the domain will be tracked and the analysis of delayed reveal domains will censor from the analysis the patients that did have that randomization assignment revealed. In the case of interventions within a delayed reveal domain, the specific modeling of the intervention effects and modeling the time varying aspects of

states will be custom to that domain and will be prespecified in a separate document, Current Statistical Modeling.

5. STATISTICAL MODELING

Inferences in this trial are based on a Bayesian statistical model, which estimates the posterior probability of all-cause mortality at 90 days (primary endpoint) for each regimen based on the evidence that has accumulated during the trial in terms of the observed 90-day mortality outcomes and assumed prior knowledge in the form of a prior distribution. This differs from conventional (frequentist) analysis methods where inferences are based on a likelihood of observed outcomes against a null hypothesis.

The statistical model takes into account the variation in outcomes by region, strata, disease states, age group, and time since the start of the trial. The model estimates treatment effects for each intervention as well as determines if these treatment effects vary by strata and if treatment effects of individual interventions in one domain vary when paired with interventions from other domains.

Let

- *R* = region
- s = disease state
- k = strata and g_k = the yes/no dichotomous status within strata *k* where g_k = 1 means the strata condition is “no” and g_k = 2 means the strata condition is “yes”
- *age* = age group
- *T* = era measured in 13-week increments since the start of the trial
- *d* = domain and d_j is intervention *j* within domain *d*

We model the log odds of the probability of 90-day all-cause mortality, π, as

$$\log\left(\frac{\pi}{1-\pi}\right) = \sum_{R=1}^{R} \nu_R + \sum_{k=1}^{K}\sum_{s=1}^{S} \alpha_{s,g_k} + \sum_{age=1}^{AGE} \lambda_{age} + \sum_{T=1}^{T} \theta_T + \sum_{d=1}^{D}\sum_{j=1}^{J_d} \beta_{d_j} + \sum_{k=1}^{K}\sum_{d=1}^{D}\sum_{j=1}^{J_d} I(g_k = 2)\gamma_{kd_j} + \sum_{d=1}^{D}\sum_{j=1}^{J_d}\sum_{d'=1}^{D}\sum_{j'=1}^{J'_{d'}} \delta_{d_j d'_{j'}}$$

The interpretation of each term in the model is:

ν_R is the covariate that adjusts for region. There is one ν_R term estimated for each R = 1,…,R where R = 1 is the referent group and the remaining terms estimate the increase or decrease in mortality associated with region

α_{s,g_k} is the covariate that adjusts for both strata and disease state. For each strata *k* where k = 1,…K, there is one term for every pairwise combination of *s* = 1,…,*S* and g_k = 1,2. The referent by strata *k* is when both s = 1 and g_k = 1. The remaining terms then estimate the increase or decrease in mortality associated with the strata and disease state combinations. When s = 1 (the referent disease state) this term estimates the increase or decrease in mortality associated with the strata condition (g_k = 2 versus g_k = 1). For g_k = 1 (the referent strata group) this term estimates the increase or decrease in mortality associated with disease state (s = 2,…,S versus s = 1). When both s > 1 and g_k = 2 this term estimates the additional effect of the strata condition (g_k = 2) in each of the disease states.

λ_{age} is the covariate that adjusts for age group. Age will be modeled as categorical age groups. There is one λ_{age} term for each age group being modeled. The referent will be a middle age group and the remaining terms estimate the increase or decrease in mortality associated with the other age group categories.

θ_T is the covariate that adjusts for time since the start of the trial. There is one term for each T = 1,…,T where each represents an era, or a 13-week period of calendar time. The trial era in which the analysis is being conducted (the most current era) will be the referent and every other θ_T then represents the increase or decrease in mortality associated with calendar time since the start of the trial.

β_{d_j} are the terms that estimate the main effects of each intervention. There is one β_{d_j} term for each intervention in each domain. Intervention j = 1 in domain d = 1 is the referent and every other β_{d_j} estimates the relative increase or decrease in mortality associated with each other intervention in the trial.

γ_{kd_j} are the terms that estimate intervention by strata interactions. There is one term for every pairwise combination between the k = 1,…, K strata in the trial and the j = 1,…,J_d interventions across all d = 1,…D domains in the trial. We define *I*(g_k = 2) as an indicator variable for g_k = 2 in strata *k*. Therefore, this term estimates the increase or decrease in morality associated with an intervention when g_k = 2 (strata condition is “yes”) versus when g_k = 1 (strata condition is “no”).

$\delta_{d_j d'_{j'}}$ are the terms that estimate the intervention by intervention interactions. There is one term for every pairwise combination between all the interventions j = 1,…, J_d in one domain all interventions $j' = 1,\ldots, J'_{d'}$ in every other domain. These terms estimate the increase or decrease in the effectiveness of each intervention when it is paired with another intervention from another domain.

As described above, there may be two types of domains. There will be immediate reveal domains that investigate interventions that do not depend on disease state and the randomization assignments in these domains can be made known immediately. There may be delayed reveal domains that investigate interventions that are appropriate only for patients in certain disease states that evolve within patients during the trial. The randomization assignment can be made known only to patients in these disease states. Therefore, there will be three groups of patients relative to a delayed reveal domain:

1. The randomization is never revealed because the patient is never in an eligible disease state
2. The patient enters the trial in the eligible disease state and the randomization assignment is effectively immediately revealed
3. The patient transitions to the eligible disease state after the initial randomization and the randomization status is a delayed reveal

We define a model that includes terms for the treatments in both immediate and delayed reveal domains. However, there will be no interaction terms estimated with the interventions in the delayed reveal domains and any other domains. This model will be fit based on all randomized patients where patients are included in the model based on the initial disease state they are in at the time they are randomized. The efficacy of delayed reveal domains among patients who transition to the eligible disease state (group 3 above) will be modeled through a "sub-model" that only informs the relative efficacy of the interventions within the delayed reveal domain. The sub-model will include adjustment for the covariates of region, age and era, and will include the main effect terms for the interventions in the delayed reveal domain. The sub-model will be dependent on the primary model in that the estimation of the sub-model will be conditional upon the estimates of region, age, and era from the primary model.

5.1. *Modeling Covariates for ineligibilities for interventions and / or domains*

The modeling of the primary endpoint is a logistic regression form:

$$\log\left(\frac{\pi}{1-\pi}\right) = f(R, k, s, age, T, d, j).$$

In order to add covariates in the model, for sensitivity or exploration they will be added as (possibly multiple covariates):

$$\log\left(\frac{\pi}{1-\pi}\right) = f(R, k, s, age, T, d, j) + \zeta Z$$

where Z is a normalized covariate and ζ is the model coefficient. Individual patients may enter the trial ineligible to one or more individual interventions within a domain or one or more domains. If a patient is ineligible for one or more interventions within a domain but there are at least two interventions for which the patient is eligible to be randomized among then the patient is allocated an intervention from among the eligible interventions and the data for such a patient is included in the full analysis set and a covariate indicating ineligibility to the interventions will be fit.

If a patient is ineligible for an entire domain then an indicator for the domain ineligibility is created and a covariate, Z, for this ineligibility is created. No treatment allocation variable nor interactions for this patient are included in the model.

The coefficients for all covariates for these ineligibility interventions/domains will have the following priors:

$$[\zeta] \sim N(0, 10^2).$$

A list of all models, model terms, and their prior distributions specific to the current state of the trial are provided in a separate document.

All models will be fit using Markov Chain Monte Carlo (MCMC) methods.

6. MISSING DATA

There will be no imputation of missing primary endpoint values. Patients with missing values for the primary endpoint will be excluded from the modeling. If randomization assignment or reveal of randomization assignment is missing, the patient will be assumed to be ineligible for that domain. Patients with unknown region, age, or era may have these covariates imputed. Where possible, missing values will be calculated based on other available data. Otherwise, the mean value will be imputed for missing values.

If strata or state is missing for a subject, it will be multiply imputed in the Bayesian algorithm. This multiple imputation will be based on the primary outcome variable and each of the variables in the model through the Bayesian posterior distribution. An important aspect of this model is a prior distribution of the missing strata or state. In some cases, this may be a specified prior (such as having a sleeping strata become active in which the status of the previous patients' strata status was never collected. The prior probability may be quite small in the case of a new pandemic). If there is no scientifically informed prior distribution then the relative frequency of the strata or state in the region and era will be used as the prior distribution for each state.

7. MODEL PRIORS

In this section, we present the prior distributions used for each of the parameters.

7.1. *Region Effects*

For identifiability, the region parameter for region 1 is considered the baseline and is set to 0. For every other region, the prior distributions for the parameter are modelled in a tiered (hierarchical) fashion. We refer to a *region* as the smallest classification of the geographical location. Typically, a region will be a site, but not always (a region may be a collection of sites). Regions are grouped hierarchically within country. We model the effects individually at the smallest unit – the regions. The model explicitly models the regions as being grouped, hierarchically, within country. For a region, label the parent country as c_R, where c_R=1,…, C. The parameter for each region is labeled ν_R and is modeled hierarchically as:

$$[\nu_R] \sim N(\mu_{C_R}, \tau^2_{C_R})\ R = 2, \ldots, N_R,$$

with hierarchical priors

$$[\mu_C] \sim N(0,1);\ [\tau_C^2] \sim IG(0.25,0.1),\ \text{where c=1,...,C.}$$

The hierarchical distribution for the region effects creates a meta-analytic type model for the estimation of individual effects. The hyper-prior distributions have a mean estimate of 0, which is the same as the baseline, Region 1, and a prior centered at 0.20^2 for the standard deviation across countries, but with a relative weight of only 0.5 observations. This prior allows the observations across regions/countries to empirically shape the hyper-distribution.

7.2. *Strata and State Effects*

For every strata and state combination a single parameter captures the relative severity of the population. For identifiability we restrict the parameter for g_k=1 and s=1 to be set at 0. Thus, for the shock stratum, g_1 = 1 and s = 1 corresponds to non-shock, not ventilated. The prior distributions for the parameters are set as fixed priors with weak prior distributions

These prior distributions are modelled separately as they are expected to be quite different, but will be shaped very quickly by the large amount of data within each group by state pair.

7.3. *Time (Era) Effects*

The time eras will be sequential "buckets" of 13-week time periods measured from the start of the trial. For identifiability, the era parameter for the most recent time period, θ_T, is considered the baseline and is set to 0. For every previous era, the prior distributions for the parameters are modelled with a first-order normal dynamic linear model (NDLM). The first-order NDLM is defined by "walking backwards" in time,

$$[\theta_{T-1}] \sim N(\theta_T, \tau_T^2);\ T = 1, \dots, N_T - 1,$$

with hyper prior on the "drift" parameter

$$[\tau_T^2] \sim IG(0.25,0.1).$$

The NDLM model for the eras allows borrowing (smoothing) the estimate of each era over the course of the trial. The drift parameter τ_T^2 is the variance component that creates the amount of borrowing from one era to the next. This is shaped by the data, using a hyper-prior distribution. The

prior distribution is equivalent to 1 observation worth of data that the era effects have small changes, 0.10^2, from one era to the next. The individual era effects will be heavily shaped by the data from patients within the eras.

7.4. *Age Effects*

For identifiability, the age parameter for the middle age group, 41 to 65 will be set to 0. We model the three remaining age effects with independent normal priors:

$$[\lambda_{age}] \sim N(0, 10^2); age = 1,3,4.$$

7.5. *Intervention Common Effects*

Each intervention parameter β_{d_j} for d=1,…,D; j=1,…,J_d is considered the relative effect of each intervention. For identifiability, the effect for the first intervention within each domain is set to 0.

For some domains, there may be sets of interventions that are considered "nested". For these nested interventions, the intervention effects are modeled hierarchically, which allows borrowing among the intervention effect estimates for the interventions within the nest. Each domain-specific appendix will specify which interventions, if any, will be considered nested for the model.

For all non-nested interventions, the intervention effects are given weak independent priors:

$$[\beta_{d_j}] \sim N(0, 10^2).$$

For the set of nested interventions within a domain, the prior for interventions within the nest is

$$[\beta_{\substack{d \\ j}}] \sim N(\mu_\beta, \tau^2_\beta),$$

With hierarchical priors

$$[\mu_\beta] \sim N(0, 10^2); [\tau^2_\beta] \sim IG(0.125, 0.00281).$$

For the set of nested interventions within a domain, the hyperparameters are selected such that the prior for τ_β is centered at 0.15 with weight 0.25. For non-nested interventions, the intervention effects are modeled separately, corresponding to large τ^2_β.

For the purpose of assessing statistical triggers that lead to platform decisions, the analysis will be repeated, with nested interventions pooled together ($\tau^2_{\beta} = 0$). However, the model with hierarchically modeled nested interventions will be the primary model that drives the adaptive randomization.

7.6. *Intervention by Strata Effects*

It is anticipated that there may be interactions between stratum membership and some interventions, but in general expected to be small. The protocol enumerates three choices for modelling the intervention by strata interaction terms. These choices are described in the protocol as the "gamma parameter" though they actually refer to choices for the standard deviation of the prior distribution for the interaction parameter. Each domain-specific appendix will pre-specify which of the following options is selected for each intervention-strata pair within that domain:

- On one extreme, the interaction parameter may be set to zero, $\gamma_{kd_j} = 0$, forcing the model to estimate no interaction; thus, the treatment effect of the intervention is not permitted to differ between strata.
- On the opposite extreme, the interaction parameter may be given a weak prior,

$$[\gamma_{kd\,j}] \sim N(0, 10^2)$$

which is described in the protocol as gamma = infinity. This prior spreads its mass over the real line.

- Finally, the prior for the interaction parameter may be selected as

$$[\gamma_{kd\,j}] \sim N(0, 0.15^2)$$

which has a standard deviation of 0.15 (referred to as gamma = 0.15 in the protocol). This prior places most of its mass on small values, effectively shrinking the estimate of the interaction towards zero. For reference, on the log-odds scale (in which the parameter γ are) an effect of 0.15 is an odds-ratio of 1.16, which would make a probability of 0.20 increase to 0.225. This prior standard deviation value was selected by the ITSC in evaluating the model behavior versus possible scenarios.

7.7. *Intervention by intervention interactions*

It is anticipated that there may be interactions between some interventions, but that these would likely be relatively small.

For all two-way interaction parameters, three choices are available for modeling purposes. These choices are described in the protocol as the "lambda parameter" though they actually refer to choices for the standard deviation of the prior distribution for the interaction parameter. One of the following options will be pre-specified for each intervention-intervention pair:

- The model may force no interaction between a pair of interventions by setting the interaction parameter equal to zero. That is, $\delta_{d_j,d'_{j'}} = 0$ for the interaction between intervention j in domain d and intervention j' in domain d' (where $d \neq d'$). In the protocol, this option is written as lambda = 0.
- On the opposite extreme, the interaction term may be given a weak prior:

$$[\delta_{d_j,d'_{j'}}] \sim N(0, 10^2)$$

which is described in the protocol as lambda = infinity.

- Finally, the prior for the interaction parameter may be selected as

$$[\delta_{d_j,d'_{j'}}] \sim N(0, 0.05^2)$$

For reference, on the log-odds scale (in which the parameter δ are) an effect of 0.05 is an odds-ratio of 1.05, which would make a probability of 0.20 increase to 0.208. These prior values were selected by the ITSC in evaluating the model behavior versus possible scenarios.

8. STATISTICAL QUANTITIES

The following statistical quantities are used in the design of the trial. The posterior distribution of the model parameters is calculated using MCMC. The algorithm allows the generating of at least M (100,000) draws from the joint posterior distribution. The following posterior quantities are calculated during the MCMC algorithm. For each regimen, r, we define π_{r,g_k} as the relative

effectiveness of the regimen, for group *g* within strata *k*. Similarly, $\pi_{r,g_k}^{(m)}$ as the relative effectiveness of regimen *r* for group *g* within strata *k*, for the *m*th draw from the MCMC algorithm.

8.1. *Probability of Optimal Regimen*

Let $O_{g_k}(r)$ be the posterior probability that a regimen, *r*, is the optimal regimen for group *g* within strata *k*. For the *m*=1,…,*M* draws from the posterior, the frequency of draws in which each unique regimen, *r*, is optimal in group g_k, is tracked. The frequency each regimen is optimal is the posterior probability that the regimen is the optimal regimen:

$$O_{g_k}(r) = \frac{1}{M}\sum_{m=1}^{M} I[\pi_{r,g_k} < \pi_{q,g_k} \text{ for all } q \neq r]$$

8.2. *Probability of Optimal Intervention*

While $O_{g_k}(r)$ tracks the posterior probability that a regimen is optimal, we also track the probability that an individual intervention is in the optimal regimen. We refer to the posterior probability an intervention *j*, from domain *d*, is in the optimal regimen for group g_k, as $\Lambda_{g_k}(d_j)$:

$$\Lambda_{g_k}(d_j) = \frac{1}{M}\sum_{m=1}^{M} I[d_j \in r | \pi_{r,g_k} < \pi_{q,g_k} \text{ for all } q \neq r].$$

9. TRIAL ADAPTATION AND STOPPING CRITERIA AND GUIDELINES FOR INTERVENTIONS

The trial design is an adaptive perpetual platform trial design. The platform aspect of the trial refers to the fact that there will be multiple investigational interventions being simultaneously studied. The trial is designed to be perpetual and continue studying severe community-acquired pneumonia (severe CAP), with no designated end. The goals of the trial are to both treat patients effectively while also investigating the relative benefit of different interventions, within different groups of patients. The design is adaptive in that the key aspects of the trial will evolve in a pre-planned way based on accruing data.

First, there will be a starting status with regard to strata, domains, and the interventions within a domain. These aspects are expected to change during the course of the REMAP trial. Strata can be

added or removed. Similarly, domains can be added or removed, and interventions within the domains can be added or removed based on internal or external information. The trial design is generic in terms of the number of strata, domains, and interventions within a domain, so that the trial functions seamlessly, based on predefined rules, as the questions being evaluated within the trial evolve. Each section below describes aspects of the trial design that will evolve in a predetermined fashion based on accruing empirical information.

9.1. *Data Sources*

All patients in the perpetual trial will become a part of the accruing data in the trial. There will be a set of patients in the primary analysis population. All patients in the primary analysis population will remain in that population for as long as the trial is running.

9.2. *Primary Analysis Population*

The primary analysis population will consist of all patients that are randomized to at least one of the interventions and at least one intervention is revealed. The primary analysis population will be used for all efficacy endpoints and will be determined in accord with the intention to treat (ITT) principle and will comprise all randomized patients, analyzed by the regimen to which they were randomized and their stratum membership as determined at the time of randomization.

Other analysis populations may be used in supportive analyses of efficacy endpoints (when a Public Disclosure has been triggered) and in the analyses of domain-specific safety endpoints.

- A modified intention to treat (mITT) population, which will include only participants who received at least 1 dose of the allocated treatment (or similarly defined in the DSA for non-pharmacological interventions)
- A per protocol (PP) population, which will include only eligible patients who received the allocated intervention with no major protocol violations and where all outcomes were observed.

9.3. *Adaptive Analyses*

Adaptive analyses will be conducted frequently throughout the trial process. The first adaptive analysis will occur when there are a significant number of patients with 90-day outcome data. After that first adaptive analysis, they will be planned to be repeated monthly, perpetually, for the

remainder of the trial. Interim analyses may be skipped if, due to seasonal variations, enrollment is slow and little new information has accrued during the month. A regular time period (e.g. first of the month) will be selected and this will trigger the running of an adaptive analysis. These adaptive analyses will consist of all currently available data being analyzed according to the current trial model. Only data for patients reaching a 90-day window from time of randomization will be used in the analysis to avoid biases that may arise from differential timing of known failure compared with known success. The model run will be used to trigger allocation updates and possible Statistical Triggers (determining superiority, inferiority, and equivalence). These rules are presented in the following sections.

9.4. *Allocation (Response Adaptive Randomization)*

The allocation during the platform trial is adaptively set based on the accruing efficacy data. The data on the primary endpoint (mortality) will shape the randomization proportions for each regimen, within each stratum.

9.5. *Initial randomization ratio*

During the start to this trial there will be a period of time, the burn-in period, in which a response adaptive randomization scheme will be used with no new data. This response adaptive randomization will be based on initial prior parameters. Unless priors are selected favoring certain treatments within stratum these probabilities will be equal for each intervention.

9.6. *Response Adaptive Randomization*

After the burn-in period, RAR will be used for the allocation for each regimen. Allocation to the regimens will be allowed to vary across the patient groups defined by the strata. Patients will be enrolled in the trial and randomized to a regimen according the group they belong to within each strata. The randomization for each patient is based on the probability that each regimen is the optimal regimen for a patient within that patient strata, but balanced by the sample size already allocated to that regimen. This balancing creates better learning about the optimal regimen by allowing a less aggressive randomization to regimens that already have a larger number of patients allocated. We refer to this scheme as maximizing the information about the optimal regimen within a stratum.

The randomization for a patient in group *g* within strata *k* is proportional to

$$\rho_{r,g_k} \propto \sqrt{\frac{O_{g_k}(r)}{n_{r,g_k}+1}}.$$

Where $O_{g_k}(r)$ is the probability that regimen *r* is optimal for patients in group *g* of strata k and n_{r,g_k} is the total number of patients in group *g* of strata *k* who have already been allocated to regimen *r*. Multiple normalizations are done to create the final randomization probabilities. The following steps are carried out.

1. Each randomization probability is normalized to sum to 1 by dividing by the sum of quantities over all regimens.
2. Any single intervention with a sum of probabilities across all regimens within a stratum less than 10% will be increased to sum to the floor randomization per intervention of 0.10. Note that a minimum randomization of 10% implies a maximum randomization probability of 90%
    a. A nuisance parameter (φ) will be added to the odds ratio for each intervention that does not achieve at least a 10% randomization probability. The value of φ will be selected to create a minimum randomization probability of 10% for each intervention.

The result is a set of randomization probabilities for each regimen, for each group as defined by the strata.

9.7. *Introduction of new interventions*

While this REMAP is running, if a new intervention is started then the randomization will be "blocked" for the new intervention in order to guarantee an initial sample size. If there are J_d interventions in a domain after the new intervention is started, then a fixed allocation of $1/J_d$ will be used to allocate patients to the new intervention. The remaining $1 - \frac{1}{J_d}$ probability will be allocated to the other interventions using the RAR. This burn-in for each intervention will last until 25 patients have been allocated to the new intervention. At that point this restriction will be removed and adaptive randomization to all regimens will be carried out.

9.8. *Intervention Efficacy Announcement / Conclusion*

At each adaptive analysis the results of the relative efficacy of different interventions can trigger adaptive decision rules. These include Public Disclosure of the results, removal of interventions within strata, and deterministic allocation to interventions within strata. The following sections present the prospective rules for these adaptive decisions. The adaptive analyses will be carried out by the Statistical Analysis Committee (SAC).

9.9. *Intervention Superiority*

At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being the optimal intervention for a strata group, $\Lambda_{g_k}(d_j) > 0.99$, and there are at least 250 patients randomized to that intervention in that strata group, then that intervention, within that domain, will be deemed as being superior within that strata group, triggering a Public Disclosure. At that point, the remaining interventions in the domain will be halted for inferiority for that strata group. All future patients in that strata group will then be allocated to that superior intervention and randomized to interventions in the other domains. This will continue until new interventions are added to the domain that contains the superior intervention.

9.10. *Intervention Inferiority*

At any adaptive analysis, if a single intervention has less than a $0.01/(J_d-1)$ posterior probability of being the optimal intervention for a strata group $\Lambda_{g_k}(d_j) < 0.01$, then that intervention will be deemed as being inferior within that domain, for that strata group, triggering a report to the Data Safety and Monitoring Board (DSMB). The DSMB then makes a judgment on whether a Platform Conclusion has been reached and whether to trigger a Public Disclosure. If so, no additional patients in that strata group will be randomized to that intervention. When simultaneous superiority/inferiority occurs (for example when there are 2 interventions they are always simultaneous), then the result will be released as an intervention demonstrating superiority.

9.11. *Intervention Equivalence*

If the two interventions within the domain have at least a 90% posterior probability that the odds ratio comparing the two within any stratum is between 1/1.2, and 1.2, the two interventions will be considered equivalent for that stratum. This result will be communicated to the ITSC and they will

take the appropriate action (Public Disclosure, removal of one intervention, no action). There is no automatic adaptation when this occurs.

9.12. *Deviation from pre-specified analyses (contingency plans, non-convergence, testing model fit etc.)*

The SAC will monitor the model behavior, including numerical stability and scientific appropriateness. Simpler models will be constructed and evaluated determining any root cause issues, data issues, or inappropriate model fit. If any numeric instabilities can be fit in statistical numeric methods, these will be done by the SAC and the adjustments recorded and noted. If the model is deemed to provide an inappropriate fit then the SAC will inform the DSMB of appropriate adjustments which will be reported to the ITSC in a way that does not risk unblinding trial results. Possible adjustments could include:

1. If there are issues within an intervention for limited data the parameter for that intervention can be fixed for model stability.
2. If there is missing data on whether there were revelations of delayed reveals and/or state values then an ITT Model ignoring the changing states will be fit to explore the effects
3. A reasonable solution should technology fail or data issues arise would be to keep the randomization unchanged, fix the randomization for an intervention, or create equal randomization for all interventions/regimens.