Online Data Supplement

The Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia (REMAP-CAP) Study: Rationale and Design

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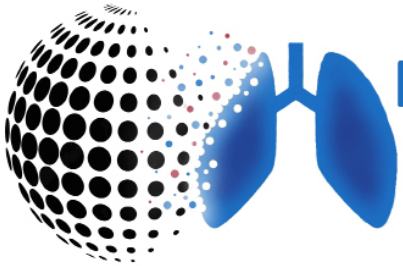

REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

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

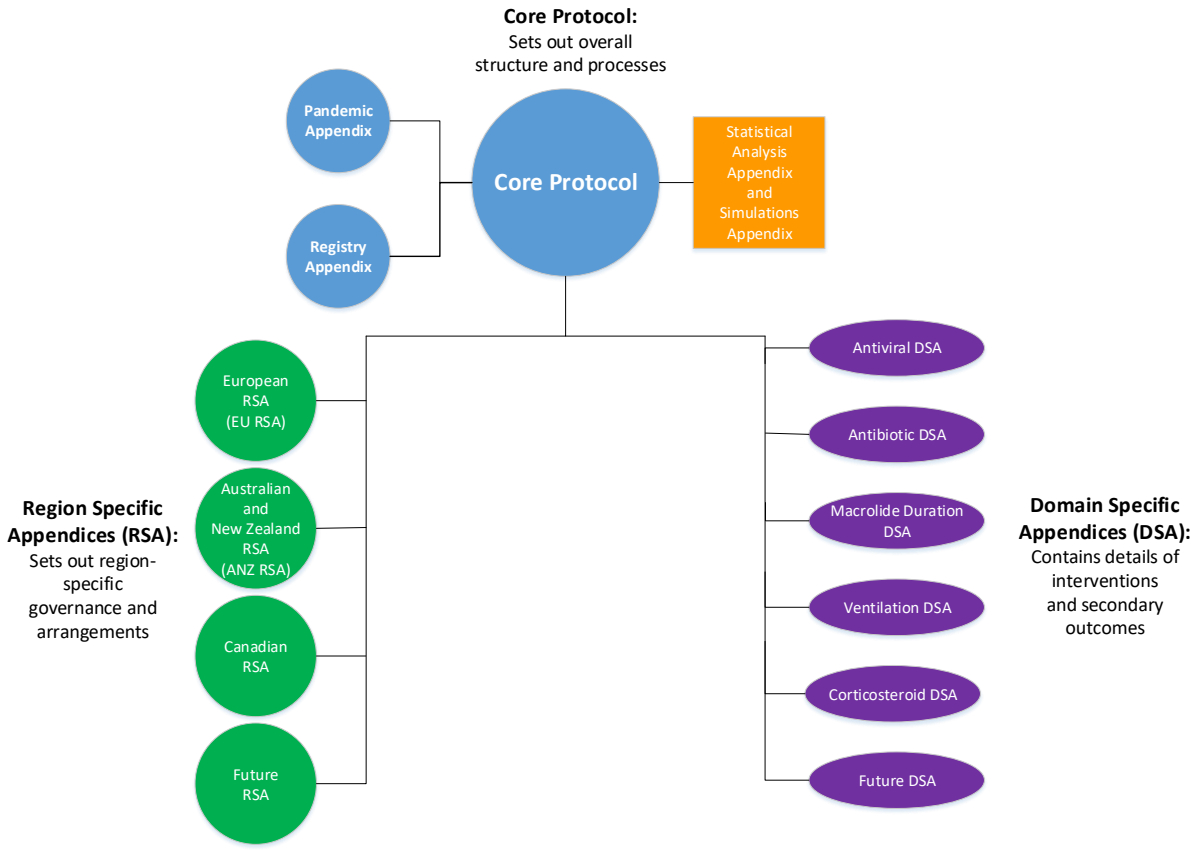
that a difference is detected or no that no difference is detected. However, when the conclusion of the statistical test is “no difference”, this could be that there truly is no meaningful difference, or that the result is indeterminate (i.e. it is possible that if more patients had been enrolled a clinically 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

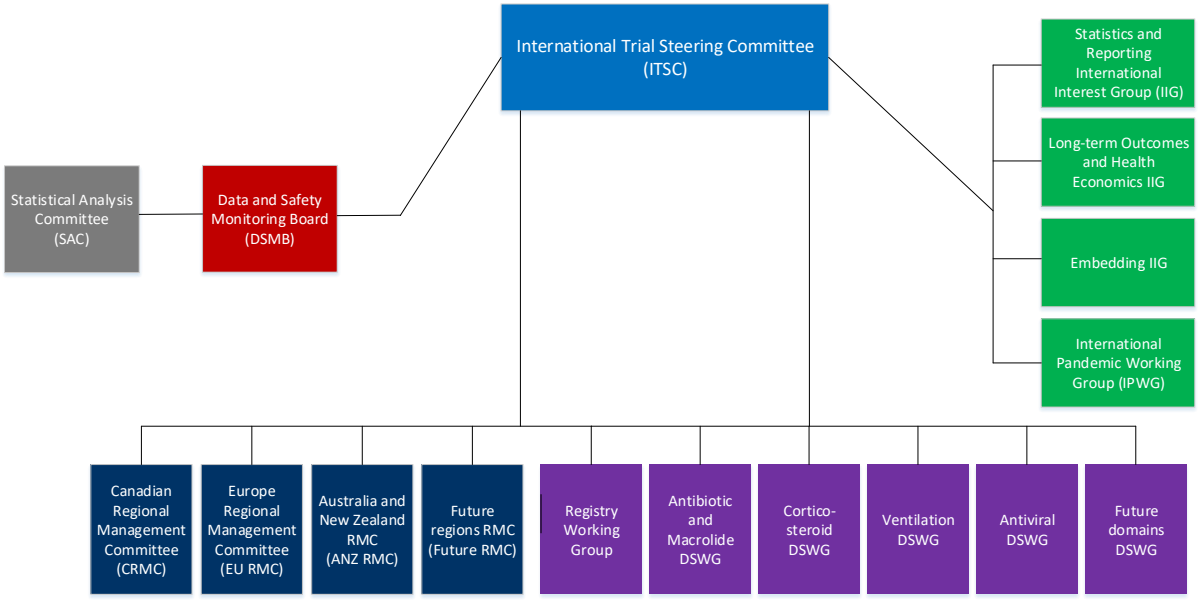
The study administration structure is designed to provide appropriate management of all aspects of the study, taking into account multiple factors including representation from regions that are participating in the trial, availability of skills and expertise related to trial conduct and statistical

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

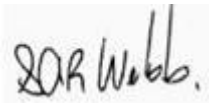
The provision of insurance is specified in each RSA.

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



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ITSC Member
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ITSC Member
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Scott Berry

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Roger Lewis

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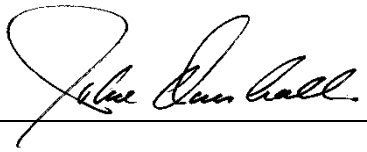

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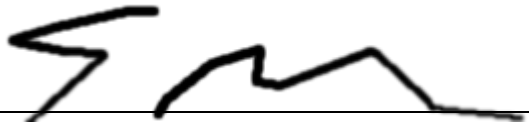

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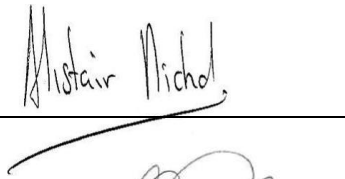

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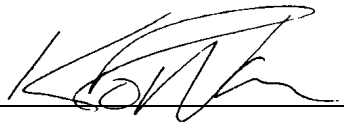

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5. BACKGROUND & RATIONALE

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.

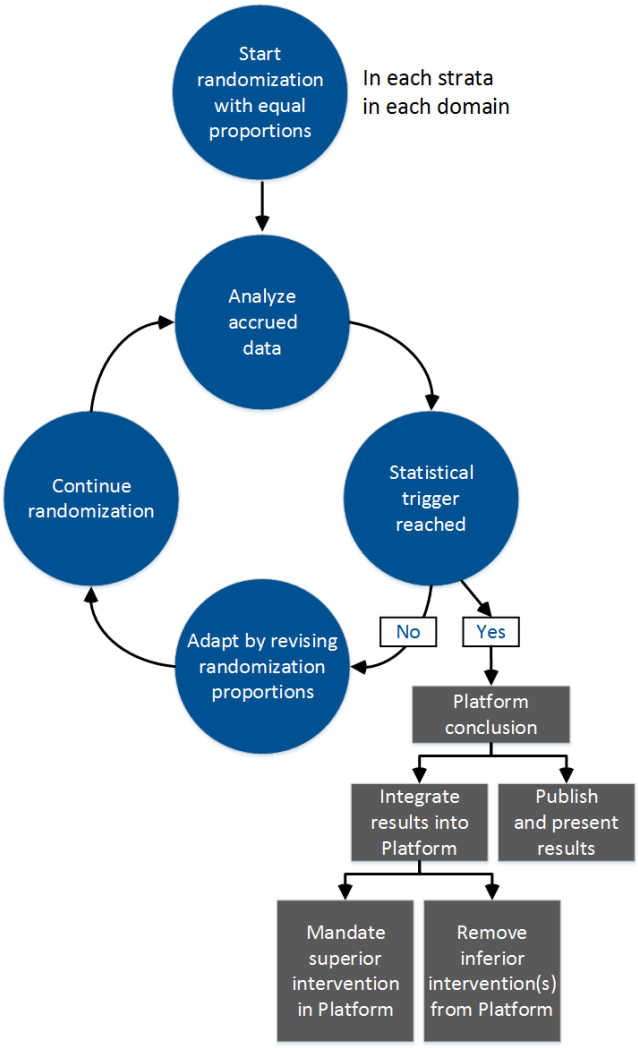
The algorithm by which a Platform Conclusion is reached is different for Statistical Triggers of superiority or inferiority, compared to those triggers that arise because of equivalence. Where the Statistical Trigger is for superiority or inferiority, so long as the DSMB is satisfied that the Statistical 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

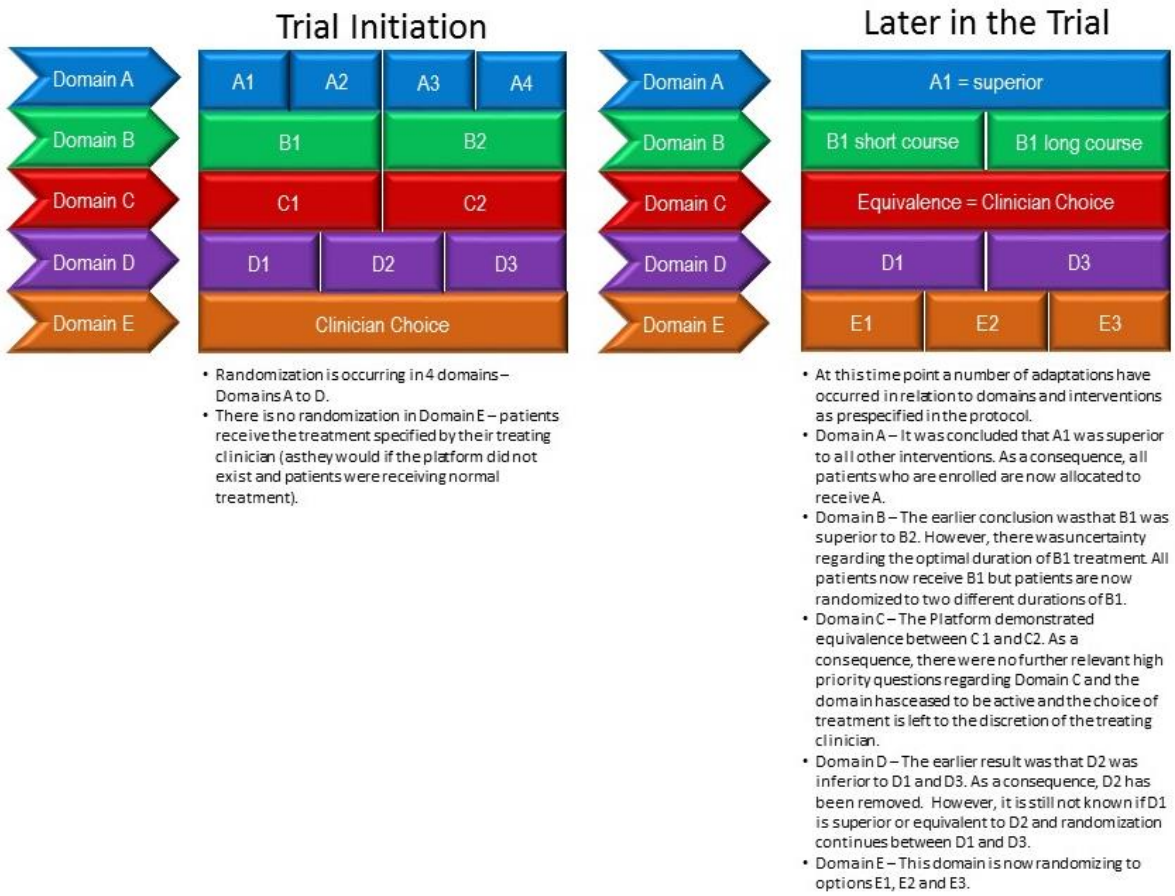
et al., 2013, Meurer et al., 2012, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016) An additional advantage is that dissemination of such results does not interrupt the conduct of the platform. In a single REMAP, there is no need for the "start-and-stop" periods 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



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).

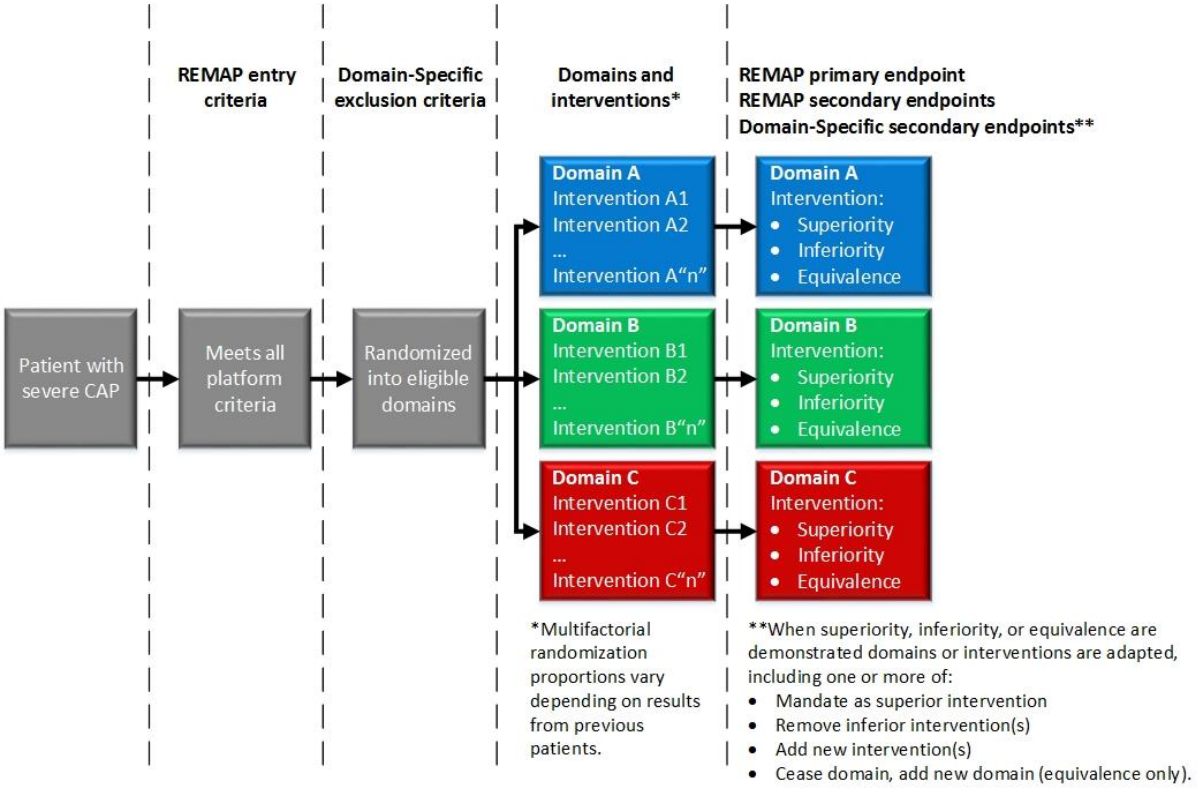
7. SUMMARY OF TRIAL DESIGN

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:

1. 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.
2. 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.
3. 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.

8.1.1. Vanguard sites

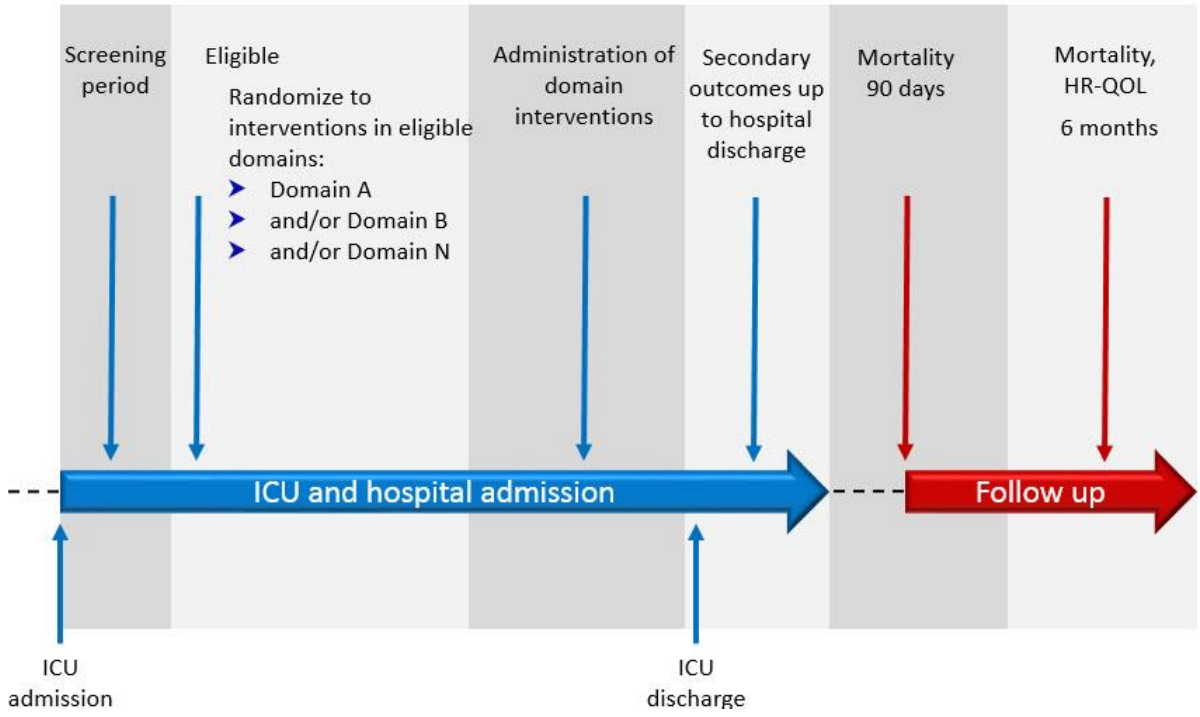
In each region or at the initiation of a new domain or both, the trial may consider commencing with only a small number of vanguard sites. The purpose of commencing the trial at vanguard sites is to learn about the effectiveness of different options for trial processes so that this information about

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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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

$$\log\left(\frac{\pi}{1-\pi}\right) = \sum_{R=1}^{R} \nu_R + \sum_{k=1}^{K}\sum_{s=1}^{S} \alpha_{s,g_k} + \sum_{age=1}^{AGE} \lambda_{age} + \sum_{T=1}^{T} \theta_T + \sum_{d=1}^{D}\sum_{j=1}^{J_d} \beta_{d_j} + \sum_{k=1}^{K}\sum_{d=1}^{D}\sum_{j=1}^{J_d} I(g_k = 2)\gamma_{kd_j} + \sum_{d=1}^{D}\sum_{j=1}^{J_d}\sum_{d'=d+1}^{D}\sum_{j'=1}^{J'_{d'}} \delta_{d_j d'_{j'}}$$

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.

$\gamma_{kd_j}$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:

$$[\nu_R] \sim N\left(\mu_{C_R}, \tau^2_{C_R}\right) R = 2, \ldots, N_R,$$

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:

$$\left[\beta_{d_j}\right] \sim N(0, 10^2).$$

For the set of nested interventions within a domain, the prior for interventions within the nest is

$$\left[\beta_{d_j}\right] \sim N\left(\mu_\beta, \tau_\beta^2\right),$$

With hierarchical priors

$$[\mu_\beta] \sim N(0, 10^2); [\tau_\beta^2] \sim IG(0.125, 0.00281).$$

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_β^2.

For the purpose of assessing statistical triggers that lead to platform decisions, the analysis will be repeated, with nested interventions pooled together ($\tau_{\beta}^{2} = 0$). 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,

$$\left[\gamma_{kd_j}\right] \sim N(0, 10^2)$$

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

$$\left[\gamma_{kd_j}\right] \sim N(0, 0.15^2)$$

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:

$$\left[\delta_{d_j,d'_{j'}}\right] \sim N(0, 10^2)$$

which is described in the protocol as lambda = infinity.

- Finally, the prior for the interaction parameter may be selected as

$$\left[\delta_{d_j,d'_{j'}}\right] \sim N(0, 0.05^2)$$

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:

$$O_{g_k}(r) = \frac{1}{M}\sum_{m=1}^{M} I\left[\pi_{r,g_k} < \pi_{q,g_k} \text{ for all } q \neq r\right]$$

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 $\Lambda_{g_k}(d_j)$:

$$\Lambda_{g_k}(d_j) = \frac{1}{M}\sum_{m=1}^{M} I\left[d_j \in r | \pi_{r,g_k} < \pi_{q,g_k} \text{ for all } q \neq r\right].$$

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.

Domain-Specific Appendix:
ANTIBIOTIC DOMAIN

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

Antibiotic Domain-Specific Appendix Version 3 dated 10 July 2019

Summary

In this domain of the REMAP-CAP trial, participants with community-acquired pneumonia admitted to participating intensive care units requiring empiric antibiotic therapy will be randomized to receive one of up to 5 antibiotic interventions depending on availability and acceptability:

- Ceftriaxone + Macrolide
- Moxifloxacin or Levofloxacin
- Piperacillin-tazobactam + Macrolide
- Ceftaroline + Macrolide
- Amoxicillin-clavulanate + Macrolide

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

<table>
<tr><th colspan="3">Beta-lactam and Macrolide Options</th></tr>
<tr><td>Beta-Lactam interventions for this site</td><td></td><td>Combined with one IV macrolide option and one enteral option chosen by site</td></tr>
<tr><td>☐ Ceftriaxone</td><td rowspan="5">One of beta-lactam interventions (randomized) combined with an Intravenous (IV) option and an enteral macrolide option</td><td rowspan="2">☐ IV Azithromycin
☐ IV Clarithromycin
☐ IV Erythromycin
☐ No IV preparation</td></tr>
<tr><td>☐ Piperacillin-tazobactam</td></tr>
<tr><td>☐ Ceftaroline</td><td rowspan="2">☐ Enteral Azithromycin
☐ Enteral Clarithromycin
☐ Enteral Roxithromycin
☐ No Enteral preparation</td></tr>
<tr><td>☐ Amoxicillin-clavulanate</td></tr>
<tr><td colspan="3">Respiratory Fluroquinolone Options</td></tr>
<tr><td>☐ Moxifloxacin</td><td rowspan="2">Fluroquinolone options chosen by site (randomized)</td><td rowspan="2"></td></tr>
<tr><td>☐ Levofloxacin</td></tr>
</table>

REMAP-CAP: Antibiotic Domain Summary	
Interventions	• Ceftriaxone + Macrolide • Moxifloxacin or Levofloxacin • Piperacillin-tazobactam + Macrolide • Ceftaroline + Macrolide • Amoxicillin-clavulanate + Macrolide
Unit-of-Analysis and Strata	There is one unit-of-analysis in this domain. Analysis and Response Adaptive Randomization are applied to all randomized patients with no strata utilized.
Evaluable treatment-by-treatment Interactions	No interactions will be evaluated with any other domain.
Nesting	There is one nest, comprising Ceftriaxone + Macrolide, Piperacillin-tazobactam + Macrolide, Ceftaroline + Macrolide, and Amoxicillin-clavunate + Macrolide
Timing of Reveal	Randomization with Immediate Reveal and Initiation
Inclusions	Inclusion criteria are the same as the REMAP see Core Protocol Section 7.4.1

Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following:
	• Received more than 48 hours of intravenous antibiotic treatment for this index illness
	• More than 24 hours has elapsed since ICU admission
	• Known hypersensitivity to all of the study drugs in the site randomization schedule
	• A specific antibiotic choice is indicated, for example:
	  ○ Suspected or proven concomitant infection such as meningitis
	  ○ Suspected or proven infection with resistant bacteria where agents being trialed would not be expected to be active. This includes cystic fibrosis, bronchiectasis or other chronic suppurative lung disease where infection with *Pseudomonas* may be suspected but does not include patients with suspected methicillin-resistant staphylococcus aureus (MRSA) infection (see MRSA below).
	  ○ Febrile neutropenia or significant immunosuppression (including organ or bone marrow transplantation, human immunodeficiency virus (HIV) Infection with CD4 cell count <200 cells/μL, systemic immunosuppressive, systemic corticosteroids comprising prednisolone, or equivalent, ≥20mg/day for > 4 preceding weeks).
	  ○ Suspected melioidosis (tropical sites during melioidosis season – see melioidosis below)
	  ○ There is specific microbiological information to guide specific antibacterial therapy
	• The treating clinician believes that participation in the domain would not be in the best interests of the patient

Intervention-Specific Exclusions	• Known non-serious hypersensitivity to penicillins will result in exclusion from receiving interventions that include piperacillin and amoxicillin • Known non-serious hypersensitivity to cephalosporins will result in exclusion from receiving interventions that include ceftriaxone and ceftaroline • Known serious hypersensitivity to beta-lactams, including penicillins or cephalosporins, will result in exclusion from interventions that include piperacillin, amoxicillin, ceftriaxone, and ceftaroline. • Known hypersensitivity to moxifloxacin or levofloxacin will result in exclusion from moxifloxacin or levofloxacin intervention • Known serious hypersensitivity to the macrolide will result in exclusion from interventions that include piperacillin, amoxicillin, ceftriaxone, and ceftaroline. • Known or suspected pregnancy will result in exclusion from moxifloxacin or levofloxacin and ceftaroline interventions. It is normal clinical practice that women admitted who

	are in an age group in which pregnancy is possible will have a pregnancy test conducted. The results of such tests will be used to determine interpretation of this exclusion criteria.
Outcome measures	Primary REMAP endpoint: all-cause mortality at 90 days. 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 enrollment): • Multi-resistant organisms (MRO) colonization/infection: Isolation of multi-drug resistant (MDR) bacteria from clinical or screening specimens including vancomycin resistant enterococci (VRE), methicillin-resistant Staphylococcus aureus (MRSA), extended spectrum beta-lactamase (ESBL)-producing enterobacteriacae, carbapenem resistant enterobacteriacae (CRE). • *C. difficile* illness based on detection from feces using current standard of care diagnostics used at site • Serious Adverse Events (SAE) as defined in CORE protocol

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1. ABBREVIATIONS

ATS	American Thoracic Society
CAP	Community Acquired Pneumonia
C. difficile	*Clostridium difficile*
CVVHF	Continuous Veno-Venous Hemofiltration
COPD	Chronic Obstructive Pulmonary Disease
CRE	Carbapenem Resistant Enterobacteriacae
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
eGFR	estimated Glomerular Filtration Rate
ESBL	Extended Spectrum Beta-Lactamase
HIV	Human Immunodeficiency Virus
hMPV	Human Metapneumovirus
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
IV	Intravenous
MDR	Multi-Drug Resistance
MERS	Middle East Respiratory Syndrome
MRO	Multi-Resistant Organisms
MRSA	Methicillin-Resistant Staphylococcus Aureus
RCT	Randomized Controlled Trial
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RAR	Response Adaptive Randomization
RSA	Region-Specific Appendix
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
VRE	Vancomycin Resistant Enterococci

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. ANTIBIOTIC DOMAIN-SPECIFIC APPENDIX VERSION

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

3.1. Version history

Version 1: Approved by the Antibiotic Domain-Specific Working Group (DSWG) on 18 November 2016

Version 1.1: Approved by the Antibiotic DSWG on 30 March 2017

Version 2: Approved by the Antibiotic DSWG on 12 December 2017

Version 3: Approved by the Antibiotic DSWG on 10 July 2019

4. ANTIBIOTIC DOMAIN GOVERNANCE

4.1. Domain members

Chair:

Professor Allen Cheng

Members:

Professor Richard Beasley

Professor Marc Bonten

Dr. Nick Daneman

Dr. Lennie Derde

Dr. Robert Fowler

Associate Professor David Gattas

Professor Anthony Gordon

Mr. Cameron Green

Associate Professor Peter Kruger

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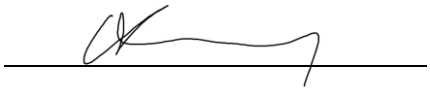
5. ANTIBIOTIC DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

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

Chair
Allen Cheng



Date 10 July 2019

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within REMAP-CAP to test the effectiveness of different empiric antibiotic treatments in patients with severe community-acquired pneumonia (CAP) who are admitted to an Intensive Care Unit (ICU).

6.2. Domain-specific background

Antibiotics are an essential component of therapy for all patients with suspected or proven CAP. In patients with sepsis (including pneumonia) who have organ dysfunction, the International Surviving Sepsis Campaign Guidelines recommend initiation of antibiotics within 60 minutes of presentation. (Dellinger et al., 2013)

6.2.1. Microbiology of CAP

In the majority of cases of CAP, no microbiological diagnosis is made. (Charles et al., 2008) In patients in whom a microbiological diagnosis is made, the organism that is isolated most commonly is *Streptococcus pneumoniae.* Other bacteria that cause CAP include *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, and a range of gram-negative organisms. Although studies have demonstrated that clinical features are not specific to bacterial aetiology, the so-called "atypical" pathogens include Legionella species, *Mycoplasma pneumoniae*, and *Chlamydiphila pneumoniae*. Since the advent of sensitive nucleic acid tests, there is an increasing recognition of the role of viral pathogens, particularly influenza viruses and respiratory syncytial virus (RSV), either as the primary pathogen or associated with secondary bacterial pneumonia. (Musher and Thorner, 2014) Pathogens associated with outbreaks include *Legionella* spp, viral pathogens (particularly in closed environments such as cruise ships and institutions) and emerging infectious diseases such as Middle East Respiratory Syndrome (MERS) coronavirus.

Many studies have characterised the microbiological cause of infection in patients with severe CAP and a summary of these has been reported previously. (Mandell et al., 2007, Lim et al., 2009, Musher et al., 2013, Woodhead et al., 2011, Wiersinga et al., 2012) While there are clinically significant differences between studies in healthcare delivery (including criteria for hospital and ICU admission), the population under study and other epidemiological features, and study methodology, the distribution of identified pathogens is remarkably consistent in temperate developed countries.

The results of studies that have reported the microbiology findings in patients with CAP are outlined in Table 1.

Table 1: Distribution of identified pathogens in hospitalized patients with CAP in selected studies

Type of organisms	Australia (2004-2008) (Charles et al., 2008)	Europe (Woodhead, 2002)	United States (Musher et al., 2013)
Gram positive bacteria	*Streptococcus pneumoniae (13.9%)* *Staphylococcus aureus (1.2%)*	*Streptococcus pneumoniae (25.9%)* *Staphylococcus aureus (1.4%)*	*Streptococcus pneumoniae (24.7%)* *Staphylococcus aureus (3.5%)*
Gram negative bacteria	*Haemophilus influenzae (5.1%)* *Pseudomonas aeruginosa (1.6%)* *Enterobacteriaecae (1.5%)* *Moraxella catarrhalis (0.8%)*	*Haemophilus influenza (4.0%)* *Moraxella catarrhalis (2.5%)* *Gram-negative enteric bacteria (2.7%)*	*Haemophilus influenza (4.6%)* *Pseudomonas aeruginosa (2.3%)* *Klebsiella pneumoniae (0.8%)* *Escherichia coli (0.8%)* *Moraxella (0.4%)*
"Atypical"	*Mycoplasma pneumoniae (8.8%)* *Legionella (3.4%)* *Chlamydophila species (1.7%)*	*Legionella* spp*. (4.9%)* *Mycoplasma pneumoniae (7.5%)* *Chlamydia pneumoniae (7.0%)* *Chlamydia psittaci (1.9%)*	
Viral pathogens	*Influenza (7.7%)* *Picornaviruses (5.2%)* *RSV (1.9%)*	*Viruses (10.9%)*	*Rhinovirus (10%)* *Coronavirus (2.7%)* *Parainfluenza virus (1.5%)* *RSV (1.2%)* *hMPV (1.2%)* *Influenza (0.4%)*
Other	*Other pathogens (2.3%)* *Unknown (54.4%)*	*Coxiella burnetii (0.8%)* *Other pathogens (2.2%)* *Unknown (43.8%)*	*Other pathogens (6.9%)* *Unknown (45.9%)*

** More than one pathogen detected in 8.5% of patients, including both a viral and bacterial pathogen in 5.3%*

Drug resistant pathogens are an increasing concern globally. Macrolide resistant pneumococci are of little clinical relevance in patients treated with beta-lactams (Cheng and Jenney, 2016) and it appears that poor outcomes linked to penicillin resistant pneumococci (Tleyjeh et al., 2006) are likely to be attributed to age, underlying disease and severity of illness rather than treatment failure. (Moroney et al., 2001, Yu et al., 2003) Of greater concern is the advent of community-acquired

methicillin resistant *Staphylococcus aureus*, particularly those associated with the Panton Valentine leucocidin. (Rubinstein et al., 2008)

6.2.2.Guidelines recommend a number of different antibiotic treatment options

A "respiratory" quinolone (moxifloxacin or levofloxacin) or combination antimicrobial therapy with a beta-lactam and a macrolide, are both recommended empiric treatment for CAP in national and international guidelines. (Mandell et al., 2000, Mandell et al., 2007, Woodhead et al., 2011) Data, mostly from retrospective observational analyses, report that guideline-concordant therapy is associated with a mortality benefit in CAP (Baudel et al., 2009, Frei et al., 2010), but whether one of these options results in a lower mortality than the other remains an open question. It has been suggested that fluoroquinolone treatment may be optimal for pneumonia due to *Legionella* spp, but randomized clinical trial data are lacking. (Asadi et al., 2012) A summary of different recommendations in guidelines for the treatment of severe CAP is displayed in Table 2.

Table 2: Empiric antibiotic treatments recommendations for patients with severe pneumonia (without risk factors for pseudomonas) requiring intensive care

Guideline	First line	Second line
British Thoracic Society (Lim et al., 2009)	1. Co-amoxiclav AND macrolide (clarithromycin)	1. Cefuroxime or ceftriaxone AND clarithromycin
United States Infectious Diseases Society of America (IDSA)/ the American Thoracic Society (ATS) (Mandell et al., 2007)	1. Cefotaxime, ceftriaxone, or ampicillin-sulbactam AND either (a) azithromycin or (b) a respiratory fluoroquinolone	1. Respiratory fluoroquinolone AND aztreonam
Australia (Antibiotic Expert Groups, 2014)	1. Ceftriaxone AND azithromycin	1. Moxifloxacin
Canada (Mandell et al., 2000)	1. Moxifloxacin or levofloxacin	1. Cefuroxime, ceftriaxone or beta-lactam/beta-lactamase inhibitor AND intravenous (IV) macrolide
Swedish guidelines (Spindler et al., 2012)	1. Cephalosporin AND macrolide 2. Benzylpenicillin AND respiratory fluoroquinolone	
Europe European Society of Clinical Microbiology and Infectious Diseases / European Respiratory	1. Non-antipseudomonal 3rd generation cephalosporin AND macrolide 2. Non-antipseudomonal 3rd generation cephalosporin AND either	

Society (Woodhead et al., 2011)	(a) Moxifloxacin or (b) Levofloxacin	
Netherlands Dutch Working Party on Antibiotic Policy / Dutch Association of Chest Physicians (Wiersinga et al., 2012)	1. Moxifloxacin or levofloxacin 2. Penicillin (or amoxicillin) AND ciprofloxacin 3. 2nd or 3rd generation cephalosporin AND macrolide.	

The most studied interventions for pneumonia have involved antibiotic interventions. A 2008 systematic review that compared respiratory quinolones with beta-lactam and macrolide combinations identified 23 clinical trials that enrolled 7885 patients. (Vardakas et al., 2008) A higher proportion of patients treated with fluoroquinolones had treatment success (defined as clinical cure or improvement) compared with comparator-treated patients (primarily beta-lactam monotherapy and or macrolides), but there were no significant differences in mortality, and the majority of patients in these studies did not have severe pneumonia and were not treated an ICU.

Clinical trials that tested the addition of a macrolide to beta-lactams have not demonstrated clinical benefit. One trial found a shorter time to clinical stability in patients with severe pneumonia although the difference in this small trial was not statistically significant. (Garin et al., 2014) Additionally, there were no differences in other groups or outcomes including length of stay or mortality. A recent cluster randomized trial of beta-lactam monotherapy, beta-lactam and macrolide combination therapy, or fluoroquinolone monotherapy in patients with moderate severity CAP (who were not admitted to ICU at the time of randomization) did not find any differences in mortality or hospital length of stay associated with any strategy. (Postma et al., 2015) A systematic review of antibiotic treatments recommended in the IDSA/ATS guideline did not find any conclusive evidence that “atypical” coverage was associated with better outcomes in clinical trials, although an association with better outcome was found for treatments that included macrolides or quinolones in lower quality observational studies. (Lee et al., 2016)

Most of these studies were performed in hospitalized patients with CAP in whom mortality was relatively low and statistical power limited. Although the available evidence suggests that patients with moderate or severe pneumonia may benefit from atypical coverage, the choice of beta-lactam and whether atypical coverage should include a macrolide (in combination with beta-lactam) or a quinolone (as monotherapy) in severe CAP remains an open question.

6.2.3. There is a diversity of antibiotics used in clinical practice

Current guidelines recommend a number of different antibiotic treatment options and it is likely that others options are also being used at individual hospitals or by individual clinicians.

A survey of Australian and New Zealand ICU specialists indicates that more than 95% administer a beta-lactam antibiotic in combination with a macrolide (azithromycin) for empiric therapy but there is substantial variation in the choice of beta-lactam. The majority of patients receive ceftriaxone, as recommended in Australian guidelines, but one third of ICU specialists use piperacillin-tazobactam (unpublished data from the REMAP-CAP investigators). Although piperacillin-tazobactam has wider microbiological coverage, it penetrates less well into lung tissue, is less potent against pneumococci (the commonest cause of severe CAP), and is predicted to impose increased selection for resistant organisms. (Sime et al., 2012)

In New Zealand, IV amoxicillin-clavulanate and cefuroxime (both not available in Australia as IV formulations currently) are also used widely. A 2013 study found that both second/third generation cephalosporins (58%) and co-amoxiclav (36%) were used in patients with severe pneumonia defined by CURB-65 score. (Aikman et al., 2013)

Studies suggest a wide diversity of antibiotic regimens are used for pneumonia in Europe; the most common antibiotics used included penicillin/beta lactamase inhibitors, macrolides, quinolones and third generation cephalosporins, broad spectrum penicillins and second generation cephalosporins (Ansari et al., 2009, Torres et al., 2014)

6.2.4. New antibiotics may be more effective but data are limited.

Ceftaroline is an antibiotic, newly licensed for CAP in a range of countries, with a similar spectrum of activity to ceftriaxone, but with the additional advantage of being active against methicillin-resistant *Staphylococcus aureus*. In some Randomized Controlled Trials (RCTs) of patients with moderate severity CAP, ceftaroline was superior to ceftriaxone in achieving clinical cure. (File et al., 2011, Low et al., 2011) Recent high-profile reviews and guidelines list ceftaroline as a recommended first-line choice for severe CAP, even though the evidence is derived from patients who were not critically ill. (Eccles et al., 2014, Musher and Thorner, 2014) Ceftaroline is approximately 500 times more expensive than ceftriaxone currently.

6.2.5. Both the efficacy as well as adverse effects of antibiotics need to be considered

RCTs that compare antibiotics to treat infections in ICU patients have demonstrated unexpected differences in mortality. For example, doripenem was associated with a higher mortality than

imipenem in patients with ventilator associated pneumonia (Kollef et al., 2012, Yahav et al., 2011) Moreover, the choice of agent may influence the risk of nosocomial super-infection including *Clostridium difficile (C. difficile)*. Despite the ubiquity of the agents used to treat severe CAP in clinical practice there have been no RCTs, conducted in critically ill patients, with sufficient statistical power to detect differences in clinically relevant endpoints. It is imperative that the comparative effectiveness of alternative beta-lactam agents and the role of respiratory quinolones is established, including any differences in acquisition of resistant organisms and *C. difficile.*

6.2.6. All antibiotics used in CAP have a well-established safety profile

Ceftriaxone, piperacillin-tazobactam, amoxicillin-clavulanate, moxifloxacin and levofloxacin have a long history of use for pneumonia as well as for other indications and are regarded as having a good safety profile. The pharmacokinetics of all drugs may be altered in critically ill patients due to pathophysiological changes including altered volumes of distribution, augmented renal clearance, renal failure and hepatic failure. (Roberts and Lipman, 2009)

Both immediate and delayed hypersensitivity have been described with ceftriaxone, piperacillin-tazobactam, amoxicillin-clavulanate and moxifloxacin, and include rare cases of anaphylaxis, Stevens-Johnson syndrome and toxic epidermal necrolysis. Diarrhea, including that due to *C. difficile*, is a recognized complication of all antibiotic therapy.

Pipericillin-tazobactam and moxifloxacin have been associated with hematological abnormalities, including agranulocytosis, hemolytic anemia and pancytopenia. Amoxicillin-clavulanate has been associated with cholestasis and hepatitis. Moxifloxacin has been associated with a prolonged QT interval and arrhythmias. Pipericillin-tazobactam, ceftaroline and moxifloxacin have been associated with seizures but this is uncommon with doses within current clinical practice guidelines.

6.2.7. Transition from empiric to targeted antibiotic therapy

Microbiological tests identify a causative organism in less than 50% of patients with CAP. (Jain et al., 2015) It is almost always the case that empiric antibiotic therapy is commenced before a microbiological diagnosis is available. Standard practice and international guidelines recommend that where a causative organism is identified and antibiotic susceptibilities are available that an antibiotic with a narrow spectrum of action that is active against the infecting organism is substituted for the initial empiric therapy. This domain tests only empiric therapy and the domain intervention is considered complete once microbiological test results are available that can guide appropriate targeted antibiotic therapy or, in the absence of identification of a causative organism

for which its antimicrobial susceptibility is known, that sufficient time and clinical improvement have occurred to warrant cessation or de-escalation of initial empiric therapy.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the comparative effectiveness of different antibiotics or antibiotic combinations for patients with severe CAP requiring empiric antibiotic therapy .

We hypothesize that the probability of all-cause mortality at 90 days after enrollment will differ based on the allocated empiric antibiotic treatment. The following interventions will be available:

- Ceftriaxone + Macrolide
- Moxifloxacin or Levofloxacin
- Piperacillin-tazobactam + Macrolide
- Ceftaroline + Macrolide
- Amoxicillin-clavulanate + Macrolide

Each participating site has the option to opt-in to two or more interventions to be included in the site randomization schedule depending on local clinical preference, usual practice, acceptable practice, and the availability of the agent at that site.

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial (see Core Protocol Section 7). Treatment allocation will be adaptive, as described in the Core Protocol Section 7.5.2.

8.1. Population

The REMAP enrolls patients with severe CAP admitted to ICU (see Core Protocol Section 7.3).

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 (see Core Protocol Section 7.4). Patients eligible for the REMAP may have conditions that exclude them from the Antibiotic Domain, or from one or more of the individual interventions available within this domain.

8.2.1. Domain inclusion criteria

Nil.

8.2.2. Domain exclusion criteria

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

- Received more than 48 hours of IV antibiotic treatment for this index illness
- More than 24 hours has elapsed since ICU admission
- Known hypersensitivity to all of the study drugs in the site randomization schedule
- A specific antibiotic choice is indicated, for example:
    - Suspected or proven concomitant infection such as meningitis
    - Suspected or proven infection with resistant bacteria where agents being trialed would not be expected to be active. This includes cystic fibrosis, bronchiectasis or other chronic suppurative lung disease where infection with *Pseudomonas* may be suspected but does not include patients with suspected methicillin-resistant staphylococcus aureus (MRSA) infection (see MRSA below).
    - Febrile neutropenia or significant immunosuppression (including organ or bone marrow transplantation, human immunodeficiency virus (HIV) Infection with CD4 cell count <200 cells/µL, systemic immunosuppressive, systemic corticosteroids comprising prednisolone, or equivalent, ≥20mg/day for > 4 preceding weeks).
    - Suspected melioidosis (tropical sites during melioidosis season – see melioidosis below)
    - There is sufficient microbiological information to guide specific antibacterial therapy
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

MRSA: Patients in whom MRSA might be suspected should be included (see Section 8.3).

Melioidosis: Sites in tropical areas (defined in Australia as hospitals located north of a latitude of 21°S) will not randomize to the Antibiotic Domain during the melioidosis season (defined as the monsoonal period according to local guidelines).

8.2.3. Intervention exclusion criteria

Prior to the study commencement, sites will select which interventions that patients at their site will be allocated to, based on the current standards of acceptable care, local epidemiology and regulatory status of antibiotics as outlined below.

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons. In such cases, patients will be randomly allocated a remaining intervention from among those available at that site. An example would include patients with a history of a penicillin hypersensitivity, who may receive a cephalosporin or moxifloxacin. Patients may have multiple intervention exclusions (e.g. both a penicillin and a cephalosporin hypersensitivity).

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

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

- Known non-serious hypersensitivity to penicillins will result in exclusion from receiving interventions that include piperacillin and amoxicillin
- Known non-serious hypersensitivity to cephalosporins will result in exclusion from receiving interventions that include ceftriaxone and ceftaroline
- Known serious hypersensitivity to beta-lactams, including penicillins or cephalosporins, will result in exclusion from interventions that include piperacillin, amoxicillin, ceftriaxone, and ceftaroline.
- Known hypersensitivity to moxifloxacin or levofloxacin will result in exclusion from moxifloxacin or levofloxacin intervention
- Known serious hypersensitivity to the macrolide will result in exclusion from interventions that include piperacillin, amoxicillin, ceftriaxone, and ceftaroline.
- Known or suspected pregnancy will result in exclusion from moxifloxacin or levofloxacin and ceftaroline interventions. It is normal clinical practice that women admitted who are in an age group in which pregnancy is possible will have a pregnancy test conducted. The results of such tests will be used to determine interpretation of this exclusion criteria.

8.3. Interventions

8.3.1. Antibiotic interventions

Patients will be randomly assigned to receive one of the following open-label study interventions. While it is expected that all sites will participate in the ceftriaxone intervention, each site has the option to opt-in to one or more of the remaining 4 interventions based on local practice and the availability of the antibiotic in the country. For sites that are including the moxifloxacin or levofloxacin intervention it is strongly encouraged that the sites participate in at least one intervention that includes a cephalosporin and one intervention that includes a penicillin so that causal inference by random allocation is possible for patients who have known non-serious intolerance to either cephalosporins or penicillins but not both. All patients receiving ceftriaxone, piperacillin-tazobactam, ceftaroline, or amoxicillin-clavulanate will also receive a macrolide. Patients allocated to the moxifloxacin or levofloxacin intervention will not receive a macrolide or any beta-lactam or monobactam agent.

The choice of macrolide (see front page) will depend on the availability and acceptability of the agents at each site in the following order of preference;

1. IV azithromycin, with switch to enteral azithromycin when appropriate
2. IV clarithromycin, with switch to enteral azithromycin when appropriate
3. Enteral azithromycin
4. Enteral clarithromycin or roxithromycin
5. IV or enteral erythromycin. Sites in which only erythromycin is available are not able to participate in the Macrolide Duration Domain.

Vancomycin, linezolid or other antimicrobials active against MRSA (other than ceftaroline) may be added if MRSA is suspected at the discretion of the treating clinician, irrespective of the intervention to which the participant is allocated.

8.3.2. Recommended antibiotic dosing

The doses specified are recommended minimum doses and may be modified according to local guidelines or practice.

- Ceftriaxone ≥1 gram IV q24h
- Moxifloxacin 400mg IV q24h or Levofloxacin 750mg IV q24h
- Piperacillin-tazobactam ≥4.5 grams IV q8h

- Ceftaroline 600 mg IV q12h
- Amoxicillin-clavulanate ≥1200mg IV q8h

If no local guidelines exist, it is recommended that subsequent doses of antibiotics will be adjusted for estimated renal function (based on estimated Glomerular Filtration Rate (eGFR)) as follows:

Table 3: Minimum doses of antibiotics, by eGFR

Agent	eGFR >50 ml/min	eGFR10-50 ml/min	eGFR <10	Continuous Veno-Venous Hemofiltration (CVVHF)
Ceftriaxone	1g-2g IV daily	1g-2g IV daily	1g IV daily	1g IV daily
Piperacillin-tazobactam	4.5g IV q6h	(eGFR 20-40) 4.5g IV q8h	(eGFR<20) 4.5g IV q12h	4.5g IV q8h
Ceftaroline	600mg IV q12h	400mg IV q12h	200mg IV q12h	400mg IV q12h
Amoxicillin-clavulanate	1200mg IV q8h	1200mg IV q8h	1200mg IV q12h	1200mg IV q8h
Moxifloxacin	400mg IV q24h	400mg IV q24h	400mg IV q24h	400mg IV q24h
Levofloxacin	750mg IV q24h	(eGFR 20-50) 750mg IV load, 750mg IV q48h	(eGFR<20) 750mg IV load, 500mg IV q48hr	750mg IV load, 500mg IV q48hr

8.3.3. Timing of initiation of antibiotics

In keeping with all international guidelines optimized empiric antibiotic treatment should commence as soon as possible. Usual practice for patients admitted to the ICU with severe CAP is either immediate administration of empiric antibiotics, if antibiotics have not already been administered, or initiation of the empiric antibiotic treatment that will be continued during admission to the ICU, even if antibiotics have been administered already. As such, initiation of antibiotic therapy to a patient with severe CAP, within this REMAP should commence immediately after admission to the ICU.

8.3.4. Duration of administration of antibiotics

The duration of empiric antibiotics will be determined by the treating clinician based on daily reviews of the following criteria:

- Change to enteral antibiotics once patient is clinically stable
- Change to a targeted antibiotic therapy if a microbiological diagnosis has been made
- Cease antibiotics if an alternative diagnosis is made
- Cease antibiotics when there is evidence of sufficient clinical improvement, no microbiological diagnosis has been made and no clinical evidence of deep infection (e.g. empyema or lung abscess). The duration of antibiotic therapy will be decided by the treating clinician and local guidelines.
- Discontinuation if the patient experiences a serious adverse event (SAE) that is thought to be related to a study drug

8.4. Concomitant care

Additional non-beta-lactam antibacterial agents, such as vancomycin, gentamicin, clindamycin or cotrimoxazole, will be permitted at the discretion of the treating clinician. Other beta-lactams, carbapenems (meropenem, imipenem, doripenem, ertapenem), monobactams (aztreonam) and quinolones are not permitted at study enrollment, but a change to these agents is permitted if clinical cultures are positive for a resistant pathogen that necessitates commencement of one of these agents. Administration of an influenza antiviral agent (i.e. oseltamivir) will also be permitted in patients with suspected or confirmed influenza.

Any subsequent change of antibiotics, based on availability of microbiological data, will be permitted at the treating clinician's discretion.

8.4.1. Implications of allocation status for eligibility in other domains

Patients randomized to intervention moxifloxacin will not be included in the Macrolide Duration Domain in this REMAP.

8.5. Endpoints

8.5.1. Primary endpoint

The primary endpoint for this domain is the REMAP primary outcome (all-cause mortality at 90 days) as specified in Core Protocol Section 7.6.1.

8.5.2. Secondary endpoints

All secondary endpoints as specified in the Core Protocol Section 7.6.2.

The domain-specific secondary outcome measures (occurring during the index hospitalization, censored at 90 days after enrollment) will be:

- Multi-resistant organisms (MRO) colonization/infection: Isolation of multi-drug resistant (MDR) bacteria from clinical or screening specimens including vancomycin resistant enterococci (VRE), MRSA, extended spectrum beta-lactamase (ESBL)-producing enterobacteriacae, carbapenem resistant enterobacteriacae (CRE).
- *C. difficile* illness based on detection from feces using current standard of care diagnostics used at site
- Serious adverse event (SAE) as defined in Core Protocol

Table 4: Organisms of interest as baseline or outcome measures

Site	Organisms of interest
Blood, lower respiratory tract (endotracheal suction, bronchoalveolar lavage, sputum), Pleural fluid (e.g. pleural aspirate, chest drain)	*Staphylococcus aureus* *Streptococcus pyogenes*, or *S. pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis* Enterobacteriacae** *Acinetobacter* spp. *Pseudomonas* spp.
Multi resistant organisms from any clinical or screening* site	VRE, MRSA, ESBL- producing Escherichia coli or Klebsiella spp Carbapenem-resistant gram-negative

*screening specimens include fecal/rectal swabs, swabs of intact skin or nose

**Enterobacteriacae includes *Escherichia coli*, *Klebsiella* spp, *Enterobacter* spp.

9. TRIAL CONDUCT

9.1. Microbiology

Isolates will be tested for susceptibility to study antibiotics using routine clinical testing. Specific isolates may be referred to a reference laboratory according to current clinical practice

9.2. Domain-specific data collection

9.2.1. Clinical data collection

Additional domain-specific data will be collected.

- Isolation or detection of MROs
- *C. difficile* isolation from feces

Refer to Core Protocol Section 8.9 for other data collection fields and processes.

9.3. Criteria for discontinuation

Refer to Core Protocol Section 8.7 for criteria for discontinuation of participation in the trial.

9.4. Blinding

9.4.1. Blinding

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

9.4.2. Unblinding

Not relevant.

10. STATISTICAL CONSIDERATIONS

10.1. 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.

10.2. Unit-of-analysis and strata

The unit-of-analysis for this domain is all patients who receive an allocation status in this domain. No strata are applied in the model that is used for analysis and specification of Response Adaptive Randomization (RAR).

10.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal and Initiation (see section 7.8.3.6 in Core Protocol)

10.4. Interactions with interventions in other domains

An *a priori* interaction with the beta-lactam antibiotics and 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 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 Antiviral Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

No interaction is evaluable between the Ventilation Domain and this domain.

10.5. Nesting of interventions

There is one nest within this domain, comprising ceftriaxone + macrolide, piperacillin-tazobactam + macrolide, amoxicillin-clavulanate + macrolide, and ceftaroline + macrolide (see Section 7.8.3.8 in Core Protocol). The rationale for this is that each of these interventions comprises a beta-lactam antibiotic combined with a macrolide. The Macrolide component contributes to all interventions and the beta-lactam agents are all members of the same class of antibiotic.

10.6. Threshold odds ratio delta for equivalence

The threshold odds ratio for equivalence in this domain is that specified in the Core Protocol (Section 7.8.8).

10.7. 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:

- The causative organism, in patients from whom a microbiological diagnosis for the qualifying pneumonia has been made on the basis of culture or other investigations (nucleic acid testing, urinary antigen testing).
- Risk factors for aspiration pneumonia (neuromuscular weakness, hazardous alcohol use)
- Elderly (≥65 years) and non-elderly (<65 years)
- Chronic Obstructive Pulmonary Disease (COPD)
- Shock strata
- Influenza strata
- All potentially evaluable treatment-by-treatment interactions with other domains

11. ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, 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 the incidence of *C. difficile* – associated diarrhea or isolation of MRO organisms.

11.2. Potential domain-specific adverse events

The antibiotics used in this domain largely have a known toxicity profile. Additionally, it is expected that a high proportion of critically ill patients who will be enrolled in this trial will experience mortality or substantial morbidity.

The following potential adverse outcomes relating to antibiotic therapy will be reported as secondary outcome measures (and do not need to be reported separately as SAEs):

- Acquisition of multi-drug resistant organisms in clinical or screening specimens (including VRE, MRSA, ESBL or CRE)
- *C. difficile* – associated diarrhea

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).

11.3. Domain-specific consent issues

All the antibiotics to be tested in this domain are approved for this indication or are in common use in many countries for CAP or both. Sites will be able to opt out of interventions for all patients at that site if they believe that an intervention is not part of reasonable care of patients with pneumonia, or are not approved for use in the country, or conflict with local antimicrobial stewardship considerations. Additionally, clinicians may choose not to enroll individual patients if they feel that participation is not in the patient's best interests, and safety criteria are used to exclude patients from individual interventions for appropriate clinical reasons (e.g. hypersensitivity to one or more study drugs).

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

Pregnant women are susceptible to pneumonia and a number of different antibiotics, including amoxicillin-clavulanate and ceftriaxone, are widely used and have a track record of safety in this population. Pregnant women will be excluded from the moxifloxacin and ceftaroline interventions.

Ceftaroline is not in widespread use but is licensed for use for CAP by regulatory agencies in Australia, New Zealand, the European Union and North America and has been recommended as appropriate therapy for patients with severe CAP in some reviews. (Jain et al., 2015)

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. This domain has not received any additional domain-specific funding.

12.2. Funding of domain interventions and outcome measures

Sites that participate in the ceftaroline intervention will have this antibiotic provided by the trial in Australia and New Zealand. Astra Zeneca have indicated in-principle support for the provision of ceftaroline for at least some participating countries (Australia and New Zealand). The contract between the trial Sponsors and Astra Zeneca must meet criteria set out in the Core Protocol for

provision of interventions by commercial entities. Arrangements for supply of ceftaroline will be set out in operational documents.

All other antibiotics will be provided by participating hospitals on the basis that if the patient was not participating in the trial, appropriate antibiotics would always have been indicated and provided by the treating hospital.

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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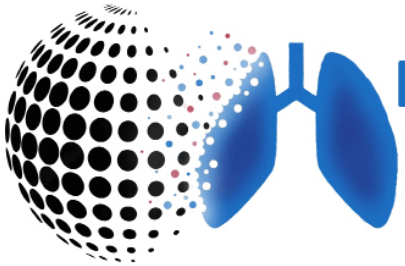

Domain-Specific Appendix:
ANTIVIRAL DOMAIN

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

Antiviral Domain-Specific Appendix Version 1.0 dated 10 July 2019

Summary

In this domain of the REMAP-CAP trial, participants with community-acquired pneumonia admitted to participating intensive care units with suspected or microbiological testing-confirmed influenza infection will be randomized to receive one of up to 3 interventions depending on availability and acceptability:

- No antiviral agents (no placebo)
- 5 days of oseltamivir
- 10 days of oseltamivir

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

☐ No antiviral agents (no placebo)

☐5 days of oseltamivir

☐10 days of oseltamivir

REMAP-CAP: Antiviral Domain Summary	
Interventions	• No antiviral agents (no placebo) • 5 days of oseltamivir • 10 days of oseltamivir
Unit of Analysis and Strata	The unit-of-analysis for this domain is the influenza present stratum. Analysis and Response Adaptive Randomization are applied by influenza strata. Some patients will be randomized who are in the influenza absent stratum and will be analysed separately, but borrowing will be permitted. The shock strata does not contribute to the unit-of-analysis for this domain.
Evaluable treatment-by-treatment Interactions	Treatment-treatment interactions will be evaluated between interventions in this domain and interventions in the Corticosteroid Domain. No other interactions will be evaluated with any other domain.
Nesting	There is one nest, comprising the 5- and 10-day duration of oseltamivir.
Timing of Reveal	Randomization with Immediate Reveal and Initiation.
Inclusions	Inclusion criteria are the same as the REMAP see Core Protocol Section 7.4.1, and • Influenza infection is suspected by the treating clinician or has been confirmed by microbiological testing
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • More than 24 hours has elapsed since Intensive Care Unit (ICU) admission • Known hypersensitivity to oseltamivir • Patient has already received two or more doses of oseltamivir or other neuraminidase inhibitors • Intention to commence or continue, if already commenced, an antiviral active against influenza other than oseltamivir • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	Nil, not applicable.
Outcome measures	Primary REMAP endpoint: all-cause mortality at 90 days. 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): • Virologic endpoints (at selected sites): o Change from baseline in influenza virus levels measured at D3 and D7 or ICU discharge in upper and lower respiratory tract specimens. o Incidence of emergence of amino acid changes associated with reduced susceptibility to oseltamivir at D3 and D7 or ICU discharge. • Serious adverse event (SAE) as defined in Core Protocol

TABLE OF CONTENTS

1. ABBREVIATIONS

BMI	Body Mass Index
CAP	Community Acquired Pneumonia
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
ECDC	European Centre for Disease prevention and Control
eGFR	estimated Glomerular Filtration Rate
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RAR	Response Adaptive Randomization
RSA	Region-Specific Appendix
SAE	Serious Adverse Event

2. PROTOCOL APPENDIX STRUCTURE

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

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

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

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

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

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

The current version of the Core Protocol, DSAs, RSAs and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org).

3. ANTIVIRAL DOMAIN-SPECIFIC APPENDIX VERSION

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

3.1. *Version history*

Version 1: Approved by the Antiviral Domain-Specific Working Group (DSWG) on 10 July 2019.

4. ANTIVIRAL DOMAIN GOVERNANCE

4.1. *Domain members*

Chair: Dr. Srinivas Murthy

Members: Professor Derek Angus
Dr. Scott Berry
Professor Marc Bonten
Professor Allen Cheng
Dr. Lennie Derde
Professor Herman Goossens
Dr. Sebastiaan Hullegie
Professor Menno de Jong
Professor John Marshall
Dr. Colin McArthur
Dr. Tim Uyeki

Professor Steve Webb

4.2. *Contact Details*

Chair:

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5. ANTIVIRAL DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

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

Chair _____ Date 10 July 2019

6. BACKGROUND AND RATIONALE

6.1. *Domain definition*

This is a domain within the REMAP-CAP to test the effectiveness of different antiviral strategies for suspected or microbiological testing-confirmed influenza virus infection in patients with concomitant severe community-acquired pneumonia (CAP) who are admitted to an Intensive Care Unit (ICU).

6.2. *Domain-specific background*

Seasonal influenza is estimated to cause approximately 300,000 to 650,000 respiratory deaths worldwide. (Iuliano et al., 2018) Achieving improvements in influenza mortality is a key focus of

public health agencies around the world, through improvements in prevention, diagnostics and therapeutics.

Currently, recommended antiviral agents have not been studied in placebo-controlled, randomized comparative studies to demonstrate a benefit on survival of the severely ill in proven influenza infection. (Dobson et al., 2015, Heneghan et al., 2016, Jefferson et al., 2014, Uyeki et al., 2019) A number of systematic reviews and meta-analyses have been performed, with conflicting results depending upon the analytic strategy employed and the datasets used. (Dobson et al., 2015, Jefferson et al., 2014, Muthuri et al., 2014) All prior fully-enrolled randomized studies have been performed in otherwise healthy outpatients, with debatable relevance to the severely ill population. These mostly reveal a reduction in fever and symptom duration of approximately 1-2 days when oseltamivir is initiated early in the symptom course. (Jefferson et al., 2014, Dobson et al., 2015) Meta-analyses of observational studies and individual-patient data meta-analyses of studies performed in hospitalized adults reveal that there is a possible benefit for reducing mortality in adults, although this result is inconsistent across studies. (Doll et al., 2017, Muthuri et al., 2014, Yang et al., 2012, Heneghan et al., 2016, Choi et al., 2017, Wolkewitz and Schumacher, 2016)

Given the importance of ensuring a robust evidence base for a high-burden disease with a possibility for a future pandemic, the objective of this domain is to determine the effectiveness of different antiviral strategies in severely ill patients with pneumonia and confirmed influenza virus infection.

Oseltamivir is a neuraminidase inhibitor that has been approved for the early treatment of uncomplicated influenza virus infection. Part of the justification for its use, in the absence of a mortality benefit in outpatient studies of early oseltamivir treatment of uncomplicated influenza that were not powered for assessing impact upon survival, is in reducing viral transmission duration (Fry et al., 2015), reducing the frequency of complications (Venkatesan et al., 2017), and decreasing hospital resource requirements. (Muthuri et al., 2014) These benefits have mostly accrued to individuals who are treated early in their course, with effect sizes decreasing with delays in initiating therapy.

Given its decades of widespread use, oseltamivir has a fairly well-known safety profile, with rates of nausea and vomiting in approximately 3-4% of patients, with possible increases in neuropsychiatric adverse events in some reports that are difficult to causally attribute. (Dobson et al., 2015, Heneghan et al., 2016, Jefferson et al., 2014) In the critically ill, its enteral formulation is generally well tolerated and well-absorbed, although randomized, placebo-controlled data in this population are lacking. (Lytras et al., 2019)

Current guidelines vary in their recommendations for the use of oseltamivir in the severely ill patient with influenza. The Infectious Diseases Society of America (IDSA) guidelines recommend neuraminidase treatment for any patient hospitalized with influenza, regardless of illness duration prior to hospitalization (A-II). (Uyeki et al., 2019) European Centre for Disease prevention and Control (ECDC) expert opinion documents state 'Treatment during seasonal influenza epidemics should be recommended on an individual basis', acknowledging limitations in the available evidence base. (2017) Duration of therapy is additionally unclear, with a C-III recommendation from the IDSA for longer durations (beyond 5 days) of antiviral treatment for patients with severe disease. (Uyeki et al., 2019)

Detection of antiviral efficacy is through both clinical and biologic endpoints. Determining a benefit on viral shedding after treatment is an important public health endpoint, with the hope that this leads to a decrease in transmissibility during outbreaks, both in the community and hospital settings. The impact on individual outcomes of duration of influenza viral shedding during treatment is unknown. (Ison et al., 2010) Ongoing surveillance for emergence of antiviral resistant influenza viruses due to treatment, as well as in circulating influenza viral strains and their impact on antiviral efficacy, (Sugaya et al., 2007) specifically under the framework of a randomized trial, will be valuable to inform long-term efficacy of antiviral strategies.

There is a possible interaction between the efficacy of antivirals and immunomodulation with corticosteroids among severely ill patients with influenza, with putative harmful effects with high-dose steroids and beneficial effects to lower-dose corticosteroids.(Hui et al., 2018) As with other antiviral studies, these have not been evaluated in prospective, comparative analyses.

Given the risks of antiviral-resistant influenza viruses, (Moscona, 2009) the costs of stockpiling antiviral medications for future pandemics, (Lugner and Postma, 2009) and the lack of high-quality randomized studies in severely ill patients, there is a need for comparative data in this population to document benefit of antivirals in the treatment of influenza.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of different antiviral strategies for patients with severe CAP who have suspected or microbiological testing-confirmed influenza virus infection.

We hypothesize that the probability of all-cause mortality at 90 days after enrollment will differ based on the allocated antiviral strategy. The following interventions will be available:

- No antiviral agent (no placebo)
- Oseltamivir (enterally) twice daily for 5 days or until hospital discharge (whichever occurs first)
- Oseltamivir (enterally) twice daily for 10 days or until hospital discharge (whichever occurs first)

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

Each participating site has the option to opt-in to two or three interventions, to be included in the site randomization schedule depending on local clinical preference, usual practice, acceptable practice, and the availability of the agent at that site. Sites that use oseltamivir routinely as part of their current treatment approach are not encouraged to participate in the option that includes the no-oseltamivir intervention. Sites that do not utilize oseltamivir routinely are encouraged to participate in the no oseltamivir and oseltamivir for 5 days interventions. Sites that do not perform routine testing for influenza in patients with severe CAP should not participate in this domain.

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial (see Core Protocol Section 7). Treatment allocation will be adaptive, as described in the Core Protocol Section 7.5.2.

8.1. *Population*

The REMAP enrolls patients with severe CAP admitted to ICU (see Core Protocol Section 7.3).

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 (see Core Protocol Section 7.4). Patients eligible for the REMAP may have conditions that exclude them from the Antiviral Domain.

8.2.1. Domain inclusion criteria

Influenza infection is suspected by the treating clinician or has been confirmed by microbiological testing.

8.2.2. Domain exclusion criteria

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

- More than 24 hours has elapsed since ICU admission
- Known hypersensitivity to oseltamivir
- Patient has already received two or more doses of oseltamivir or other neuraminidase inhibitors
- Intention to prescribe an antiviral active against influenza other than oseltamivir
- 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

Nil.

8.3. *Interventions*

8.3.1. Antiviral interventions

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

- No antiviral agent (no placebo)
- Oseltamivir (enterally) twice daily for 5 days or until hospital discharge (whichever occurs first)
- Oseltamivir (enterally) twice daily for 10 days or until hospital discharge (whichever occurs first)

It is required that all sites will participate in the 5-day intervention, and each site has the option to opt-in to one or both of the remaining interventions based on local practice.

8.3.2. Recommended oseltamivir dosing

Dosing is determined by the treating clinician and the following are provided as a guide. The standard dose for oseltamivir for adult patients is 75 mg enterally twice per day. No dosage adjustment is suggested for Body Mass Index (BMI), pregnancy, or for extracorporeal membrane oxygenation. Dose adjustment for renal dysfunction will be per local guidelines. If no local guideline exists, recommendations based on estimated Glomerular Filtration Rate (eGFR) are as follows:

Agent	eGFR <30 ml/min	Hemo(dia)filtration (1-1.8 L/hr exchange)	Hemo(dia)filtration (>1.8 L/hr exchange)
Oseltamivir	30 mg twice daily	30 mg twice daily	75 mg, twice daily

8.3.3. Antiviral administration in patients negative for influenza

In patients with suspected influenza who receive an allocation status to receive oseltamivir but who subsequently test negative for influenza after allocation should have treatment with oseltamivir ceased unless the treating clinician believes that doing so is not clinically appropriate.

8.4. *Concomitant care*

Additional antiviral agents active against influenza should not be administered. In patients who have received an allocation status in the Antibiotic Domain, and have microbiological testing confirmed influenza continuation of empiric anti-bacterial agents will be as per the Antibiotic Domain-Specific Appendix (Section 8.3).

8.5. *Endpoints*

8.5.1 Primary endpoint

The primary endpoint for this domain is the REMAP primary outcome (all-cause mortality at 90 days) as specified in Core Protocol Section 7.6.1.

8.5.2 Secondary endpoints

All secondary endpoints as specified in the Core Protocol Section 7.6.2.

The domain-specific secondary outcome measures (occurring during the index hospitalization, censored 90 days after enrollment) will be:

- Virologic endpoints, at selected sites:
    - Change from baseline in influenza virus levels, measured at D3 and at D7 or ICU discharge (whichever occurs first) in upper and lower respiratory tract specimens.

- Incidence of emergence of amino acid changes in influenza viruses associated with reduced susceptibility to oseltamivir at D3 and D7 or ICU discharge, whichever occurs first, in upper and lower respiratory tract specimens all patients.

- Serious adverse event (SAE) as defined in Core Protocol

9. TRIAL CONDUCT

9.1. *Microbiology*

Microbiological testing will be performed as per local practice, including bacterial and viral testing to guide clinical care. Domain-specific data collection will consist of viral sampling collected at baseline, 3, and D7 or ICU discharge, whichever occurs first, for participating patients in selected sites, from paired sampling of nasopharyngeal swabs of all patients and tracheal aspirates from patients who are intubated.

Samples will be stored locally and batch shipped for central analysis at national or regional reference labs for quantitative influenza virus titers and resistance testing, as described above in secondary endpoints. These results will not be clinically available to treating teams. Samples may be retained dependent on local ethical approval and consent requirements.

9.2. *Domain-specific data collection*

9.2.1. Clinical data collection

No additional clinical data, in addition to that in Core Protocol Section 8.9, will be collected for this domain.

9.3. *Criteria for discontinuation*

Refer to Core Protocol Section 8.7 for criteria for discontinuation of participation in the REMAP-CAP trial.

9.4. *Blinding*

9.4.1. Blinding

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

9.4.2. Unblinding

Not relevant.

10. STATISTICAL CONSIDERATIONS

10.1. *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.

10.2. *Unit-of-analysis and strata*

The unit-of-analysis, for both analysis of treatment effect and the Response Adaptive Randomization (RAR), will be the influenza present stratum, as specified in the Core Protocol. The population that will be used to determine a Statistical Trigger and Platform Conclusion are patients in the influenza present stratum as defined in Core Protocol, i.e. microbiological testing-confirmed influenza or patients enrolled in the domain who do not have influenza testing performed. Some patients will be randomized who are in the influenza absent stratum and will be analyzed separately. The statistical model will permit borrowing as specified in Core Protocol Section 7.8.3.3.

Safety analyses will be conducted at each adaptive analysis for patients randomized in this domain who are in the influenza absent stratum, as defined in Core Protocol (i.e. patients who are tested and are negative for influenza). At the time of a Platform Conclusion, results will be reported for all randomized patients, patients in the influenza present stratum, and patients in the influenza negative stratum.

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

10.3. *Timing of revealing of randomization status*

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal and Initiation (see section 7.8.3.6 in Core Protocol)

10.4. *Interactions with interventions in other domains*

An *a priori* interaction with the Antibiotic 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 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 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.

10.5. *Nesting of interventions*

There is one nest within this domain, comprising the 5- and 10-day duration of oseltamivir (see Section 7.8.3.8 in Core Protocol). The rationale for this is that the treatment effect of both oseltamivir interventions is more likely to be similar than no oseltamivir.

10.6. *Threshold odds ratio delta for equivalence*

The threshold odds ratio delta for equivalence in this domain is that specified in the Core Protocol (Section 7.8.8).

10.7. *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:

- Immunocompromised, defined as receiving immunosuppressive treatment or having immunosuppressive disease.
- Proven concomitant bacterial co-infection, defined as having isolation or detection of a known pathogen that causes CAP from blood, pleural fluid, or lower respiratory tract specimen.
- Shock strata
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

11.ETHICAL CONSIDERATIONS

11.1. *Data Safety and Monitoring Board*

The DSMB should be aware that the superiority, 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 hospital length-of-stay or virus shedding.

There will be patients enrolled into this domain who will be subsequently determined to be influenza-negative. These patients will likely have been exposed to a small number of oseltamivir doses before test results become available. The DSMB will receive and evaluate outcomes in these patients to determine safety events relevant to antiviral administration, in addition to the patients that are influenza-positive, and report to the chair of the ITSC where relevant.

11.2. *Potential domain-specific adverse events*

The antiviral agent used in this domain has a known low toxicity profile. Nausea and vomiting are recognized adverse events in ambulatory patients but this is of limited relevance to critically ill patients. Additionally, it is expected that a high proportion of critically ill patients who will be enrolled in this trial will experience mortality or substantial morbidity. There are no domain-specific adverse events requiring specific data collection instruments for oseltamivir administration.

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).

11.3. *Domain-specific consent issues*

The antiviral to be tested in this domain is approved by the FDA for the treatment of uncomplicated influenza in outpatients whose symptoms have not lasted more than two days. (2019) Guidelines in some regions recommend administration of oseltamivir to all hospitalized patients with suspected or microbiological testing-confirmed influenza, regardless of symptom duration. (Uyeki et al., 2019) However, this is based on low quality evidence, especially for ICU patients. Some clinicians do not administer oseltamivir to some or all patients with microbiological testing-confirmed influenza because of uncertainty about the effectiveness of oseltamivir in critically ill patients with influenza (see Background Section 6).

Investigators will be able to choose to not include the no-oseltamivir (no placebo) intervention at their site. The recommendation of the trial is that sites should only participate in the no-oseltamivir intervention if that sites current policy is to not administer oseltamivir or if the site has concerns about the balance between safety and benefit of oseltamivir. Sites that routinely use oseltamivir can participate in this domain by restricting the allocation options at their site to the two interventions that result in administration of oseltamivir. Additionally, clinicians are directed to not enroll an individual patient if the treating clinician believes that participation in this domain is not in the best interests of the patient. Enrolment criteria are used to exclude patients from individual interventions for appropriate clinical reasons (e.g. hypersensitivity to study drug). To ensure adequate recruitment into all three arms proposed, sites that participate in the 'no antiviral agent' intervention are encouraged to restrict the interventions to the no antiviral agent and the 5-day oseltamivir arm.

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

The only samples obtained will be airway specimens, for the purposes of influenza virus analyses. These samples will be stored regionally for analyses. No genetic information about the individual patient will be obtained.

Pregnant women are susceptible to influenza and are at higher risk of a worse outcome; they are not excluded from this domain.

If the predominant circulating influenza virus strains, either regionally or globally, have been identified by public health authorities to be resistant to oseltamivir then this domain may be suspended, either locally or globally. This will be through the decision-making of the ITSC, in conjunction with one or more RMCs if the distribution of oseltamivir resistant isolates is regional.

12.GOVERNANCE ISSUES

12.1. *Funding of domain*

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. This domain has not received any additional domain-specific funding.

12.2. *Funding of domain interventions and outcome measures*

Oseltamivir will be provided by participating hospitals on the basis that if the patient was not participating in the trial, appropriate antivirals may have been indicated and provided by the treating hospital. For sites participating in the viral sampling component, the costs of additional sampling, shipping, central storage and analysis will be met by the trial.

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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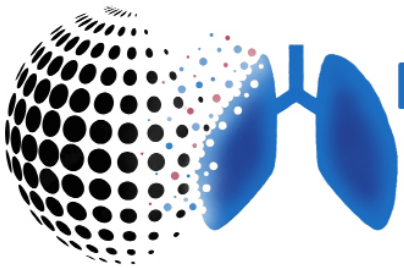

Domain-Specific Appendix:

MACROLIDE DURATION DOMAIN

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

Macrolide Duration Domain-Specific Appendix Version 3 dated 10 July 2019

Summary

In this domain of the REMAP-CAP trial, participants with community-acquired pneumonia admitted to intensive care units and allocated to receive a beta-lactam antibiotic intervention in the Antibiotic Domain will be randomized to receive:

- Standard course macrolide (for 3 to 5 days)
- Extended course macrolide (for 14 days)

At this participating site the following one intravenous and one enteral macrolide have been selected within this domain:

Intravenous: ☐ Azithromycin ☐ Clarithromycin

Enteral: ☐ Azithromycin ☐ Clarithromycin ☐ Roxithromycin

REMAP-CAP: Macrolide Duration Domain Summary	
Interventions	• Standard course macrolide discontinued after 3 to 5 days unless there is confirmed or strongly suspected microbiological cause for prolonged administration • Extended course macrolide for 14 days or hospital discharge, whichever occurs first
Unit-of-analysis and Strata	There is one unit-of-analysis in this domain. Analysis and Response Adaptive Randomization are applied to all randomized patients and with no strata utilized.
Evaluable treatment-by-treatment Interactions	No interactions will be evaluated with any other domain.
Nesting	None
Timing of Reveal	Randomization with Deferred Reveal
Inclusions	Patients are eligible for this domain only if they have been allocated a beta-lactam plus macrolide intervention within the Antibiotic Domain.
Domain-Specific Exclusions	Domain exclusions: • Agreement to participate in this domain has been declined or has not been requested before the end of study day 5 • There is microbiological confirmation or the clinician strongly suspects Legionella or any other form of atypical pneumonia • Macrolide antibiotics have already been discontinued for more than 36 hours • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	Nil, not applicable
Outcome measures	Primary REMAP endpoint: all-cause mortality at 90 days. Secondary REMAP endpoints refer to Core Protocol Section 7.6.2 Secondary domain endpoints (censored 90 days from the date of enrollment): • Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital. • Serious Adverse Events (SAE) as defined in CORE protocol

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1. ABBREVIATIONS

ATS	American Thoracic Society
CAP	Community Acquired Pneumonia
COPD	Chronic Obstructive Pulmonary Disease
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
IV	Intravenous
RAR	Response Adaptive Randomization
RCT	Randomized Controlled Trial
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event

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. MACROLIDE DURATION DOMAIN-SPECIFIC APPENDIX VERSION

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

3.1. *Version history*

Version 1: Approved by the Macrolide Duration Domain-Specific Working Group (DSWG) on 20 November 2016

Version 1.1: Approved by the Macrolide Duration DSWG on 30 March 2017

Version 2: Approved by the Macrolide Duration DSWG on 12 December 2017

Version 3: Approved by the Macrolide Duration DSWG on 10 July 2019

4. MACROLIDE DURATION DOMAIN GOVERNANCE

4.1. *Domain members*

Chair:

Professor Allen Cheng

Members:

Professor Richard Beasley

Professor Marc Bonten

Dr. Nick Daneman

Dr. Lennie Derde

Dr. Robert Fowler

Associate Professor David Gattas

Professor Anthony Gordon

Mr. Cameron Green

Associate Professor Peter Kruger

Dr. Colin McArthur

Dr. Steve McGloughlin

Dr. Susan Morpeth

Dr. Srinivas Murthy

Professor Alistair Nichol

Professor David Paterson

Professor Mathias Pletz

Associate Professor Gernot Rohde

Professor Steve Webb

4.2. *Contact Details*

Chair:

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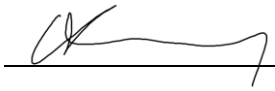
5. MACROLIDE DURATION DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The Macrolide Duration Domain-Specific Working Group (DSWG) have read the appendix and authorize it as the official Macrolide Duration Domain-Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair
Allen Cheng



Date 10 July 2019

6. BACKGROUND AND RATIONALE

6.1. *Domain definition*

This is a domain within the REMAP-CAP to test the effectiveness of different durations of macrolide administration in patients with severe community-acquired pneumonia (CAP) who are admitted to an Intensive Care Unit (ICU).

6.2. *Domain-specific background*

Antibiotics are an essential component of therapy for all patients with suspected or proven CAP. In patients with sepsis (including pneumonia) requiring admission to intensive care with organ dysfunction, guidelines recommend initiation of antibiotics within 60 minutes of presentation. (Dellinger et al., 2013)

6.2.1. Guidelines recommend either macrolides or quinolones to treat "atypical" respiratory pathogens

Macrolide antibiotics include azithromycin (available for intravenous (IV) or enteral administration), clarithromycin (available for IV or enteral administration), roxithromycin (available only for enteral administration), and erythromycin (available for IV or enteral administration). Erythromycin is an older macrolide, the use of which has declined substantially.

All international guidelines for the empiric treatment of severe CAP recommend treatment with either a macrolide or a fluoroquinolone to provide antimicrobial treatment for "atypical" respiratory pathogen such as legionella (see Table 1). All of these guidelines recommend adjustment of prescribing when a causative organism is identified which, if the causative organism is an 'atypical'

pathogen (comprising legionella, *Mycoplasma pneumonia*, *Chlamydophila (Chlamydia) pneumonia, or Chlamydophila (Chlamydia) psittaci*) is a prolonged (minimum of 14 days) course of either a macrolide antibiotic or a fluoroquinolone.

Table 1: Empiric antibiotic treatments recommendations for patients with severe pneumonia (without risk factors for pseudomonas) requiring intensive care

Guideline	First line	Second line
British Thoracic Society (Lim et al., 2009)	1. Co-amoxiclav AND macrolide (clarithromycin)	1. Cefuroxime or ceftriaxone AND clarithromycin
United States Infectious Diseases Society of America (IDSA)/ the American Thoracic Society (ATS) (Mandell et al., 2007)	1. Cefotaxime, ceftriaxone, or ampicillin-sulbactam AND either (a) azithromycin or (b) a respiratory fluoroquinolone	1. Respiratory fluoroquinolone AND aztre onam
Australia (Antibiotic Expert Groups, 2014)	1. Ceftriaxone AND azithromycin	1. Moxifloxacin
Canada (Mandell et al., 2000)	1. Moxifloxacin or levofloxacin	1. Cefuroxime, ceftriaxone or beta-lactam/beta-lactamase inhibitor AND IV macrolide
Swedish guidelines (Spindler et al., 2012)	1. Cephalosporin AND macrolide 2. Benzylpenicillin AND respiratory fluoroquinolone	
Europe European Society of Clinical Microbiology and Infectious Diseases / European Respiratory Society (Woodhead et al., 2011)	1. Non-antipseudomonal 3rd generation cephalosporin AND macrolide 2. Non-antipseudomonal 3rd generation cephalosporin AND either (a) Moxifloxacin or (b) Levofloxacin	
Netherlands Dutch Working Party on Antibiotic Policy / Dutch Association of Chest Physicians (Wiersinga et al., 2012)	1. Moxifloxacin or levofloxacin 2. Penicillin (or amoxicillin) AND ciprofloxacin 3. 2nd or 3rd generation cephalosporin AND macrolide.	

The IDSA guidelines recommend administration of azithromycin for between 3 and 5 days but other guidelines do not provide any recommendation regarding the duration of administration of macrolide antibiotics. A survey of Australian and New Zealand ICU specialists indicated that more than 85% administer azithromycin, a macrolide antibiotic, to cover atypical organisms and that just over half of specialists cease azithromycin after 3 days if there is no microbiological evidence of

infection with atypical organisms. Studies suggest a wide diversity of antibiotic regimens are used for pneumonia in Europe; the most common antibiotics used include penicillin/beta-lactamase inhibitors, macrolides, quinolones and third generation cephalosporins, broad spectrum penicillins and second generation cephalosporins but there is little information available about the duration of macrolide therapy when macrolides are used. (Ansari et al., 2009, Torres et al., 2014)

As such, all patients with severe CAP, both in usual practice or within this REMAP, will receive either a macrolide or a fluoroquinolone antibiotic. If a macrolide is included in the choice of empiric antibiotics it is typically continued if an 'atypical' cause of pneumonia is identified. The time interval for the results of microbiological tests to become available varies between sites, but at the vast majority of sites results for tests of Legionella and other atypical organisms are available before day 3 to 5. It is usual practice is to continue a macrolide antibiotic, until the results of such tests are available and to then cease the macrolide unless 'atypical' pneumonia is confirmed or strongly suspected.

6.2.2. Macrolide antibiotics have anti-inflammatory properties

Azithromycin has well-described immunomodulatory effects including inhibiting the production of inflammatory cytokines and neutrophils. (Kanoh and Rubin, 2010) These effects are consistent in cell culture, animal studies, in patients with chronic pulmonary inflammatory diseases, and appear to be multiphasic, with an initial inflammatory effect followed by a sustained decrease in cytokine production. Other non-antimicrobial effects of macrolides include a reduction in mucus secretion (Rubin et al., 1997), downregulation of adhesion molecules and chemoattractants (Tamaoki, 2004), and inhibition of neutrophil reactive oxygen species. (Levert et al., 1998)

6.2.3. Severe CAP is intertwined with the host systemic inflammatory response

The clinical manifestation of pneumonia is a product of the interaction between an infective pathogen and the local and systemic inflammatory responses of the host. Interestingly, a more pronounced and aggressive inflammatory response has been shown in several studies to be associated with treatment failure and increased rates of mortality. (Antunes et al., 2002) In support of this hypothesis that an over-active immune response is deleterious, higher levels of pro-inflammatory cytokines and chemokines (i.e. IL-6 and IL-8) have been detected in patients with severe CAP and associated with increased rates of mortality. (Antunes et al., 2002) It has been postulated that a potential dampening of this 'abnormal' immune response to infection could improve outcomes. The immunomodulatory properties of macrolide antibiotics provide a rationale

for why an extended course may be superior to usual practice, in patients who do not have a microbiological reason (i.e. identification of an 'atypical' organism) to continue the macrolide. High profile reviews have identified the role of extended administration of azithromycin in patients with CAP as a high priority research question. (Dellinger et al., 2013, Wilkinson and Woodhead, 2004)

6.2.4. Macrolides have been associated with improved clinical outcomes in inflammatory lung diseases in some studies

Additional supportive evidence of the potentially beneficial effects of macrolides, that are believed to be mediated by their immunomodulatory properties, comes from trials of macrolides in patients with various forms of chronic inflammatory lung disease. Clinical evidence for an anti-inflammatory effect of macrolides was first noted in patients with diffuse panbronchiolitis, a rare disease found exclusively in Japan. (Schultz, 2004) In Randomized Controlled Trials (RCTs), long term azithromycin has been resulted in improved outcomes in patients with Chronic Obstructive Pulmonary Disease (COPD) (Albert et al., 2011, Uzun et al., 2014), non-cystic fibrosis associated bronchiectasis (Altenburg et al., 2013, Valery et al., 2013), and to prevent or treat bronchiolitis obliterans or chronic rejection in patients who have undergone lung transplantation. (Corris et al., 2015, Vos et al., 2011).

6.2.5. The use of macrolide antibiotics has been associated with improved outcomes in CAP even when the causative organism is resistant to macrolides.

A further rationale for a potential beneficial immunomodulatory effect of macrolide therapy in patients with severe CAP is that outcome may be better for patients with CAP who are treated with macrolide antibiotics, even when the organism that is responsible for causing pneumonia is resistant to macrolides. This evidence is less strong, being derived from observational studies. (Restrepo et al., 2013, Yanagihara et al., 2009).

Clinical trials adding a macrolide to beta-lactams, compared with a beta-lactam alone, for CAP have not demonstrated clinical benefit. One trial found that the addition of clarithromycin to a beta-lactam (cefuroxime or amoxicillin-clavulanate) was associated with a shorter time to clinical stability in patients with moderately severe CAP, although the difference in this small trial was not statistically significant. (Garin et al., 2014) A recent cluster randomized trial of patients with CAP that required hospitalization did not find any differences in mortality or hospital length of stay but did not include patients with severe CAP. (Postma et al., 2015)

6.2.6. Macrolide antibiotics safety profile

The safety profile of macrolide antibiotics is well established. However, there are also safety concerns regarding macrolides with reports of life-threatening cardiac rhythm disorders, although this is rare. (Juurlink, 2014, Svanstrom et al., 2013)

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of standard course versus extended course macrolide treatment, in patients co-treated with a beta-lactam antibiotic who do not have a known microbiological indication for administration of extended course of macrolide, in the treatment of severe CAP.

We hypothesize that the probability of all-cause mortality at 90 days after enrollment will differ based on the duration of administration of a macrolide. The following interventions will be available:

- Standard course macrolide discontinued between day 3 and day 5
- Extended course macrolide for 14 days or hospital discharge, whichever occurs first

Azithromycin is the preferred macrolide but at sites where azithromycin is not available, the use of other macrolides will be permitted (see Section 8.3).

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial (see Core Protocol Section 7). Treatment allocation will be adaptive, as described in the Core Protocol Section 7.5.2.

8.1. *Population*

The REMAP enrolls patients with severe CAP admitted to ICU (see Core Protocol Section 7.3).

8.2. *Eligibility criteria*

Participants are included in the platform if they have all the platform-level inclusions and none of the platform-level exclusion criteria (see Core Protocol Section 7.4). Eligibility criteria for this domain can only be understood in conjunction with knowledge of the entry criteria for the Antibiotic Domain.

8.2.1. Domain inclusion criteria

Patients are eligible for this domain only if they have been allocated a beta-lactam plus macrolide intervention within the Antibiotic Domain. In this regard, the Macrolide Duration Domain sits solely within the beta-lactam plus macrolide interventions of the Antibiotic Domain. Patients allocated to receive moxifloxacin or levofloxacin in the Antibiotic Domain are not eligible for this domain.

8.2.2. Domain exclusion criteria

Reveal of allocation status will not be permitted, resulting in exclusion from this domain, if:

- Study day 6 has commenced
- Agreement to participate in this domain has not been obtained
- There is microbiological confirmation or the clinician strongly suspects Legionella or any other form of atypical pneumonia
- Macrolide antibiotics have already been discontinued for more than 36 hours
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

It should be noted that patients with known Legionella, at the time of first enrollment in the Platform, are not eligible for the Antibiotic Domain (because specific antimicrobial therapy is indicated) and patients with known intolerance to macrolides have an intervention-level exclusion to receive beta-lactam plus macrolide interventions within the Antibiotic Domain.

8.2.3. Intervention exclusion criteria

Nil.

8.3. *Interventions*

8.3.1. Macrolide intervention

Patients will be randomly assigned to receive one of the following open-label study interventions.

- Standard course macrolide discontinued between day 3 and day 5
- Extended course macrolide for 14 days or hospital discharge, whichever occurs first

The dosing of and route of administration of macrolide antibiotics are not specified in the protocol but the following guidance is provided:

- Initial IV administration of a macrolide is strongly preferred
- The preferred IV macrolide is azithromycin, but IV clarithromycin may be substituted.
- The preferred enteral macrolide is azithromycin, but enteral clarithromycin or roxithromycin may be substituted.
- Sites where erythromycin is the only available macrolide will not be able to participate in this domain.

8.3.2. Recommended macrolide dosing

The following doses (Table 2) are provided as guidance and may be modified according to local guidelines or practice. The dose of all macrolides is the same for IV and enteral administration and no dose adjustment is required for alterations in renal function including if the patient is receiving renal replacement therapy. A switch from IV to enteral macrolide is permitted as directed by the treating clinician.

Table 2: Minimum doses of intravenous or enteral macrolide

Agent	Dose
Azithromycin	500mg daily
Clarithromycin	500mg daily
Roxithromycin	150mg q12hr

If, at any time after reveal, there is confirmed diagnosis (or a strong clinical suspicion) of legionellosis or other microbiological diagnosis of an 'atypical' organism, then effective treatment for 'atypical' organisms must be provided. This can be either prolonged macrolide treatment or substitution with a fluoroquinolone or other active agent. Any patient randomized to standard course macrolide, in whom legionellosis or another 'atypical' organism is diagnosed after cessation of macrolide, must commence treatment that is effective against the organisms such as a macrolide or fluoroquinolone.

8.3.3. Timing of initiation of intervention

Reveal of allocation status can occur at any time before the end of study day 5 when sufficient information is available to evaluate the exclusion criteria necessary for reveal. If reveal occurs before study day 3, and the patient is allocated to standard course macrolide, the intervention should be ceased on study day 3. If reveal occurs after study day 3, and the patient is allocated to standard course macrolide, discontinue immediately. Irrespective of the timing of reveal, if the patient is allocated to extended course macrolide, continuation to study day 14 should be prescribed.

8.3.4. Duration of administration of macrolide

The duration of macrolide therapy is the primary research question in this domain. In the standard course intervention, patients will receive 3 to 5 days of macrolide therapy. In the extended course therapy intervention, patients will continue to receive the macrolide for 14 days or until discharge from hospital, if hospital discharge occurs before 14 days have elapsed.

For patients who are discharged from the ICU before 14 days, it is the responsibility of ICU staff to prescribe the macrolide for administration for a total of 14 days. However, it is not the responsibility of ICU medical or research staff to ensure continuation of the study drug after discharge from the ICU.

The Macrolide should be discontinued if the patient experiences a serious adverse event (SAE) that is thought to be related to the study drug and may be discontinued at the discretion of the treating clinician if continued treatment is not in the best interests of the patient. In this regard, consideration should be given to the development of ventricular dysrhythmias and evaluation of the QT interval, particularly at the time of discharge from the ICU.

8.4. *Concomitant care*

The use of low dose erythromycin (up to 250mg q6h) to promote gastric emptying is discouraged, but is not considered a protocol deviation.

Any subsequent change of antibiotics, other than macrolides, based on availability of microbiological data, will be permitted at the treating clinician's discretion. However, the duration of macrolide therapy will not be affected by macrolide susceptibility or resistance in any pathogens isolated from participants.

8.5. *Endpoints*

8.5.1. Primary endpoint

The primary endpoint for this domain is the REMAP primary outcome (all-causes mortality at 90 days) as specified in Core Protocol Section 7.6.1.

8.5.2. Secondary endpoints

All secondary endpoints as specified in the Core Protocol Section 7.6.2.

The domain-specific secondary outcome measures (occurring during the index hospitalization, censored at 90 days after enrollment) in addition to the Antibiotic Domain will be:

- Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital
- SAE as defined in CORE Protocol

9. TRIAL CONDUCT

9.1. *Microbiology*

Isolates will be tested for susceptibility to macrolide antibiotics using routine clinical testing. Specific isolates may be referred to a reference laboratory according to current clinical practice.

9.2. *Domain-specific data collection*

9.2.1. Clinical data collection

In addition to Domain-specific data required as a consequence of participation in the Antibiotic Domain, patients who are randomized in this domain will have the following data collected:

- Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital.
- SAE as defined in Core Protocol

Refer to Core Protocol Section 8.9 for other data collection fields and processes.

9.3. *Criteria for discontinuation*

Refer to Core Protocol Section 8.7 for criteria for the discontinuation of participation in the REMAP-CAP trial.

9.4. *Blinding*

9.4.1. Blinding

Macrolides will be administered on an open-label basis.

9.4.2. Unblinding

Not relevant.

10.STATISTICAL CONSIDERATIONS

10.1. *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.

10.2. *Unit-of-analysis and strata*

The unit-of-analysis for this domain is all patients who receive an allocation status in this domain. No strata are applied in the model that is used for analysis and specification of Response Adaptive Randomization (RAR).

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 Deferred Reveal after domain-specific exclusion criteria have been evaluated (see section 7.8.3.6 in Core Protocol).

10.4. *Interactions with interventions in other domains*

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 beta-lactam specified in the Antibiotic Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain. By design, no interaction is evaluable between this domain and administration of moxifloxacin or levofloxacin in the Antibiotic Domain.

An *a priori* interaction with the Antiviral Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

No interaction is evaluable between the Ventilation Domain and this domain.

10.5. *Nesting*

Nesting is not applicable to this domain.

10.6. *Threshold odds ratio delta for equivalence*

The threshold odds ratio for equivalence in this domain is that specified in the Core Protocol (Section 7.8.8).

10.7. *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:

- A microbiological diagnosis of pneumococcal pneumonia

- Elderly (≥65 years) and non-elderly (<65 years)
- Chronic Obstructive Pulmonary Disease (COPD)
- Azithromycin versus other macrolides
- Shock strata
- Influenza strata
- All potentially evaluable treatment-by-treatment interactions with other domains.

11. ETHICAL CONSIDERATIONS

11.1. *Data Safety and Monitoring Board*

The DSMB should be aware that the superiority, inferiority, or equivalence of different interventions with respect to the primary endpoint is possible, and if equivalence is demonstrated, the optimal treatment may be based on secondary endpoints, such as the incidence of cardiovascular endpoints.

11.2. *Potential domain-specific adverse events*

The antibiotics used in this domain have a known toxicity profile and adverse events are rare.

Domain-specific harms related to macrolide therapy include:

- Cardiac arrhythmia (particularly torsades de pointes)

- Gastrointestinal intolerance
- Hypersensitivity
- Abnormal liver function

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).

11.3. *Domain-specific consent issues*

Azithromycin is approved and is in common use in many countries for CAP. Most international guidelines do not specify the duration of treatment where a specific diagnosis (e.g. Legionella) has not been diagnosed.

The use of prolonged courses of azithromycin is widely used for specific types of pneumonia (e.g. legionellosis). Sites will be able to opt out of this domain for all patients at that site if they believe that this intervention is not part of reasonable care of patients with pneumonia, or are not approved for use in the country or conflict with antimicrobial stewardship considerations. Additionally, clinicians may choose not to enroll individual patients if they feel that participation is not in the patient's best interests.

Although many CAP patients receive 3 to 5 days of macrolide treatment as standard of care, extended duration macrolide therapy is not part of the spectrum of standard care. On this basis eligibility for this domain requires the agreement of either the participant or an authorized representative.

Pregnant women are susceptible to pneumonia and azithromycin is widely used safely in this population. Azithromycin and roxithromycin are preferred to clarithromycin in pregnant women.

12.GOVERNANCE ISSUES

12.1. *Funding of domain*

Funding sources for the REMAP-Cap trial are specified in the Core Protocol Section 2.5. This domain has not received any additional domain-specific funding.

12.2. *Funding of domain interventions and outcome measures*

The macrolide will be provided by participating hospitals on the basis that, in the absence of the REMAP, a proportion of patients with severe CAP would otherwise have received a macrolide. In New Zealand, Health Research Council funding will be available to reimburse sites for up to two doses per patient of IV azithromycin (see ANZ RSA Section 9.2.2).

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:

CORTICOSTEROID DOMAIN

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

Corticosteroid Domain-Specific Appendix Version 3 dated 12 July 2019

Summary

In this domain of the REMAP-CAP trial, participants with community-acquired pneumonia admitted to participating intensive care units will be randomized to receive one of up to three steroid-use strategies depending on availability and acceptability:

- No corticosteroid including hydrocortisone (no placebo)
- Fixed duration hydrocortisone for 7 days
- Shock-dependent hydrocortisone while the patient is in septic shock

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

☐ No corticosteroid including hydrocortisone (no placebo)

☐Fixed duration hydrocortisone for 7 days

☐Shock-dependent hydrocortisone while the patient is in septic shock

REMAP-CAP: Corticosteroid Domain Summary	
Interventions	• No corticosteroid including hydrocortisone (no placebo) • Fixed duration hydrocortisone for 7 days • Shock-dependent hydrocortisone while the patient is in septic shock
Unit-of-analysis and Strata	There are four units-of-analysis for this domain, specified by the combination of shock and influenza strata status. Analysis and Response Adaptive Randomization are applied by shock and influenza status, with borrowing permitted.
Evaluable treatment-by-treatment Interactions	Treatment-treatment interactions will be evaluated between interventions in this domain and interventions in the Antiviral Domain. No other interactions will be evaluated with any other domain.
Nesting	None
Timing of Reveal	Randomization with Immediate Reveal and Initiation
Inclusions	Inclusion criteria are the same as the Platform see Core Protocol Section 7.4.1
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • Known hypersensitivity to hydrocortisone • An indication to prescribe systemic corticosteroids for a reason that is unrelated to the current episode of CAP (or direct complications of CAP), such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven *Pneumocystis jiroveci* pneumonia • More than 24 hours have elapsed since ICU admission • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	Nil, not applicable
Outcome measures	Primary REMAP endpoint: all-cause mortality at 90 days. 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 enrollment): • Serious Adverse Events (SAE) as defined in CORE protocol

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1. ABBREVIATIONS

ADRENAL	ADjunctive coRticosteroid trEatment iN criticAlly ilL Patients With Septic Shock Study
APROCCHSS	Activated PROtein C and Corticosteroids for Human Septic Shock
ARDS	Acute Respiratory Distress Syndrome
ARDSNet	Acute Respiratory Distress Syndrome Clinical Trial Network
CAP	Community Acquired Pneumonia
CORTICUS	The Corticosteroid Therapy of Septic Shock Study
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
HPA	Hypothalamic–Pituitary–Adrenal
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
IV	Intravenous
kg	Kilogram
LOS	Length of Stay
LUNG-SAFE	Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE
MODS	Multiple Organ Dysfunction Score
mg	milligram
OFFD	Organ Failure Free Days
P:F Ratio	Ratio of Partial Pressure of Oxygen in Arterial Blood and Fraction of Inspired Oxygen Concentration
RAR	Response Adaptive Randomization
RCT	Randomized Controlled Trial
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
VFD	Ventilator Free Days

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 Region-Specific Appendices (RSA) (detailing regional management and governance).

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

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

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

3.1. Version history

Version 1: Approved by the Corticosteroid Domain-Specific Working Group (DSWG) on 19 November 2016

Version 1.1: Approved by the Corticosteroid DSWG on 30 March 2017

Version 2: Approved by the Corticosteroid DSWG on 12 December 2017

Version 3: Approved by the Corticosteroid DSWG on 12 July 2019

4. CORTICOSTEROID DOMAIN GOVERNANCE

4.1. Domain members

Chair:

Professor Derek Angus

Members:

Ms. Wilma van Bentum-Puijk
Dr. Lennie Derde
Professor Anthony Gordon
Dr. Sebastiaan Hullegie
Associate Professor Peter Kruger

Dr. Ed Litton

Professor John Marshall

Dr. Colin McArthur

Dr. Srinivas Murthy

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Professor Bala Venkatesh

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4.2. Contact Details

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5. CORTICOSTEROID DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

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

Chair
Derek Angus

Derek C. Angus

Date 12 July 2019

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP to test the effectiveness of systemic corticosteroids in patients with severe community-acquired pneumonia (CAP) who are admitted to an Intensive Care Unit (ICU).

6.2. Domain-specific background

There is significant uncertainty regarding the use of corticosteroids in patients with CAP who are treated in an ICU. This uncertainty applies to both patients with and without septic shock secondary to CAP. The existing evidence is derived from trials that enrolled overlapping populations. Some trials enrolled patients with septic shock, many of whom had CAP as the source of sepsis, and other enrolled patients with severe CAP, but only a proportion of these patients had septic shock. These trials have largely utilized hydrocortisone as the corticosteroid but have employed a range of doses and delivery strategies (infusion versus intermittent dosing).

Several studies and meta-analyses of randomized controlled trials (RCTs) have indicated that benefit may exist. (MacDonald, 2018) However, existing evidence is not sufficient to provide guidance to clinicians that is definitive. If there is a benefit, there is limited evidence to suggest that benefit is more likely in patients who are more severely ill. (Annane et al., 2018, Venkatesh et al., 2018) It is also recognized that corticosteroids have a range of potentially adverse effects. Clinicians remain uncertain about the role of corticosteroid treatment in patients with severe CAP. This uncertainty necessitates the conduct of a large pragmatic study to address this question and provide definitive guidance to clinicians.

6.2.1. Corticosteroids in critical illness

In health, endogenous corticosteroids production is regulated by the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis is central to maintaining homeostasis in the face of exogenous stress. Infectious disease is a common source of exogenous stress that is encountered by humans. As part of an integrated response to infection the host produces additional (above normal homeostasis) corticosteroids. It is speculated that this occurs to calibrate the innate and acquired host response to infection so as to protect the host organism from an excessive immune response, which can damage host tissues. Corticosteroids are immunomodulatory hormones that can stimulate, as well as suppress, immune function depending on the type of immune response, the immune compartment,

and the cell type involved. (Silverman et al., 2005, Prina et al., 2016) Exogenously administered corticosteroid drugs (e.g. hydrocortisone) elucidate effects similar to endogenously produced cortisol on the host immune response. Furthermore, critically ill patients may benefit from corticosteroid administration due to the presence of relative adrenal insufficiency or inadequate adrenal function in some cases of severe CAP. (Maxime et al., 2009)

6.2.2. Clinical questions regarding corticosteroids in patients with CAP

There are several interrelated and overlapping clinical questions regarding the role of corticosteroids in patients with severe CAP. The first of these is whether patients who have septic shock as a complication of severe CAP benefit from corticosteroids. The second is whether patients with severe CAP who do not have septic shock benefit from corticosteroids. The third is whether patients with severe CAP due to influenza respond differently to corticosteroids. Lastly, there is uncertainty about the role of corticosteroids in patients who develop Acute Respiratory Distress Syndrome (ARDS) secondary to severe CAP.

6.2.3. Role of corticosteroids in septic shock secondary to CAP

The studies investigating corticosteroids that enrolled patients with septic shock (or sepsis without shock) included patients with a range of different sites of primary infection. In most trials, around half of enrolled patients had CAP. The results of these studies are varied, and this is reflected in international guidelines.

The 2013 iteration of the Surviving Sepsis Campaign Guidelines suggests that the administration of intravenous (IV) hydrocortisone should be avoided if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability, but that hydrocortisone should be administered if hemodynamic stability cannot be achieved. (Dellinger et al., 2013) This recommendation is graded as a weak recommendation based on low quality evidence. There are two major trials that influenced this recommendation. In a study by Annane et al, hydrocortisone improved the duration of survival (within the first 28 days) but not the number of patients who survived; and resulted in more rapid reversal of septic shock in the (non-stratified) sub-group of patients with relative adrenal insufficiency. (Annane et al., 2002) In the CORTICUS study, septic shock was also reversed more rapidly but there was no difference in mortality although this result may have been influenced by inclusion of patients at lower risk of death. (Sprung et al., 2008) A more recent Cochrane meta-analysis suggests that corticosteroid treatment reduces mortality among patients with sepsis, but the quality of evidence was rated as low because of imprecision and inconsistency of results across trials, as well as the inclusion of trials with different study populations and the use of different doses

and duration of treatment. (Annane et al., 2015) The recommendation in the current, 2016 International Surviving Sepsis Campaign Guidelines is not changed from the 2013 recommendation. (Rhodes et al., 2017)

Since the publication of the Cochrane meta-analysis and the 2016 Guidelines, two additional trials have been published, but have not provided sufficient clarification. A RCT of hydrocortisone in 3,800 patients with septic shock (ADRENAL) showed no reduction in 90-day mortality. (Venkatesh et al., 2018) In this trial, duration of treatment was 7 days or until ICU discharge, whichever occurred first. For patients who still required vasopressor support on day 7, there was evidence of deterioration after steroids were ceased. The other trial, APROCCHSS, investigating hydrocortisone-plus-fludrocortisone in patients with septic shock, reported lower 90-day mortality in the intervention group (RR 0.88, 95% CI 0.78-0.99). (Annane et al., 2018)

These trials (Table 1) have not resulted in changes to international guidelines. As a consequence of this uncertainty, there is substantial variation in clinical practice. (Annane et al., 2002, Bollaert et al., 1998, Briegel et al., 1999, MacDonald, 2018)

Table 1: Selected studies of corticosteroids in sepsis

Reference	Design, population and intervention	Results
Annane et al. (2015)	Meta-analysis of RCTs of corticosteroids in adult patients with severe sepsis or septic shock	No overall effect on mortality at day 28, ICU discharge or hospital discharge. Reversal of shock occurs more rapidly with corticosteroids. Lower mortality at day 28 for hydrocortisone dose ≤ 300 mg per day for at least 5 days
Venkatesh et al. (2018)	Multicenter RCT (n=3800) in ventilated patients with septic shock of hydrocortisone (200 mg per day via continuous infusion) for 7 days versus placebo	No difference in mortality at day 90, but faster reversal of shock and reduced duration of mechanical ventilation with corticosteroids
Annane et al. (2018)	Multicenter RCT (n=1241) in patients with definite or probable septic shock of hydrocortisone (50 mg every 6 hours and fludrocortisone 50 µg enterally daily) for 7 days versus placebo	Reduced mortality at day 90, with more vasopressor- and organ-failure free days

In both ADRENAL and APROCCHSS hydrocortisone was administered for a maximum of 7 days and ceased even if the patient remained in shock. There is anecdotal evidence that many clinicians, who do choose to administer hydrocortisone to patients with septic shock do not administer for a fixed duration (i.e., 7 days) but will administer hydrocortisone for a shorter or longer duration,

corresponding to the duration of shock (as determined by vasopressor administration). This strategy has not been evaluated in randomized clinical trials.

The role of corticosteroids in patients with sepsis but not septic shock is also uncertain, with a recent study reporting that corticosteroids were not effective in preventing the development of shock. (Keh et al., 2016) This raises the possibility that the effect of corticosteroids in patients with sepsis may be different depending on the presence of absence of shock at the time of enrollment.

Overall, there is legitimate uncertainty regarding whether corticosteroids are beneficial in patients with septic shock secondary to CAP and, if so whether there are differences in benefit from administration of a fixed-course compared with a duration that is variable corresponding to the duration of septic shock.

6.2.4. Role of corticosteroids in CAP irrespective of septic shock

The clinical manifestations of pneumonia are a product of the interaction between an infective pathogen and the local and systemic inflammatory responses of the host. A more pronounced and aggressive inflammatory response has been shown in several studies to be associated with treatment failure and increased rates of mortality. (Antunes et al., 2002) In support of this hypothesis that an over-active immune response is deleterious, higher levels of pro-inflammatory cytokines and chemokines (i.e. IL-6 and IL-8) have been detected in patients with severe CAP and associated with increased rates of mortality. (Antunes et al., 2002) This raises the possibility of a beneficial effect of dampening of this 'abnormal' immune response with corticosteroids, irrespective of the presence of septic shock.

A number of trials have evaluated the effect of administration of corticosteroids in patients with severe CAP. These studies have been reviewed by Prina and colleagues (2016), and are summarized in Table 2 (modified from *Prina et al*, 2016). A 2011 Cochrane meta-analysis by Chen et al. (6 RCTs, n=437) suggested that corticosteroid therapy increased the speed of resolution of symptoms and shortened the time-interval to achieve clinical stability but did not demonstrate any effect to reduce mortality. (Chen et al., 2011) A more recent meta-analysis by Nie et al. (9 RCTs, n=1001) showed that administration of corticosteroids did not result in a demonstrable decrease in mortality, across all studies, but a beneficial effect on mortality may be present among the sub-group of patients with severe CAP when patients received more than 5 days of corticosteroid treatment. (Nie et al., 2012) A 2016 meta-analysis by Wan et al. (9 RCTs, n=1,667 and six cohort studies, n=4,095) of adult CAP were analyzed and the authors reported that treatment with corticosteroids is safe and may reduce the risk of ARDS, and shorten the duration of disease. (Wan et al., 2016) These meta-analyses

included heterogeneous populations of CAP (mild, moderate and severe CAP) and heterogeneous interventions (low to very high dose of steroids). Another meta-analysis by Cheng et al. (4 RCTs, n=264), which included only patients with severe CAP concluded that, although corticosteroid therapy may reduce mortality for adult patients with severe CAP, the results should be interpreted with caution due to the instability of the pooled estimates. (Cheng et al., 2014) The authors concluded that reliable treatment recommendations could only be produced if additional multicenter studies with sufficient statistical power were conducted. (Cheng et al., 2014)

Two recent relatively large high quality multicenter RCTs have been published regarding the use of corticosteroids in CAP that were not included in the meta-analyses of patients with CAP. Blum et al. conducted a multicenter, double-blind, randomized, placebo-controlled trial (n=785) of patients with CAP who were randomized to receive either prednisone (50 mg, oral) or placebo for 7 days. The trial reported that corticosteroids reduced the time to reach clinical stability and that hyperglycemia was more common in the corticosteroid group but that the mortality rate was not different between the two groups. (Blum et al., 2015) In the second study, by Torres et al, 2015, a multicenter severe CAP RCT (n=120), participants were randomized to receive either corticosteroids (methylprednisolone at a dose of 0.5mg/kilogram (kg) every 12 hours for 5 days) or not. Treatment with corticosteroids reduced treatment failure in comparison with the placebo group, but not hospital mortality. (Torres et al., 2015)

As highlighted in Table 2, the aggregate conclusion from these studies is that there is reasonable evidence to indicate that use of corticosteroids in CAP may result in the following benefits: reduced hospital length of stay (LOS), reduced time to clinical stability, and prevention of ARDS. However, none of these are patient-centered end-points and, as yet, there is no definitive answer regarding the effect of corticosteroids on mortality. This, combined with the huge heterogeneity in current clinical practice indicating clinical equipoise exists, makes now the time to conduct such a large adequately powered study examining patient centered outcomes.

Table 2: Studies on corticosteroids in CAP (adapted from Prina et al, 2016)

Reference	Study design, population and intervention	Main results (effect of corticosteroids)
Confalonieri et al. (2005)	Multicenter RCT (n=46), severe CAP Hydrocortisone (200 mg bolus + infusion (10 mg/hour) for 7 days) versus placebo	Increased PaO2/FiO2, higher chest radiograph score, lower CRP, delayed septic shock, reduced hospital LOS and mortality
Garcia-Vidal et al. (2007)	Retrospective observational study patients with severe CAP, systemic steroids	reduction in mortality
Snijders et al. (2010)	Single center RCT (n=230), CAP Prednisolone (40mg daily for 7 days) versus placebo	Clinical cure at day 7 unchanged Late failure (>72 hours) increased with prednisolone
Meijvis et al. (2011)	Bicenter RCT (n=304), CAP Dexamethasone (5 mg daily for 4 days) versus placebo	Reduced hospital LOS
Chen et al. (2011)	Meta-analysis (6 RCTs, n=437), CAP	Faster resolution of symptoms Faster clinical stability Lower rate of relapse
Nie et al. (2012)	Meta-analysis (9 RCTs, n= 1001), CAP	No change in mortality overall Reduced mortality in severe CAP
Shafiq et al. (2013)	Meta-analysis (8 RCTs, n=1119), CAP	Reduced hospital LOS, No change in mortality
Cheng et al. (2014)	Meta-analysis (4 RCTs, n=264), severe CAP	Reduced hospital LOS and mortality
Torres et al. (2015)	Multicenter RCT (n=120), CAP Methylprednisolone (0.5 mg/ kg 12 hourly for 5 days) versus placebo	Less treatment failure, No difference for in-hospital mortality
Blum et al. (2015)	Multicenter RCT (n=785), CAP Prednisolone (50mg daily for 7 days) versus placebo	Reduced time to clinical stability
Siemieniuk et al. (2015)	Meta-analysis (12 RCTs, n= 1974), CAP	Reduced all-cause mortality, mechanical ventilation and ARDS, reduced time to clinical stability, shorter duration of hospitalization
Wan et al. (2016)	Meta-analysis (9 RCTs, n=1667)	No effect on mortality in CAP and Severe CAP, less ARDS

6.2.5. Role of corticosteroids in CAP secondary to influenza

The role of corticosteroids in patients with CAP caused by or occurring in association with influenza infection has been a longstanding controversy. Existing evidence is derived predominantly from observational studies. During the 2009 H1N1 influenza pandemic, among patients admitted to an ICU, approximately one third of patients received corticosteroids (Falagas et al., 2010) as either a primary therapy or as a rescue therapy for patients with severe ARDS. (Kumar et al., 2009, Dominguez-Cherit et al., 2009) This widespread use occurred despite the absence of any evidence from RCTs regarding the effectiveness of corticosteroids in CAP secondary to influenza. A systematic

review and meta-analysis (nine cohort studies, n = 1405, and 14 case-control studies, n = 4700) and a recent secondary analysis of a Spanish cohort study, using propensity matching, showed increased mortality with corticosteroid treatment in influenza H1N1 infection. (Zhang et al., 2015, Moreno et al., 2018) However, it is likely that severity of illness will be a confounding factor in these studies and commonly, in studies enrolling patients who are critically ill, adjustment of confounding may be inadequate. As such, the role of corticosteroids in patients with severe CAP secondary to influenza remains uncertain and both beneficial or harmful effects are possible.

6.2.6. Role of corticosteroids in Acute Respiratory Distress Syndrome

ARDS is common in the critically ill and severe CAP is a common primary etiological factor for its development. Several studies have evaluated the effects of corticosteroids in patients with ARDS including patients with severe CAP. Meduri and colleagues conducted a small (n=24) double blind placebo controlled RCT where patients with severe ARDS who failed to improve by day 7 of respiratory failure were randomized to receive methylprednisolone versus placebo. (Meduri et al., 1998) This study demonstrated that corticosteroid treatment reduced ICU mortality, improved oxygenation and reduced the Multiple Organ Dysfunction Score (MODS). (Meduri et al., 1998), The sample size of this study was small and it is also important to note that there were marked differences in baseline characteristics between groups. (Meduri et al., 1998) A subsequent Acute Respiratory Distress Syndrome Clinical Trial Network (ARDSNet) study randomized (n=180) patients with late ARDS (day 7 to 28) to receive methylprednisolone or placebo. This study demonstrated no difference in 60-day mortality but an increased death rate in those commenced on steroids after 2 weeks. (Steinberg et al., 2006) There was no increase in nosocomial infections but a trend towards increased neuromyopathy and an increased number of ventilator-free days (VFDs), ICU-free days and shock-free days in the first 28 days after treatment. (Steinberg et al., 2006). A recent single center randomized controlled trial (n=197) study of severe sepsis induced ARDS demonstrated that patients randomized to receive hydrocortisone (50mg, IV 6hourly) was associated with significantly improved pulmonary physiology (partial pressure of oxygen in arterial blood and fraction of inspired oxygen concentration ratio (P:F ratio), lung injury score) but had no survival benefit. (Tongyoo et al., 2016)

These findings have variably been interpreted to mean either “current evidence does not support the efficacy of steroids in ARDS” (Agarwal et al., 2007) or “prolonged glucocorticoid treatment substantially and significantly improves meaningful patient-centered outcome variables and has a distinct survival benefit”. (Meduri et al., 2007) Reflecting this apparent controversy the recent LUNG-SAFE study reported low levels of usage of corticosteroid in ARDS globally. (Bellani et al., 2016) It is

clear that there is uncertainty if patients with severe CAP who develop ARDS should receive corticosteroids.

6.2.7. Corticosteroid-associated complications in critical illness.

The complications associated with the systemic use of corticosteroids treatment have been well described. The duration of administration of corticosteroids in patients with severe CAP is short (up-to a week) and, as a consequence, long-term complications of corticosteroid administration, such as diabetes mellitus, weight gain, and osteoporosis are not considered to be likely. However, risks associated with the short-term use in patients with severe CAP include in increased risk of nosocomial infection (due to the immunosuppressive effect of corticosteroids), hyperglycemia (which can be treated with insulin), and myopathy, which may lead to prolongation of the period of mechanical ventilation and weakness during the recovery phase after critical illness. It remains uncertain, in critically ill CAP patients, what is the overall effect of these potential complications on patient-centered outcomes, including survival.

6.2.8. Definitively addressing the role of corticosteroids in severe CAP.

As outlined above, despite RCTs and meta-analyses, more studies are needed to clarify the effect of corticosteroids on mortality. The most important clinical questions are:

- For patients with CAP who develop septic shock, does administration of hydrocortisone affect mortality and, if so, does duration of therapy influence this effect?
- For patients with CAP but who do not develop septic shock does administration of hydrocortisone affect mortality?
- For patients with influenza infection and CAP does hydrocortisone affect mortality?

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of different strategies of corticosteroid utilization in the treatment of severe CAP.

We hypothesize that the probability of all-cause mortality at 90 days after enrollment will differ based on the allocated corticosteroid strategy. The following interventions will be available:

- No corticosteroid (hydrocortisone is not prescribed; no other corticosteroid is permitted; no administration of a placebo)
- Fixed duration hydrocortisone (IV hydrocortisone 50mg every 6 hours for 7 days)

- Shock-dependent duration hydrocortisone (IV hydrocortisone 50mg every 6 hours while in septic shock)

We hypothesize that the treatment effect of different corticosteroid strategies is different depending on the presence or absence of shock at the time of enrollment (strata-by-intervention interaction).

We hypothesize that the treatment effect of different corticosteroid strategies is different depending on the presence or absence of influenza infection at the time of enrollment (strata-by-intervention interaction).

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

The analytic structure of this domain enables several questions to be addressed. First, is the effect of corticosteroids for CAP general to all of CAP, or different in the subset with shock? Second, is the effect of corticosteroids for CAP general to all of CAP, or different in the subset with influenza? Third, is the effect of corticosteroids different when titrated to the period where the patient is clinically in septic shock, rather than by administering a fixed one-week course?

8. TRIAL DESIGN

This domain will be conducted as part of a REMAP-CAP trial (see Core Protocol Section 7). Treatment allocation will be adaptive, as described in the Core Protocol Section 7.5.2.

8.1. Population

The REMAP enrolls patients with severe CAP admitted to ICU (see Core Protocol Section 7.3).

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 (see Core Protocol Section 7.4). Patients eligible for the REMAP may have conditions that exclude them from the Corticosteroid Domain.

8.2.1. Domain inclusion criteria

Nil.

8.2.2. Domain exclusion criteria

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

- Known hypersensitivity to hydrocortisone
- Intention to prescribe systemic corticosteroids for a reason that is unrelated to the current episode of CAP (or direct complications of CAP), such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven *Pneumocystis jiroveci* pneumonia
- More than 24 hours have elapsed since ICU 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

Nil.

8.3. Interventions

8.3.1. Corticosteroid strategy interventions

Patients will be randomly assigned to receive one of the following open-label study interventions.

Patients allocated to the *no corticosteroid* intervention are not to receive any systemic corticosteroid, including hydrocortisone, for this episode of CAP and its direct complications up until study day 28. There is no administration of placebo. If a patient has been receiving any corticosteroid for CAP or its direct complications prior to enrollment, this medication must be ceased. Administration of a systemic corticosteroid, including hydrocortisone, is permitted only for the treatment of new illnesses that develop in the course of a patient's ICU stay, such as asthma or treatment of an allergic reaction. All use of systemic corticosteroids is recorded and the reason for any administration is documented.

Patients allocated to the *fixed-duration hydrocortisone* intervention are to be prescribed a course of hydrocortisone 50mg IV every 6 hours for 7 days only. Administration is to commence immediately after the allocation status is revealed at the time of enrollment on study day 1. The 7-day course will be administered until at least the end of study day 7 and no longer than the end of study day 8. From completion of the 7-day course onwards, patients allocated to this intervention are not to receive any systemic corticosteroid, including hydrocortisone, for this episode of CAP and its direct complications up until study day 28. Administration of a systemic corticosteroid, including hydrocortisone, after completion of the 7-day course is permitted only for the treatment of new

illnesses that develop in the course of a patient's ICU stay, such as asthma or treatment of an allergic reaction. All use of systemic corticosteroids is recorded and the reason for any administration from study day 9 onwards is documented.

For patients who are discharged from the ICU before the end of the 7-day course of hydrocortisone, it is the responsibility of ICU staff to prescribe hydrocortisone to complete the 7-day course. However, it is not the responsibility of ICU medical or research staff to ensure continuation of the hydrocortisone after discharge from the ICU and it is not a protocol deviation if the course of hydrocortisone is not completed after ICU discharge.

Patients allocated to the *shock-dependent duration hydrocortisone* intervention, will have hydrocortisone, IV 50 mg every 6 hours, commenced if septic shock develops as a result of the patient's initial episode of CAP, up until study day 28. Hydrocortisone is to be commenced as soon as septic shock is diagnosed, including immediately after enrollment if septic shock has already been diagnosed. For the purposes of this intervention, septic shock is defined as administration of any vasopressor by continuous infusion where the treating clinician believes that the vasopressor requirement is caused by CAP and is not being administered for another reason such as untreated hypovolemia or solely to offset the effects of other ICU interventions such as administration of sedation or mechanical ventilation. The exact dose of vasopressor that defines septic shock is not set by the protocol but is based on the treating clinician's judgement. The rationale for avoiding an exact dose is because no particular dose signifies 'shock' unambiguously. Dosage guidance of vasopressor for initiation of corticosteroids for this intervention is described in a separate operational document.

Hydrocortisone administration is to cease when the clinician believes that septic shock has resolved. Septic shock would always be regarded as having resolved if vasopressor infusion has not been administered in the preceding 24 hours. A clinician may regard septic shock to have resolved if vasopressor infusion is being administered intermittently or at sufficiently low dose. If, after cessation of hydrocortisone, but during the same ICU admission, there is redevelopment of septic shock due to CAP (as defined above), then hydrocortisone IV 50 mg every 6 hours is to be recommenced until resolution. Hydrocortisone should be ceased prior to ICU discharge.

For all patients in this domain who remain in ICU after study day 28, data on the administration of corticosteroids is not collected, and administration of corticosteroids after study day 28 is at the discretion of the treating clinician. The interventions in this domain apply to any ICU readmission, up until study day 28, noting that the criteria related to CAP and its direct complications still apply. If septic shock develops during the first or any subsequent ICU admission for a reason other than CAP,

such as nosocomial infection, administration of corticosteroids is at the discretion of the treating clinician.

8.4. Concomitant care

New or additional systemic corticosteroids may be administered to any patient who has received an allocation status in this domain for a new clinical indication other than CAP and its direct complications. All use of systemic corticosteroids is recorded and the reason for any new or additional administration is documented.

The administration of etomidate after enrollment is not permitted and will be considered a protocol deviation.

8.5. Endpoints

8.5.1. Primary endpoint

The primary endpoint for this domain is the REMAP primary outcome (all-cause mortality at 90 days) as specified in Core Protocol Section 7.6.1.

8.5.2. Secondary endpoints

All secondary endpoints as specified in the Core Protocol Section 7.6.2.

The domain-specific secondary outcome measures (occurring during the index hospitalization, censored at 90 days after enrollment) will be:

- serious adverse events (SAE) as defined in CORE Protocol

There are no additional domain-specific secondary outcome measures. It is accepted as being established that treatment with corticosteroids results in increase in blood sugar levels and decreases the duration of vasoactive therapy. It is not an objective of this trial to re-evaluate these questions but determine the aggregate effect of treatment with corticosteroids on mortality. It is also known that treatment with corticosteroids can result in myopathy and muscle weakness but this effect will be evaluated by the aggregate effect of treatment, in conjunction with other factors, on the duration of mechanical ventilation and long-term outcomes, for participants enrolled at sites that are collecting long-term outcomes.

9. TRIAL CONDUCT

9.1. Domain-specific data collection

9.1.1. Clinical data collection

Additional domain-specific data will be collected.

- Administration of systemic corticosteroids
- Administration of etomidate between index hospital admission and randomization, and between randomization and the end of study day 8

Refer to Core Protocol Section 8.9 for data collection fields and processes.

9.2. Criteria for discontinuation

Refer to Core Protocol Section 8.7 for criteria for the discontinuation of participation in the REMAP-CAP trial.

9.3. Blinding

9.3.1. Blinding

Hydrocortisone will be administered on an open-label basis.

9.3.2. Unblinding

Not relevant.

10. STATISTICAL CONSIDERATIONS

10.1. 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.

10.2. Unit-of-analysis and strata

There are four units-of-analysis for this domain, specified by the combination of shock and influenza strata status. Analysis and Response Adaptive Randomization are applied by shock and influenza status. The statistical model will permit borrowing between all stratum as specified in Core Protocol Section 7.8.3.3.

It is noted that the definition of shock that is specified in the Core Protocol (presence or absence of inotrope or vasopressor infusion at baseline) determines strata status, and not the definition of septic shock that is used to define administration of hydrocortisone in the *shock-dependent duration hydrocortisone* intervention.

10.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal and Initiation (see Section 7.8.3.6 in Core Protocol). For patients allocated to the *shock-dependent duration hydrocortisone* intervention, who are not in septic shock at the time of randomization, Immediate Reveal and Initiation is interpreted as intention to commence hydrocortisone if septic shock develops.

10.4. Interactions with interventions in other domains

An *a priori* interaction with the Antibiotic Domains is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

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 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.

10.5. Nesting

The interventions in this domain will be analyzed without application of nesting. This is because the *shock-dependent duration hydrocortisone* intervention will be more like the *fixed-duration hydrocortisone* intervention in patients who develop septic shock and more like the *no corticosteroid*

intervention in patients who do not develop septic shock (i.e. no hydrocortisone is administered). This divergence in potential similarity cannot be accommodated within the statistical model to allow nesting. For reasons of participant safety and relevance to public health, the DSMB are empowered to request a secondary model to be performed which does allow nesting, if the DSMB believes that it is appropriate to do so.

10.6. Threshold odds ratio delta for equivalence

The threshold odds ratio for equivalence in this domain is that specified in the Core Protocol (Section 7.8.8).

10.7. Post-trial Subgroups

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:

- All other potentially evaluable treatment-by-treatment interactions with other domains

11. ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, 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.

11.2. Potential domain-specific adverse events

Potential domain-specific harms related to corticosteroid therapy include hyperglycemia, nosocomial infections and ICU-acquired weakness. However, the relevant clinical endpoint related to these potential harms is a reduction in VFDs or organ failure free days (OFFDs), an increased LOS in ICU or hospital, or death. We will collect these endpoints as described in the Core Protocol.

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).

11.3. Domain-specific consent issues

Hydrocortisone has been used by clinicians for patients with severe CAP for decades. However, there is substantial variation between clinicians within and between countries and hospitals within countries. This variation in practice occurs, predominantly, because the limited high-quality evidence is contradictory. If this domain were not part of this REMAP it is reasonable to presume that some, but far from all, patients at sites that are participating in the REMAP would receive corticosteroid treatment.

Corticosteroids are not contraindicated in women who are pregnant and patients who are pregnant will not be excluded from this domain.

The choice of which the three interventions are available at any site (i.e. any two or all three interventions) is determined by the participating site. Sites for which standard care is to routinely administer hydrocortisone to patients with septic shock should not participate in the *no hydrocortisone* intervention. The remaining two interventions administer hydrocortisone to patients who have or develop septic shock, but do so for different durations for which may sites will have clinical equipoise.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. This domain has not received any additional domain-specific funding.

12.2. Funding of domain interventions and outcome measures

Hydrocortisone will be provided by participating hospitals on the basis that, in the absence of the REMAP, a proportion of patients with severe CAP would otherwise have received corticosteroids. Additionally, hydrocortisone is no longer a medication protected by patent in any country that is participating in the Platform and the cost of hydrocortisone is minimal.

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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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 1.0 dated 31st January, 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

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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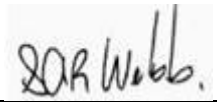
5. PANDEMIC WORKING GROUP AUTHORISATION

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 31st January, 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.

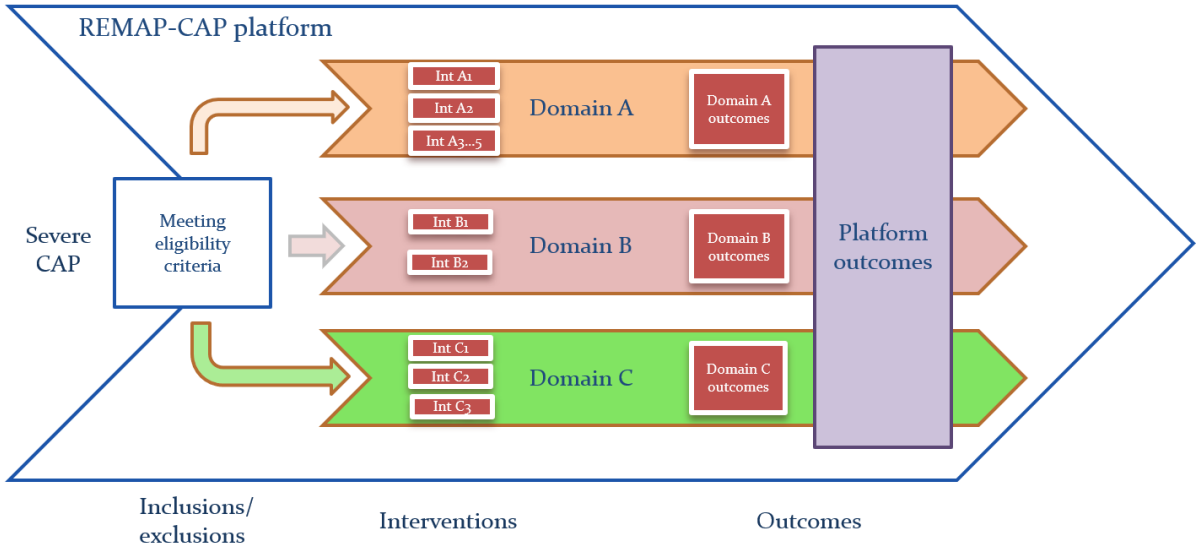


Figure 1. The multifactorial structure of REMAP-CAP

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*).

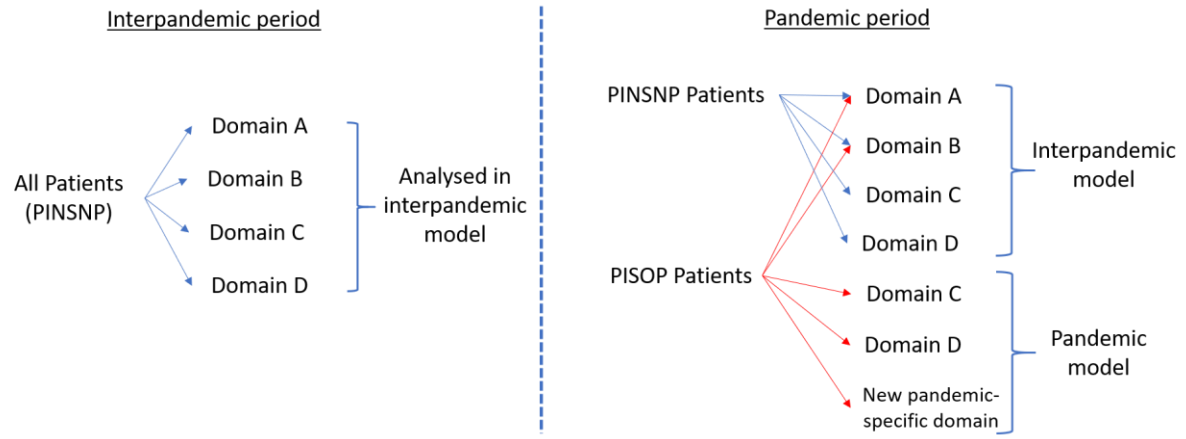


Figure 2. Diagram of the interpandemic and pandemic models

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

REGISTRY APPENDIX

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

Registry Appendix Version 1.0 dated 11 September 2019

Summary

This is an Appendix within REMAP-CAP to provide an observational dataset of patients who are admitted to an Intensive Care Unit (ICU) for community acquired pneumonia (CAP). It includes patients who are allocated to an intervention within one or more REMAP-CAP Domain(s) ("platform-randomized") and patients meeting a minimum set of eligibility criteria but not allocated an intervention within a Domain ("registry-only").

The objectives are to describe the characteristics, outcomes, and associations with risk factors for all patients admitted to participating ICUs for CAP; to compare the platform ineligible, platform eligible but not randomized, and platform eligible and randomized populations to facilitate site feedback and development of domains; and to evaluate the effect of allocation status for platform-randomized patients on long-term outcomes.

Admissions of adult patients to ICU for CAP will be linked to existing healthcare-related registries and databases in participating countries or regions. These will include the relevant national or regional ICU patient benchmarking registry or database, and may include other non-ICU patient benchmarking registries, death registries and hospital discharge coding databases. In some countries or regions additional data for Registry-only participants may also be obtained from the clinical record. Registries and databases, methods for linkage and data to be obtained are specified in a regional addendum.

The primary outcome is mortality at hospital discharge (censored at 90 days). Secondary outcomes include severity of illness, intensity of organ support, length of ICU and hospital stay, ICU re-admissions, hospital discharge destination, mortality after discharge, and subsequent hospital re-admissions. Exposures include baseline risk factors, microbiological causation, and allocation status for randomized patients. Statistical analyses will be undertaken as pre-specified in a separate statistical analysis plan.

REMAP-CAP: Registry Appendix Summary	
Population	Patients allocated to an intervention within one or more REMAP-CAP Domains ("platform-randomized") and patients meeting a minimum set of eligibility criteria but not allocated an intervention within a Domain ("registry-only")
Interventions	This appendix specifies only collection of data. It does not specify any interventions.
Inclusions	Adult patient admitted to an ICU for acute CAP with: • Symptoms or signs or both that are consistent with lower respiratory tract infection, AND • Radiological evidence of new onset infiltrate of infective origin (in patients with pre-existing radiological changes, evidence of new infiltrate)
Exclusions	Healthcare-associated pneumonia, defined as: • Prior to this illness, is known to have been an inpatient in any healthcare facility within the last 30 days, OR • Resident of a nursing home or long-term care facility.
Outcome measures	Those available from the linked ICU patient benchmarking databases and, where feasible, other routinely collected data sources in each participating country or region.

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1. ABBREVIATIONS

APACHE II	Acute Physiology, Age, Chronic Health Evaluation II
CAP	Community Acquired Pneumonia
CONSORT	Consolidated Standards of Reporting Trials
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
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix

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), this Registry Appendix, 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. REGISTRY APPENDIX VERSION

The version of the Registry Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the Registry Working Group on 11 September 2019

4. REGISTRY GOVERNANCE

4.1. Registry Working Group

Chair: Dr. Colin McArthur

Members: Associate Professor Sean Bagshaw

Professor Michael Baker

Professor Frank Brunkhorst

Dr. Lennie Derde

Professor David Harrison

Dr. Alex Kazemi

Associate Professor Peter Kruger

Dr. Ed Litton

Dr. Susan Morpeth

Mr. Paul Mouncey

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4.2. Contact Details

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5. REGISTRY WORKING GROUP AUTHORIZATION

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

Chair
Colin McArthur

Date 11 September 2019

6. BACKGROUND AND RATIONALE

6.1. Definition

This is an appendix to the REMAP-CAP protocol, to provide an observational dataset of patients with CAP who are admitted to an ICU that is participating in REMAP-CAP.

6.2. Registry-specific background

All patients admitted to ICU as a result of CAP form a population of interest for this REMAP, as it is from this population that qualifying patients are assigned treatment within domains. However, some patients admitted to ICU as a result of CAP will not meet the criteria for inclusion in the platform or

any of the available domains. Although basic eligibility screening data is available for the reporting of patient flow consistent with Consolidated Standards of Reporting Trials (CONSORT) guidelines, it is important to understand some wider characteristics of excluded patients who have the disease of interest. This facilitates other aspects of general trial management and interpretation such as the generalizability of results, the identification of selection bias and to provide feedback to sites. For this REMAP, this additional observational data also assists in the refinement of the platform and its existing domains, and in the development of further domains. Furthermore, in combination with the data from participants assigned treatment within the domains, a full descriptive analysis of the entire population of patients receiving treatment in an ICU for CAP can be undertaken. Finally, as patients who are assigned to interventions within domains have individual follow-up to a maximum of 180 days, this additional data will facilitate the evaluation of the effect of allocation status on long-term outcomes.

7. REGISTRY OBJECTIVES

The objectives are to:

1. Describe the characteristics, outcomes and associations with risk factors for all patients admitted to participating ICUs for CAP. This may include specific analyses to achieve regional objectives.

2. Describe the characteristics and outcomes of patients admitted to an ICU for CAP to compare the platform ineligible, platform eligible but not randomized, and platform eligible and randomized populations.

3. Evaluate the effect of allocation status for randomized patients on long-term outcomes.

8. STUDY DESIGN

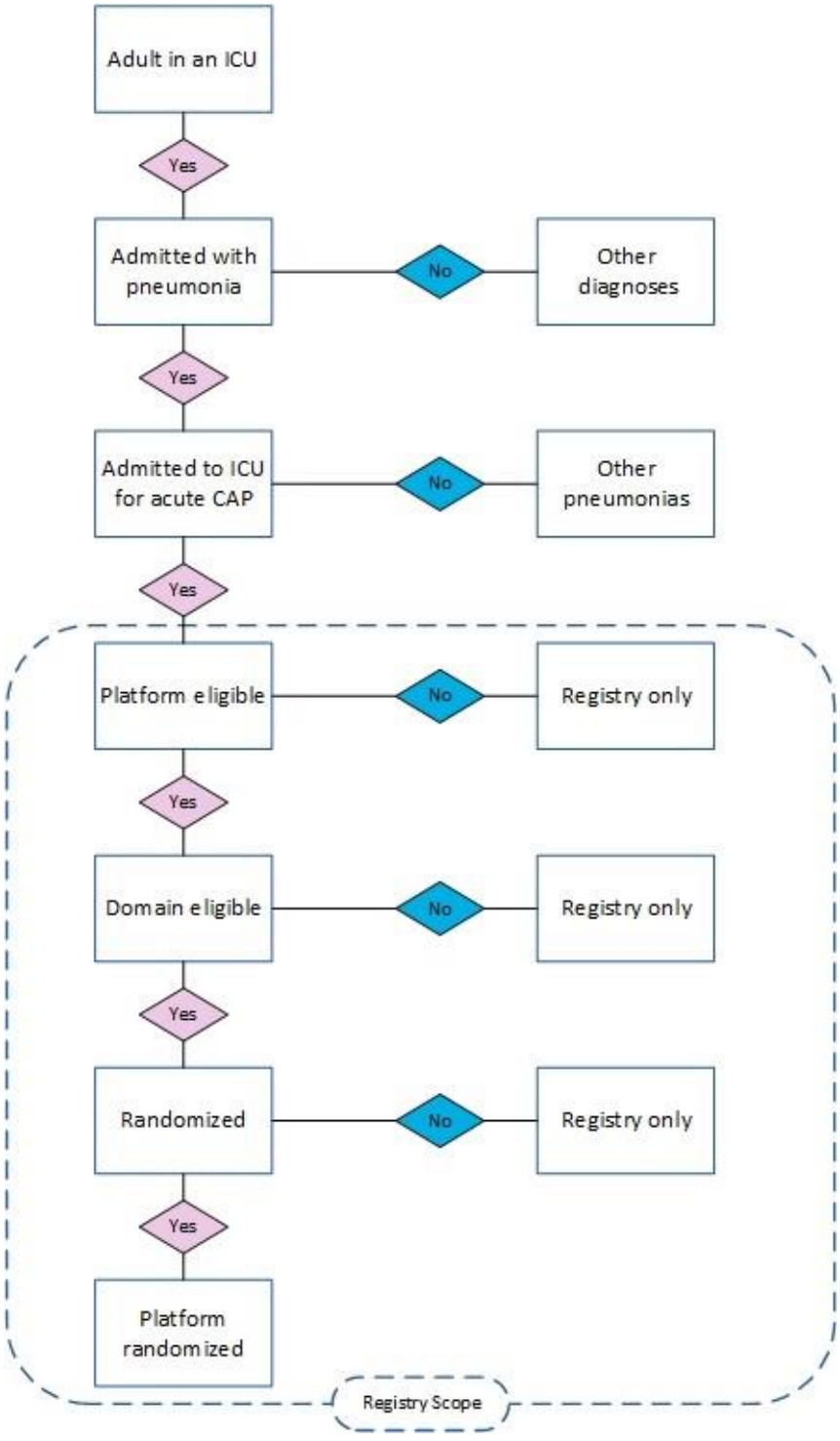
This Registry will be conducted as part of the REMAP trial for severe CAP (see Core Protocol Section 5.3.8).

8.1. Population

The study population for the Registry comprises all adult patients admitted to a participating ICU for CAP. This population is divided into two mutually exclusive cohorts: those eligible for the platform

and assigned treatment within one or more REMAP-CAP domains (“Platform-randomized”); and a cohort who are either not platform eligible, or are platform eligible but not assigned treatment within a Domain (“Registry-only”).

Figure 1: Registry population



8.2. Eligibility criteria

Patients are eligible for the Registry if they meet a reduced set of the REMAP-CAP platform-level inclusion and exclusion criteria (see Core Protocol Section 7.4), which are consistent with standard international guideline definitions (Mandell et al, 2007).

The Platform inclusion criteria which are not applied are:

- The time-window requirement that patients with CAP must be admitted to an ICU within 48 hours of hospital admission
- The requirement to receive organ support up to 48 hours after ICU admission

Platform exclusion criteria which are not applied are:

- 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
- Previous participation in this REMAP within the last 90 days

The Registry inclusion and exclusion criteria are therefore as follows:

8.2.1. Registry inclusion criteria

Adult patient admitted to an ICU for acute CAP with:

a. symptoms or signs or both that are consistent with lower respiratory tract infection, AND
b. radiological evidence of new onset infiltrate of infective origin (in patients with pre-existing radiological changes, evidence of new infiltrate)

8.2.2. Registry exclusion criteria

Healthcare-associated pneumonia, defined as:

a. Prior to this illness, is known to have been an inpatient in any healthcare facility within the last 30 days, OR
b. Resident of a nursing home or long-term care facility.

8.3. Interventions

The Registry specifies no interventions and only collects data previously obtained and recorded for clinical care and administration.

8.4. Data points

8.4.1. Data sources

All adult ICU patients considered to have CAP are assessed for eligibility for participation in REMAP-CAP. Those patients meeting the Registry inclusion criteria and none of the Registry exclusion criteria (Section 8.2) will be linked to existing healthcare-related registries and databases to obtain data. These will include the relevant national or regional ICU patient benchmarking registry or database (which enrolls all patients admitted to all participating ICUs), and may include one or more of other non-ICU patient benchmarking registries, death registries, and hospital discharge coding databases. Linkage may be performed using national or local patient identifiers in accordance with national and local data governance requirements.

The minimum data requirement for site participation is the availability of linked data from the relevant regional or national ICU patient benchmarking registry for each ICU admission meeting the Registry inclusion criteria and none of the exclusion criteria. In some countries or regions additional data for Registry-only participants may be obtained from the clinical record using a Registry-only CRF.

Country or region-specific data sources and methods for data linkage are described in the addendum (Section 14).

8.4.2. Intensive care registries and databases

The following data will be obtained from existing ICU registries or databases in participating countries or regions:

- Patient demographic information
- Dates and times of hospital and ICU admission and discharge
- Patient co-morbidities
- Admission diagnosis and reason for admission
- Physiological and treatment data used to calculate severity of illness scores

- Organ support
- Vital status and, for survivors, discharge destination

8.4.3. Case Report Form data variables

The follow data may be obtained from the clinical record in regions where it is feasible for all or some patients:

- Additional demographic information
- Baseline physiology
- Risk factors for community-acquired pneumonia
- Additional co-morbidities
- Microbiological causative organism(s)
- Level of organ support on days 1 – 3

8.4.4. Other linked data variables

The following data may be obtained by data linkage with death registries and hospital discharge coding databases in regions where feasible:

- Hospital readmissions, and diagnoses and procedures carried out during readmissions
- Mortality after discharge from the index hospitalization

9. STUDY CONDUCT

9.1. Registry-specific data collection

Platform-randomized cohort:

- Data linkages to healthcare-related registries and databases as specified in Sections 8.4.2 and 8.4.4 above, and regional addendum.
- Census-based socio-economic unit (in some regions as per regional addendum)
- It is noted that data to be collected on Platform-randomized patients is specified in Core Protocol and relevant DSAs and that no additional data is collected directly from the case-record during the index hospitalization

Registry-only cohort:

- Registry-only CRF variables (in some regions as per regional addendum, see Section 8.4.3 above)
- Data linkages to healthcare-related registries and databases as specified in Sections 8.4.2 and 8.4.4 above and in the regional addendum.
- Census-based socio-economic unit (in some regions as per regional addendum)

10. STATISTICAL CONSIDERATIONS

This is a prospectively defined observational cohort study with retrospective data linkage and collection. The population is patients admitted to ICU for CAP. The primary outcome is mortality at hospital discharge (censored at 90 days). Secondary outcomes include severity of illness (APACHE II), intensity of organ support, length of ICU and hospital stay, ICU re-admissions during the index hospitalization, hospital discharge outcome, mortality after discharge from index hospitalization, time to death, and subsequent hospital re-admissions. Exposures include age, sex at birth, baseline co-morbidities, weight, body mass index, pregnancy status, socio-economic status, ethnicity, microbiological causation, and allocation status for randomized patients.

Statistical analyses will be undertaken as pre-specified in a separate statistical analysis plan for the Registry.

11. ETHICAL CONSIDERATIONS

11.1. Principles

This observational study utilizes retrospective collection of existing clinical data and routinely collected healthcare and administrative data only. There are no interventions. Risk to participants is therefore very low, and primarily relate to the secure handling of data. Data linkage will be undertaken utilizing the minimum individual identifiers and only obtaining the variables relevant to the study.

11.2. Consent

Country-specific requirements for consent to research involving observational data will be submitted for health research ethical and regulatory approval as appropriate at each participating site. In view of the low-risk nature of this study, applications for approval may include a waiver of participant consent for registry-only patients. For platform-randomized patients, information related to

additional data collection by record linkage will be incorporated within the consent process for such patients. Patients who are platform-randomized but withdraw from the trial may also withdraw from the registry components outlined in this appendix. Ethical issues that are specific to a participating country are outlined in the regional addendum.

12. GOVERNANCE ISSUES

12.1. Funding of Registry

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. This domain has not received any additional domain-specific funding.

Registry participation may be supported with payments to sites, depending on the resources available and workload required for participation in each specific country or region.

12.2. Registry-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 are publicly accessible on the study website.

13.REFERENCES

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14. NEW ZEALAND REGISTRY ADDENDUM

14.1. Data sources

14.1.1. Registry Case Report Form

Data variables extracted retrospectively by ICU staff from the clinical and administrative records for the index hospitalization as per Section 8.4.3, including those required to facilitate data linkage as per 14.2.2 and 14.2.3 below. These variables include up to two NZ Level 2 ethnicities and socio-economic decile derived from NZDep2013 score attributable to the census meshblock of the address of domicile. Only the derived socio-economic decile will be submitted, not the address.

14.1.2. Australia and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation (CORE) Adult Patient Database (APD)

All participating ICUs in New Zealand submit data on all admissions to the Australian and New Zealand Intensive Care Society Adult Patient Database (APD) for benchmarking risk-adjusted performance. Each ICU patient is allocated a non-identifying 'APD number' at the time of submission of data to the APD. Following agreement with participating ICUs, patients meeting the entry criteria specified in this Appendix will be linked to the APD record for the same ICU admission by the submission to the REMAP-CAP database of the 'APD number' with linkage supplemented, where appropriate, by additional variables such as age, sex, and hospital and ICU admission dates and times to allow for transcription errors in the 'APD number'. Patient-level data variables as per Section 8.4.2 for the index ICU admission and subsequent ICU admissions in the same hospitalization will be obtained from the APD.

14.1.3. Ministry of Health National Minimal Dataset and Death Registry

REMAP-CAP will utilize each patient's National Health Index number to link to data on the same individual held by the Ministry of Health in the National Minimum Dataset (NMDS) related to diagnosis and procedure codes for hospital admissions for that individual both before and after the index hospitalization, as well as Death Register.

14.2. Ethical issues and approvals

This Registry retrospectively utilizes existing data sources relevant to the index ICU admission for CAP for research purposes, and meets to the requirements of the Health Information Privacy Code

for secondary use of health information without consent as data will not be published in a form that could reasonably be expected to identify any individual. However, as consent from will be sought from platform-randomized participants when competent, this additional data linkage and utilization will be included in the consent process for those participants.

15. AUSTRALIA REGISTRY ADDENDUM

15.1. Data sources

15.1.1. Registry Case Report Form

Registry CRF data will not be collected at Australian sites.

15.1.2. Australia and New Zealand Intensive Care Society (ANZICS) Centre for Outcome and Resource Evaluation (CORE) Adult Patient Database

All ICUs in Australia that are participating in the REMAP-CAP registry submit data on all admissions to the ANZICS CORE Adult Patient Database (APD). All patients admitted to these ICUs are allocated a unique 'APD number' at the time of first submission of data to the APD at that hospital and the same number if used for subsequent ICU admissions at that hospital, including during subsequent hospitalizations.

Data submitted to the APD includes information related to dates and times of ICU admission, admission diagnoses, physiological and treatment data from the first 24 hours of ICU admission used to calculate severity of illness scores, provision of organ support, survival status at hospital discharge, and, for survivors, discharge destination (corresponding to the data outlined in section 8.4.2). The APD also undertakes additional linkage to other databases and registries including the death registry. Where such additional linkage has been undertaken this data may be requested for REMAP-CAP registry patients. All secondary use of data is dependent on approval from the data custodian of that dataset.

Patients meeting the entry criteria specified in this Appendix will be linked to the APD record by submission of the 'APD number' to the REMAP-CAP database. Linkage will be supplemented, where appropriate, by additional variables such as age, sex and hospital and ICU admission dates and times to allow for transcription errors in the 'APD number' and to enable linkage to the correct ICU episode. Patient level data linkage is required, this will be conducted by staff at ANZICS CORE or REMAP-CAP investigators and will be determined at the time linkage is required.

Neither REMAP-CAP, nor the APD, collect or hold identifier variables such as patient name, address, hospital record number. At the time of evaluation for eligibility for REMAP-CAP, patient initials and date of birth are entered and used to prevent duplicate entry into REMAP-CAP and to enable site staff to identify the participant for study management and data collection. These variables are encrypted in the database and are not accessible centrally by the research team. Both date of birth and initials for registry-only patients will be deleted from the database by the site as soon as they are no longer necessary for study management purposes, with the guidance provided to sites being that this should occur as soon as the APD number is entered into the REMAP-CAP CRF. ANZICS CORE does not collect patient initials but does collect date of birth, but data for this variable will not be made available to REMAP-CAP at any time.

15.2. Ethical issues and approvals

At ICUs in Australia, data collection and submission to the APD occurs with neither provision of information nor consent. The APD provides quality assurance information to participating ICUs by benchmarking their risk-adjusted performance (i.e. adjusted for age, diagnosis, and severity of illness) against all other participating ICUs. The APD is supported financially by all State and Territory health departments in Australia. It has been deemed that the critical quality assurance nature of the APD is such that a complete dataset, comprising all admitted patients, is necessary. The APD is hosted by The Australian Institute of Health and Welfare (AIHW) in Canberra. The APD regards the custodian of data to be the ICU Director at each of the participating ICUs.

A waiver of consent is requested and is consistent with the requirements of the National Statement. The REMAP-CAP registry involves no more than low risk to participants; the only identifier variables are those collected as part of eligibility screening for REMAP-CAP (initials and date of birth), these are encrypted in the database, accessible only to the participating site, and not accessible centrally to REMAP-CAP staff; the benefits from the research outweigh the risks of harm associated with not obtaining consent as linkage provides valuable information for generalizability of trial conclusions and long-term outcome information; there is sufficient protection of privacy and confidentiality (as it is extremely difficult, and more likely impossible, for any person, other than those associated with the site, to identify an individual); and the results of analysis will have neither significance to the health of participants nor commercial significance. It is not practicable to obtain consent as many participants will not be competent to consent and those who are competent will have or be

recovering from critical illness. All data will be handled in a secure manner and sent via secure file transfer.

Linkage to the ANZICS CORE APD allows the REMAP-CAP registry to be conducted efficiently and with minimum expenditure, and enables collection of reliable data at lower burden to individual sites and clinicians. Participation in the REMAP-CAP registry is contingent on each site agreeing to share their ANZICS CORE data with REMAP-CAP. Any release of data is also contingent on approval by the ANZICS CORE management committee.

16.UNITED KINGDOM REGISTRY ADDENDUM

16.1. Data sources

16.1.1. Registry Case Report Form

Registry CRF data will not be collected at United Kingdom (UK) sites.

16.1.2. Intensive Care National Audit & Research Centre (ICNARC) Case Mix Programme (CMP) Database

All adult general critical care units in England, Northern Ireland and Wales that are participating in REMAP-CAP submit data on all admissions to the ICNARC CMP Database. Each admission to critical care is allocated a unique 'CMP admission number (CMP ADNO)'. Data submitted to the CMP Database includes information related to dates and times of ICU admission(s), admission diagnoses, physiological and treatment data from the first 24 hours of ICU admission used to calculate severity of illness scores, provision of organ support, survival status at hospital discharge, and, for survivors, discharge destination (corresponding to the data outlined in section 8.4.2). Patients meeting the entry criteria specified in this Appendix will be linked to the CMP Database record for the same patient by the submission to the REMAP-CAP database of the 'CMP ADNO' with linkage supplemented, where appropriate, by additional variables such as hospital and critical care admission dates and times. Patient's NHS number will be obtained from the CMP Database to facilitate identification of further admissions to a participating critical care unit and record linkage to other databases.

16.1.3. NHS Digital and NHS Wales Informatics Service

NHS Digital has responsibility for collecting data from across health and social care in England. Data held includes civil registrations for England and Wales and Hospital Episode Statistics (HES) for details of all admissions, outpatient appointments and Accident and Emergency attendances at NHS hospitals in England. The NHS Wales Informatics Service (NWIS) holds details of all admissions, outpatient appointments and Accident and Emergency attendances at NHS hospitals in Wales in the Patient Episode Database for Wales (PEDW). For REMAP-CAP registry patients, longer term survival including date of death after hospital discharge, will therefore be obtained through data linkage to NHS Digital. Subsequent hospital readmissions will be determined in England from data linkage to HES via NHS Digital and for Wales via data linkage to PEDW via NWIS.

16.2. Ethical issues and approvals

At critical care units in the UK, data collection and submission to the CMP occurs without provision of consent. The CMP provides quality assessment information to participating ICUs by benchmarking their risk-adjusted performance (i.e. adjusted for age, diagnosis, and severity of illness) against all other participating ICUs. The CMP operates under Section 251 of the NHS Act 2006 permitting the use of patient identifiable data without consent for specified purposes. In addition, to approval from the Health Research Authority (HRA) and research ethics committee, study specific approval from the HRA Confidentiality Advisory Group will be sought in order to access patient information without consent for the purposes of the Registry.

All “platform-randomized” patients will be approached using the consent procedures for participation in the interventional domains. For “Registry-only” patients, information regarding the processing of data, including how to opt-out, for the Registry will be made available by the participating units. It is not practicable to obtain consent as many participants will not be competent to consent and those who are competent will have or be recovering from critical illness. In addition, many patients will be identified retrospectively after discharge from the ICU. All data will be handled in a secure manner and will preserve participant confidentiality.

Region-Specific Appendix:

AUSTRALIA AND NEW ZEALAND

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

REMAP-CAP Australia and New Zealand Region-Specific Appendix Version 3 dated 24 August 2019

THIS STUDY IS SUPPORTED BY THE AUSTRALIAN AND NEW ZEALAND INTENSIVE CARE SOCIETY CLINICAL TRIALS GROUP (ANZICS CTG)

TABLE OF CONTENTS

1. ABBREVIATIONS

ANZ	Australia and New Zealand
ANZIC-RC	Australian and New Zealand Intensive Care Research Centre
ANZICS CORE	Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation
ANZICS CTG	Australian and New Zealand Intensive Care Society Clinical Trials Group
ANZ RCC	Australia and New Zealand Regional Coordinating Center
ANZ RMC	Australia and New Zealand Regional Management Committee
CAP	Community-acquired pneumonia
CRF	Case Report Form
CTA	Clinical Trial Agreement
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
eCRF	Electronic Case Report Form
HRC	Health Research Council
HREC	Human Research Ethics Committee
IIG	International Interest Group
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
IV	Intravenous
MRINZ	Medical Research Institute of New Zealand
NHMRC	National Health and Medical Research Council
NZBOR	New Zealand Bill of Rights
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia
RCC	Regional Coordinating Center
RMC	Regional Management Committee
RSA	Region-Specific Appendix
SAE	Serious Adverse Event

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 interventions 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).

2.1. Region-Specific Protocol version

The version of the Australia and New Zealand (ANZ) RSA is in this document's header and on the cover page.

2.2. Version History

Version 1: Approved by the Australia and New Zealand Regional Management Committee (ANZ RMC) on 20 November 2016

Version 1.1: Approved by the ANZ RMC on 10 April 2017

Version 2: Approved by the ANZ RMC on 12 December 2017

Version 3: Approved by the ANZ RMC on 24 August 2017

3. AUSTRALIA AND NEW ZEALAND REGION

The ANZ region comprises sites in the countries of Australia and New Zealand, plus sites in other countries that may be added subsequently but does not include any site that is located in any country that is active as part of an existing REMAP-CAP region.

The countries to which this appendix applies are:

- Australia (commenced 2016)
- New Zealand (commenced 2016)

4. AUSTRALIA AND NEW ZEALAND STUDY ADMINISTRATION STRUCTURE

4.1. Coordinating center and data management

The Regional Coordinating Center (RCC) of REMAP-CAP in ANZ (ANZ RCC) is the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), Department of Epidemiology and Preventive Medicine, Monash University, in conjunction with the Medical Research Institute of New Zealand (MRINZ). This document outlines the combined responsibilities of the ANZIC-RC and the MRINZ. The ANZIC-RC will have predominant responsibility for the region plus management of sites in Australia and the MRINZ will have primary responsibility for management of sites in New Zealand. The exact specification of roles will be as documented in the contract between the ANZIC-RC and the MRINZ.

4.1.1. Responsibilities

The ANZ RCC is responsible for the following aspects of study management in ANZ:

- Liaison with the ITSC and other RCCs in relation to data management, Case Report Forms (CRFs), and site management
- CRF design for any region-specific data collection
- Management of study budget and liaison with funding bodies
- Development, maintenance, and administration of the regional database
- Recruitment and selection of sites
- Data management
- Protocol training of site investigators and research coordinators
- Preparation and arrangement of investigator payments
- Management of regulatory affairs (for example, Therapeutic Goods Administration etc.)
- Management of study set up including assistance with Human Research Ethics Committee (HREC) applications
- Monitoring and close-out site visits
- Organization of investigator meetings
- Serious adverse event notification to DSMB
- Coordination of data entry and feedback of data enquiries
- Administrative assistance to the Regional Management Committee (RMC), Domain-Specific Working Groups (DSWG), Interest Groups (IIG), and the ITSC, as required
- Public relations for the study

- Liaison with other RMCs to develop study documents and materials that are standardized as much as possible

4.2. Australia and New Zealand Regional Management Committee

4.2.1. Responsibilities

The ANZ RMC is responsible for the following aspects of study management in ANZ:

- Liaison with the staff of the ANZ RCC
- Funding applications to and negotiations and communications with funding bodies located in ANZ, or located in other countries, but for which funding will be used to support trial activities in the ANZ region
- Study budget
- Approval of the RSA
- Approval and establishment of feasibility of domains and interventions in the region
- Development and approval of the RSA and study materials for the region
- Development and approval of data management systems for the region
- General study management issues
- Consumer engagement
- Liaison with the ITSC, DSWGs, IIGs, and other RCCs with regard to analysis and interpretation of results, and collaboration on publications and presentations
- Liaison with and reporting to the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG)

4.2.2. Members

Executive Director and Chief Investigator in Australia

Professor Steve Webb

Deputy Executive Director and Chief Investigator in New Zealand

Dr. Colin McArthur

Chair

Dr. Shay McGuinness

Members

Professor Allen Cheng

Dr. Lennie Derde

Professor Andrew Forbes

Associate Professor David Gattas

Mr Cameron Green

Associate Professor Stephane Heritier

Ms. Lisa Higgins

Associate Professor Peter Kruger

Dr. Ed Litton

Professor Alistair Nichol

Associate Professor Rachael Parke

Ms. Jane Parker

Associate Professor Jeffrey Presneill

Mr. Tony Trapani

Ms. Anne Turner

Dr. Paul Young

4.3. Contact Details

Executive Director

Professor Steve Webb

Department of Epidemiology and Preventive Medicine

School of Public Health and Preventive Medicine, Monash University

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Melbourne, Victoria, 3004

AUSTRALIA

Phone +61 3 9903 0343

Fax +61 3 9903 0247

Email steven.webb@monash.edu

Deputy Executive Director

Dr. Colin McArthur

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Auckland District Health Board Critical Care Medicine
2 Part Road,
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Auckland, 1023
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Phone +64 9 307 4949 Ext 24800
Fax +64 9 307 4827
Email colinm@adhb.govt.nz

4.3.1.Coordinating Center

Coordinating Center

The Australian and New Zealand Intensive Care Research Centre
Department of Epidemiology and Preventive Medicine
School of Public Health and Preventive Medicine, Monash University
Level 3, 533 St Kilda Road
Melbourne, Victoria, 3004
AUSTRALIA
Phone +61 3 9903 0247
Fax +61 3 9903 0071
Email jane.parker@monash.edu
Web http://www.anzicrc.monash.org

Coordinating Center

The Medical Research Institute of New Zealand
Private Bag 7902, Newtown, Wellington 6242, New Zealand
Level 7, Clinical Services Building
Wellington Hospital
Riddiford St, Newtown
Wellington, 6021
NEW ZEALAND
Phone +64 4 805 0248
Fax +64 4 389 5707
Web http://www.mrinz.ac.nz

4.3.2.Project Management

4.3.2.1. Global Project Manager

Cameron Green

Global Project Manager

The Australian & New Zealand Intensive Care Research Centre

Department of Epidemiology and Preventative Medicine

School of Public Health and Preventative Medicine, Monash University

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4.3.2.2. Australia

Jane Parker

Project Manager

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E-mail jane.parker@monash.edu

4.3.2.3. New Zealand

Anne Turner

Project Manager

The Medical Research Institute of New Zealand

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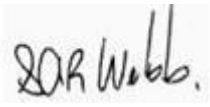
NEW ZEALAND
Phone +64 4 805 0268
Fax +64 4 389 5707
Mobile +64 (0)27 655 8440
Email anne.turner@mrinz.ac.nz

5. ANZ REGIONAL MANAGEMENT COMMITTEE AUTHORIZATION

The ANZ RMC have read the appendix and authorize it as the official ANZ Regional appendix for the study entitled REMAP-CAP. Signed by on behalf of the committee,

Executive Director Steve Webb		Date	24 August 2019
Deputy Director Colin McArthur		Date	24 August 2019

6. TRIAL REGISTRATION

Participation in this trial and involvement of sites is registered ClinicalTrials.gov. The registration number NCT02735707 and was registered on 12 April 2016.

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

7. FUNDING OF REGION

7.1. Sources of funding

In Australia, the trial has been funded by the National Health and Medical Research Council (NHMRC) (APP1101719) for Australian dollars $4,413,145. Funding for the REMAP-CAP study in Australia is included for approximately 2000 patients.

In New Zealand, the trial has been funded by the Health Research Council (HRC) (16/631) for New Zealand dollars $4,814,924. Funding for the REMAP-CAP study in New Zealand is included for approximately 800 patients.

7.2. Site costs

Per-patient and any other project-related payments to sites will be as specified in the Clinical Trial Agreement (CTA) between the Sponsor and each site.

7.3. Sponsors

The sponsor in Australia is Monash University.

The sponsor in New Zealand is the MRINZ.

7.4. Role of sponsor

The role of the sponsor is to act as the legal entity for those trial related activities that can only be undertaken by a legal entity. CTAs will be between the sponsor and participating sites. All other activities, including but not limited to trial design, conduct, safety monitoring, and reporting, are the responsibility of trial steering and management committees and working groups, as specified in the Core Protocol and appendices.

7.5. Insurance

The sponsor/investigator has insurance in accordance with the relevant legal requirements in each country.

8. TRIAL BACKGROUND AND RATIONALE

There are no anticipated issues that are specific to the background and rationale in the Core Protocol of the trial in ANZ. However, some interventions may not be available in all countries or participating sites within the region.

9. TRIAL DESIGN

9.1. Study setting

As described in the Core Protocol Section 7.3.

9.2. Interventions

The RMC will offer all interventions that are available in ANZ to all participating sites in which the intervention is available and feasible.

9.2.1. Antibiotic Domain

All antibiotics that are specified in the Antibiotic Domain-Specific Appendix that are licensed for use in each country within this region will be made available to any site. Ceftaroline will only be made available in New Zealand if it can be supplied without utilizing budget that is available in New Zealand. Intravenous (IV) amoxicillin/clavulanic acid is not licensed for use in Australia.

All antibiotic interventions, except ceftaroline, are off-patent and will be provided by the hospital (as the hospital would have otherwise been provided by that site). Ceftaroline will be provided by the study. See Section 10.3 for information about distribution of any medications provided by the study.

9.2.2. Macrolide Duration Domain

The macrolide duration domain will be offered to any site in this region. IV Azithromycin is licensed for use in New Zealand and oral Azithromycin is widely used, but, due to the cost of IV Azithromycin to hospitals the IV formulation is not widely used. In New Zealand, HRC funding will be available to reimburse sites for up to two doses per patient of IV azithromycin to allow for initial IV loading and patients who are unable to receive enteral azithromycin.

9.2.3. Corticosteroid Domain

The steroid domain will be offered to any site in this region.

9.2.4. Antiviral Domain

The antiviral domain will be offered to all sites in this region.

9.2.5. Ventilation Domain

The ventilation domain will be offered to all sites in this region.

9.2.6. Registry

Participation in the Registry will be mandatory in ANZ. The study population for the Registry comprises adult patients admitted to an Intensive Care Unit for CAP. This population is divided into two mutually exclusive cohorts: those eligible for the platform and assigned treatment within one or more REMAP-CAP domains ("Platform-randomized") and a cohort who are either not platform eligibility, or are platform eligible but not assigned treatment within a domain ("Registry-only"). The purpose of the registry is to provide limited information on all patients with CAP so that the characteristics of patients who are randomized within the Platform are understood in comparison to the admitted population of patients with CAP at participating sites. The registry will aim to collect a dataset that overlaps with, and is not more extensive than, the minimum dataset collected for patients who are randomized within the Platform. The Registry specifies no interventions and only utilizes data recorded for clinical care and administration.

9.3. Endpoints

Data will be collected as set out in the Core Protocol and DSAs. It is mandated in ANZ that trial endpoints that occur after day 90 are collected at sites in ANZ.

9.4. Co-enrollment

As described in the Core Protocol Section 7.9.

10. TRIAL CONDUCT

10.1. Recruitment and embedding

As described in the Core Protocol Section 8.3.

10.2. Treatment allocation

Central randomization will occur online and be managed and operated by Spiral Web Solutions Ltd (New Zealand) at https://remapcap.spinnakersoftware.com.

10.3. Distribution of study drug

The processes and management of distribution of any drug provided by the study will be outlined in operational documents and, as required, specified in the CTA.

10.4. Data collection

Data collection will be as outlined in the Core Protocol Section 8.9. The collection of data from time-points after day 90 will be mandatory in this region.

10.5. Data management

Data will be entered into a secure, password protected web based CRF designed by Spiral Web Solutions Ltd (New Zealand). Data entry and data management will be coordinated by the Project Managers and the coordinating centers including programming and data management support.

Region-specific data points will be:

- Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation (ANZICS CORE) Adult Patient Database number for each enrolled patient

10.6. Trial group linkage / participation

REMAP-CAP has been accorded 'supported' status by the ANZICS CTG. The RMC is responsible for ensuring that all aspects of the study comply with the requirements of supported status, as set out by the ANZICS CTG. Re-application for supported status will be made for each new domain that is being considered.

10.7. Site start up and initiation

A site initiation teleconference or visit will be conducted before site activation; at least 1 routine monitoring visit will be conducted during the recruitment period; and a close out visit. Additional monitoring visits will be planned based on patient inclusion rate or indication. Email and telephone communication will supplement site visits.

Standardized procedures will be in place to educate sites on the trial and trial procedures before site initiation. These include printed material, face-to-face start up meetings, webinars, and on-line study materials.

10.8. Quality assurance and monitoring

10.8.1. Quality assurance

As described in the Core Protocol Section 8.11.

10.8.2. Monitoring

The study will be monitored by a representative of the ANZIC-RC in Australia and the MRINZ in New Zealand. Monitoring will be conducted by quality control reviews of protocol compliance, data queries and safety reporting. The study will use a monitoring plan that is developed on a risk-based approach. Details can be found in the monitoring plan.

A monitoring report will be prepared following each visit and reviewed by the management committee 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 ANZIC-RC and the MRINZ representative for these monitoring visits during the course of the study and at the completion of the study as needed.

10.9. Safety reporting

Safety reporting will occur as outlined in the Core Protocol Section 8.13.

All Serious Adverse Events (SAEs) will be recorded in the electronic case report form (eCRF). All SAEs must be reported to the coordinating center via the trial website within 72 hours of the investigators becoming aware of the event.

The investigator should notify the Institutional / Ethics Committee of the occurrence of the serious adverse event in accordance with local requirements.

Web address https://remapcap.spinnakersoftware.com

Contact phone numbers for SAE advice:

ANZIC-RC	+61 3 9903 0937
MRINZ	+64 4 805 0268

A 24 hour per day contact number for Australia and New Zealand will be provided to all sites before recruitment commences.

11.ETHICAL CONSIDERATIONS

11.1. Ethical and regulatory issues

The trial will be conducted in accordance with legislation in Australia and New Zealand. Research ethics approval will be obtained prior to the start of the study at each institution from the responsible local or national HREC. It is the principal investigator's responsibility to ensure that all conditions for approval of the study are met and that amendments to the protocol or SAEs are also reported to the HREC as required by that committee.

11.1.1. Australia

In the jurisdictions where it is available ethics approval will be sought under the National Mutual Acceptance scheme for mutual acceptance of single ethical review for multicenter clinical trials. Each participating site will submit this protocol and any other relevant study documentation to the responsible local governance office for site specific assessment. In States and Territories that are not participating in the National Mutual Acceptance scheme site or jurisdictional ethical approval will be sought, as required in that location.

11.1.2. New Zealand

This trial will be conducted in compliance with relevant New Zealand legislation including the Health Information Privacy Code, the Health and Disability Code and the NZ Bill of Rights (NZBOR) Act. Ethical approval will be sought from the New Zealand Health and Disability Ethics Committee. Most patients enrolled in this trial will lack capacity to give consent at the time of trial enrollment. We will use an approach consistent with section 7.4 of the Health and Disability Code which outlines the appropriate approach to providing treatment to patients who are unable to consent for themselves. The specific approach will be: 1. to consider whether participation is in the best interests of each individual patient and, 2. as soon as it is practical and reasonable to do so, to seek the advice of persons interested in the patient's welfare to establish that study participation is consistent with the patient's wishes. We will specifically discuss the issues of patient privacy, and responsibilities in relation to the Health and Disability Consumer Code of Rights, and the NZBOR Act as part of NZ trial start-up meetings to ensure that all investigators are aware of their legal responsibilities.

Region-Specific Appendix:
Canada

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

REMAP-CAP Canada Region-Specific Appendix Version 2 dated 05 July, 2019

CCCTG
Canadian Critical Care
Trials Group

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

TABLE OF CONTENTS

1. ABBREVIATIONS

AHRC	Applied Health Research Centre
CAPTIC	Canadian Adaptive Platform Trial in Intensive Care
CaRCC	Canada Regional Coordinating Centre
CaRMC	Canada Regional Management Committee
CCCTG	Canadian Critical Care Trials Group
CRF	Case Report Form
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
eCRF	Electronic Case Report Form
IIG	International Interest Group
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
IV	Intravenous
RCC	Regional Coordinating Center
REB	Research Ethics Board
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia
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RSA	Regional-Specific Appendix
SAE	Serious Adverse Event

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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.

At any one time there will be the same current version of the Core Protocol, in all regions, with accompanying Region-Specific and Domain-Specific Appendices that change over time and between regions.

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).

2.1. Region-Specific Protocol version

The version of the Canada RSA is in this document's header and on the cover page.

2.2. Version History

Version 1: Approved by the Canadian regional Management Committee (CaRMC) November 2018

Version 2: Approved by the CaRMC on July 5, 2019

3. CANADA REGION

The Canada region comprises the country of Canada.

4. CANADA STUDY ADMINISTRATION STRUCTURE

4.1. Coordinating center and data management

The Regional Coordinating Center (RCC) of REMAP-CAP in Canada CaRCC is St. Michael's Hospital, Unity Health Toronto. This document outlines the responsibilities of the CaRCC.

4.1.1. Responsibilities

The CaRCC is responsible for the following aspects of study management in Canada:

- Liaison with the ITSC and other RCCs in relation to data management, Case-Report Forms (CRFs), and site management
- CRF design for any region-specific data collection
- Management of study budget and liaison with funding bodies
- Recruitment and selection of sites
- Protocol training of site investigators and research coordinators
- Management of study set up including assistance with Research Ethics Board (REB) applications
- Monitoring and close-out site visits
- Organization of investigator meetings
- Serious adverse event notification to DSMB.
- Coordination of data entry and feedback of data enquiries with Monash University database managers
- Administrative assistance to the RMC, Domain-Specific Working Groups (DSWG), International Interest Groups (IIG), and the ITSC, as required
- Public relations for the study
- Liaison with other RMCs to develop study documents and materials that are standardized as much as possible

4.2. Canada Regional Management Committee

4.2.1. Responsibilities

The CaRMC is responsible for the following aspects of study management in Canada:

- Liaison with the staff of the CaRCC
- Funding applications to and negotiations and communications with funding bodies located in Canada, or located in other countries, but for which funding will be used to support trial activities in the Canada region
- Study budget
- Approval of the RSA
- Approval and establishment of feasibility of domains and interventions in the region
- Development and approval of the RSA and study materials for the region
- Development and approval of data management systems for the region

- General study management issues
- Consumer engagement
- Liaison with ITSC, DSWGs, IIGs, and other RCCs with regard to analysis and interpretation of results, and collaboration on publications and presentations

4.2.2.Members

Executive Director and Chief Investigator in Canada

John Marshall

Deputy Executive Director

Srinivas Murthy

Members

Sean Bagshaw

Zahra Bhimani

Nick Daneman

Niall Ferguson

Francois Lamontagne

Cheryl Misak

Marlene Santos

4.3. Contact Details

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4.3.1.Coordinating Center

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CANADA

4.3.2. Project Management

4.3.2.1. CAPTIC Project Management

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4.3.2.2. REMAP-CAP Project Management

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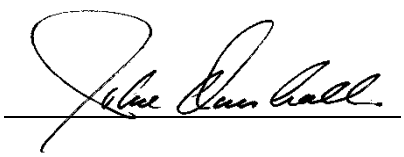
5. CANADIAN REGIONAL MANAGEMENT COMMITTEE AUTHORIZATION

Canada REGIONAL MANAGEMENT COMMITTEE AUTHORISATION
The CaRMC have read the appendix and authorize it as the official Canada Region Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Canada Executive Director
John Marshall



Date 05th July 2019

6. TRIAL REGISTRATION

Participation in this trial and involvement of sites in Canada is registered at ClinicalTrials.gov. The registration number for the international trial is NCT02735707 and was registered on 12 April 2016.

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

7. FUNDING OF REGION

7.1. Sources of funding

The trial is funded as part of the CAPTIC consortium of the Canadian Institutes of Health Research, Strategy for Patient-Oriented Research (CIHR SPOR) Innovative Clinical Trials Program Operating Grant number 158584.

7.2. Site costs

Per-patient and any other project-related payments to sites will be as specified in the contract between the Sponsor and each site.

7.3. Sponsors

The sponsor in Canada is St. Michael's Hospital, Unity Health Network.

7.4. Role of sponsor

The role of the sponsor is to act as the legal entity for those trial related activities that can only be undertaken by a legal entity. Contracts will be between the sponsor and participating sites. All other activities, including but not limited to trial design, conduct, safety monitoring, and reporting, are the responsibility of trial steering and management committees and working groups, as specified in the Core Protocol and appendices.

7.5. Insurance

The sponsor/investigator has insurance in accordance with the relevant legal requirements in each country.

8. TRIAL BACKGROUND AND RATIONALE

There are no anticipated issues that are specific to the background and rationale in the Core Protocol of the trial in Canada. However, some interventions may not be available in all countries or participating sites within the region.

9. TRIAL DESIGN

9.1. Study setting

As described in the Core Protocol Section 7.3.

9.2. Interventions

The RMC will offer all interventions that are available in Canada to all participating sites in which the intervention is available and feasible

9.2.1. Antibiotic Domain

The antibiotic domain will be offered to any site in Canada for drugs that are available in Canada. All antibiotic strategies that are off-patent will be provided by the treating hospital (as the patient would have always required antibiotic treatment that the hospital would have otherwise provided).

9.2.2. Macrolide Duration Domain

The macrolide duration domain will be offered to any site in Canada. Intravenous (IV) Azithromycin is licensed for use in Canada and enteral Azithromycin is widely used. The IV formulation is not widely used, and not available in all sites. In Canada, enteral Azithromycin or other enteral or parenteral macrolides will be allowed as an alternative to Azithromycin IV, as described in the Macrolide Duration DSA.

9.2.3. Corticosteroid Domain

The steroid domain will be offered to any site in this region.

9.2.4. Antiviral Domain

The antiviral domain will be offered to all sites in this region.

9.2.5. Ventilation Domain

The ventilation domain will be offered to all sites in this region.

9.2.6. Registry

The registry will only be offered to sites that participate in regional registries.

9.3. Endpoints

Data will be collected as set out in the Core Protocol and DSAs.

9.4. Co-enrollment

As described in the Core Protocol Section 7.9.

10. TRIAL CONDUCT

10.1. Recruitment and embedding

As described in the Core Protocol Section 8.3.

10.2. Treatment allocation

Central randomization will occur online and be managed and operated by Spiral Web Solutions Ltd (New Zealand) at https://remapcap.spinnakersoftware.com.

10.3. Distribution of study drug

The processes and management of distribution of any possible drug provided by the study, will be outlined in operational documents and, as required, specified in the contract.

10.4. Data collection

Data collection will be as outlined in the Core Protocol Section 8.9. The collection of data from time-points after discharge from the index hospitalization will be voluntary in this region.

10.5. Data management

Data will be entered into a secure, password protected web based CRF designed by Spiral Web Solutions Ltd (New Zealand). The Project Managers and the coordinating center will coordinate data entry and data management.

10.6. Trial group linkage / participation

REMAP-CAP is conducted under the auspices of the Canadian Critical Care Trials Group (CCCTG) and in collaboration with funded initiatives in Europe, Australia, and New Zealand. It is one component of the Canadian Adaptive Platform Trial in Intensive Care (CAPTIC) program that is exploring the wider use of the platform trial model in critical care research.

10.7. Site start up and initiation

A site initiation teleconference or visit will be conducted before site activation; at least 1 routine monitoring visit will be conducted during the recruitment period; and a close out visit. Additional monitoring visits will be planned based on patient inclusion rate or indication. Email and telephone communication will supplement site visits.

Standardized procedures will be in place to educate sites on the trial and trial procedures before site initiation. These include printed material, face-to-face start up meetings, webinars, and on-line study materials.

10.8. Quality assurance and monitoring

10.8.1. Quality assurance

As described in the Core Protocol Section 8.11.

10.8.2. Monitoring

A representative of CaRCC will monitor the study. Monitoring will be conducted by quality control reviews of protocol compliance, source data verification, data queries and safety reporting.

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 monitor for these visits during the course of the study and at the completion of the study as needed.

10.9. Safety reporting

Safety reporting will occur as outlined in the Core Protocol Section 8.13.

All Serious Adverse Events (SAE) will be recorded in the electronic Case Report Form (eCRF). For sites in Canada, all SAEs must be reported via the trial website within 72-hours of the investigators becoming aware of the event.

The investigator should notify the Institutional / Ethics Committee of the occurrence of the serious adverse event in accordance with local requirements.

A 24-hour contact number for Canadian sites will be provided to all sites before recruitment commences.

11.ETHICAL CONSIDERATIONS

11.1. Ethical and regulatory issues

The trial will be conducted in accordance with Canadian legislation. Research ethics approval will be obtained prior to the start of the study at each institution from the responsible local REB. It is the principal investigator's responsibility to ensure that all conditions for approval of the study are met and that amendments to the protocol or serious adverse events are also reported to the REB as required by that committee.

Region-Specific Appendix:

EUROPE

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

REMAP-CAP European Region-Specific Appendix Version 3 dated 23 August 2019

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1. ABBREVIATIONS

AE	Adverse Event
AMG	Arzneimittelgesetz (German drug law)
CRF	Case Report Form
CA	Competent Authority
CSCC	Center for Sepsis Control & Care
DGIIN	Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
eCRF	Electronic Case Report Form
EC	Ethics Committee
Eu	Europe
EU	European Union
EudraCT	European Clinical Trials Database
Eu RCC	European Regional Coordinating Center
Eu RMC	European Regional Management Committee
GDPR	General Data Protection Regulation
ICH-GCP	International Conference on Harmonization-Good Clinical Practice
ICNARC	The Intensive Care National Audit & Research Centre
IIG	International Interest Group
IRB	Institutional Review Board
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
IV	Intravenous
NET-GER	Network Germany
NFU	Netherlands Federation of University Medical Centres
PREPARE	Platform for European Preparedness Against (Re-)emerging Epidemics
RCC	Regional Coordinating Center
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia
RMC	Regional Management Committee
RSA	Regional-Specific Appendix

SAE	Serious Adverse Event
UK	United Kingdom
UMC Utrecht	University Medical Center Utrecht
WP8	Work Package 8

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). Additionally, any of the adjustments made in the protocol as described in Section 5.3.7.7 of the Core Protocol or a change in the statistical evaluation concept will

be considered as a substantial amendment of the protocol and will be provided as such to the Ethics Committee (EC) and Competent Authority (CA) for approval and will only be implemented when approval is obtained from EC and CA.

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) and the PREPARE Workpackage 5 website (https://www.prepare-europe.eu/About-us/Workpackages/Workpackage-5)
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2.1. *Region-Specific Protocol version*

The version of the European RSA is in this document's header and on the cover page.

2.2. *Version History*

Version 1: Approved by the Europe Regional Management Committee (Eu RMC) on 20 November 2016

Version 1.1: Approved by the Eu RMC on 09 May 2017

Version 2: Approved by the Eu RMC on 12 December 2017

Version 2.1: Approved by the Eu RMC on 24 May 2018

Version 2.2: Approved by the Eu RMC on 26 October 2018

Version 2.3: Approved by the Eu RMC on 26 March 2019

Version 2.4: Approved by the Eu RMC on 25 April 2019

Version 3.0: Approved by the Eu RMC on 23 August 2019

3. EUROPEAN REGION

The European (Eu) region comprises sites in the 28 European Union (EU) member states, plus sites in other countries that may be added subsequently but does not include any site that is located in any country that is active as part of an existing REMAP-CAP region.

The countries to which this appendix applies are:

- Austria
- Belgium
- Bulgaria
- Croatia
- Cyprus
- Czech Republic
- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- Ireland
- Italy
- Latvia
- Lithuania
- Luxembourg
- Malta
- Netherlands
- Poland
- Portugal
- Romania
- Slovakia
- Slovenia
- Spain
- Sweden

- United Kingdom

4. EUROPEAN STUDY ADMINISTRATION STRUCTURE

4.1. *Coordinating center and data management*

The Regional Coordinating Center (RCC) of REMAP-CAP in Europe (Eu RCC) is the University Medical Center Utrecht (UMC Utrecht), Department Julius Center for Health Sciences and Primary Care. This document outlines the responsibilities of the UMC Utrecht. The UMC Utrecht will have predominant responsibility for the region plus management of sites in all 28 EU member states and associated countries, as described above, and any countries that joins the EU as member state or associated countries in the future.

4.1.1. Responsibilities

The Eu RCC is responsible for the following aspects of study management in Europe:

- Liaison with the ITSC and other RCCs in relation to data management, Case-Report Forms (CRFs), and site management
- CRF design for any region-specific data collection
- Management of study budget and liaison with funding bodies
- Development, maintenance, and administration of the regional database
- Recruitment and selection of sites
- Data management (in cooperation with Work Package 8 (WP8) of Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE) and SPIRAL Web Solutions Ltd.)
- Protocol training of site investigators and research coordinators
- Preparation and arrangement of investigator payments
- Management of regulatory affairs
- Management of study set up including assistance with Institutional Review Board (IRB) applications
- Initiation, monitoring and close-out site visits
- Organization of investigator meetings
- Serious adverse event notification to DSMB and EU regulatory authorities.
- Coordination of data entry and feedback of data enquiries
- Administrative assistance to the RMC, Domain-Specific Working Groups (DSWG), International Interest Groups (IIG), and the ITSC, as required

- Public relations for the study
- Liaison with other RMCs to develop study documents and materials that are standardized as much as possible

4.2. *European Regional Management Committee*

4.2.1. Responsibilities

The Eu RMC is responsible for the following aspects of study management in Europe:

- Liaison with the staff of the Eu RCC
- Funding applications to and negotiations and communications with funding bodies located in EU, or located in other countries, but for which funding will be used to support trial activities in the Eu region
- Study budget
- Approval of the RSA
- Approval and establishment of feasibility of domains and interventions in the region
- Development and approval of the RSA and study materials for the region
- Development and approval of data management systems for the region
- General study management issues
- Consumer engagement
- Liaison with ITSC, DSWGs, IIGs, and other RCCs with regard to analysis and interpretation of results, and collaboration on publications and presentations

4.2.2. Members

Executive Director and Chief Investigator in Europe

Professor Marc Bonten

Co-chairs

Professor Marc Bonten

Dr. Lennie Derde

Members

Dr. Farah Al-Beidh

Professor Derek Angus

Ms. Wilma van Bentum-Puijk

Dr. Scott Berry

Professor Frank Brunkhorst

Dr. Lennie Derde

Professor Herman Goossens

Professor Anthony Gordon

Dr. Sebastiaan Hullegie

Dr. Colin McArthur

Mr. Paul Mouncey

Professor Alistair Nichol

Professor Mathias Pletz

Professor Gernot Rohde

Professor Kathy Rowan

Professor Steve Webb

4.3. *Contact Details*

Executive Director and Chief Investigator

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5. Eu REGIONAL MANAGEMENT COMMITTEE AUTHORISATION

The Eu RMC have read the appendix and authorize it as the official Eu Regional appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Eu Executive Director
Marc Bonten

Date 23 August, 2019

6. TRIAL REGISTRATION

Participation in this trial and involvement of sites in Europe is registered at ClinicalTrials.gov. The registration number is NCT02735707 and was registered on 12 April 2016.

Additionally, this study is registered at European Clinical Trials Database (EudraCT). The registration number is 2015-002340-14 and was registered on 20 May 2015.

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

7. FUNDING OF REGION

7.1.*Sources of funding*

The PREPARE consortium is funded by the EU, FP7-HEALTH-2013-INNOVATION-1, grant number 602525. Within the PREPARE consortium, funding for the REMAP-CAP study is included for approximately 4000 patients.

7.2. *Site costs*

Per-patient and any other project-related payments to sites will be as specified in the contract between the Sponsor and each site.

7.3. *Sponsors*

The sponsor in Europe is the University Medical Center Utrecht.

7.4. *Role of sponsor*

The role of the sponsor is to act as the legal entity for those trial related activities that can only be undertaken by a legal entity. Contracts will be between the sponsor and participating sites. All other activities, including but not limited to trial design, conduct, safety monitoring, and reporting, are the responsibility of trial steering and management committees and working groups, as specified in the Core Protocol and appendices.

7.5. *Insurance*

The sponsor/investigator has insurance in accordance with the relevant legal requirements in each country.

8. TRIAL BACKGROUND AND RATIONALE

There are no anticipated issues that are specific to the background and rationale in the Core Protocol of the trial in Europe. However, some interventions may not be available in all countries or participating sites within the region.

9. TRIAL DESIGN

9.1. *Study setting*

As described in the Core Protocol Section 7.3.

9.2. *Interventions*

The RMC will offer all interventions that are available in Europe to all participating sites in which the intervention is available and feasible

9.2.1.Antibiotic Domain

The antibiotic domain will be offered to any site in this region. All antibiotic strategies that are off-patent will be provided by the treating hospital (as the patient would have always required antibiotic treatment that the hospital would have otherwise provided).

9.2.2.Macrolide Duration Domain

The macrolide duration domain will be offered to any site in this region. Intravenous (IV) Azithromycin is licensed for use in Europe and oral Azithromycin is widely used. The IV formulation is not widely used, and not available in all sites. In Europe, enteral Azithromycin or other enteral or parenteral macrolides will be allowed as an alternative to Azithromycin IV, as described in the Macrolide Duration DSA.

9.2.3.Corticosteroid Domain

The steroid domain will be offered to any site in this region.

9.2.4. Antiviral Domain

This antiviral domain will be offered to any site in this region.

9.2.5.Ventilation Domain

The ventilation domain will be offered to any site in this region.

9.2.6.Registry

Site(s) participation in the Registry is optional within the EU. Participation is possible by countries, or by regions within countries, where there is an existing healthcare-related registry or database, which routinely captures data on the entire study population specified for the Registry.

The study population specified for the Registry comprises adult patients admitted to an ICU for CAP. This population is divided into two mutually exclusive cohorts: those eligible for the platform and assigned treatment within one or more REMAP-CAP domains (“Platform-randomized”) and those who are either platform ineligible or platform eligible but not assigned treatment within one or more REMAP-CAP domains (“Registry-only”).

The purpose of the Registry is to provide limited information on all patients admitted to an ICU with CAP so that the characteristics of patients who are randomized within the Platform (“Platform-randomized”) can be compared with the patients with CAP admitted to an ICU at participating sites

("Registry-only"). Registry data will overlap with, but will not be more extensive than, the minimum dataset collected for patients who are randomized within the Platform.

The Registry does not specify any interventions and only utilizes the routine data captured for administration and clinical care.

9.3. *Endpoints*

Data will be collected as set out in the Core Protocol and DSAs.

9.4. *Co-enrollment*

As described in the Core Protocol Section 7.9.

9.5. *Criteria for termination of the trial*

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

Current estimated end date for recruitment in Europe is 31st January 2021. The last patient last follow-up in Europe would be 6 months later and would be the end date of the trial in Europe.

10. TRIAL CONDUCT

10.1. *Recruitment and embedding*

As described in the Core Protocol Section 8.3.

10.2. *Pregnancy testing and breastfeeding*

For specifically identified countries in the EU, according to local requirements, pregnancy testing is mandatory for female patients of childbearing age. This is necessary because in such countries

pregnancy will be a platform-level exclusion criteria, i.e. excludes a patient from receiving a randomization allocation in all domains, but does not exclude the patient from the registry.

For specifically identified countries in the EU, according to local requirements, breastfeeding is also a platform-level exclusion criteria, i.e. excludes a patient from receiving a randomization allocation in all domains, but does not exclude the patient from the registry.

Countries to which this requirement applies will be listed in operational documents.

10.3. *Treatment allocation*

Central randomization will occur online and be managed and operated by SPIRAL Web Solutions Ltd.. Data management and transfer will comply with GDPR requirements in the country in which a site is located.

10.4. *Distribution of study drug*

The processes and management of distribution of any possible drug provided by the study, will be outlined in operational documents and, as required, specified in the contract. 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.

10.5. *Unblinding of allocation status*

Unblinding of any blinded treatment by site research staff or the treating clinician should only occur only 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 a future 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.

10.6. *Data collection*

Data collection will be as outlined in the Core Protocol Section 8.9. The collection of data at day 90 will be mandatory, the collection of data from time-points after day 90 will be voluntary in this region.

10.7. *Data management*

Data used to establish eligibility will be entered into a secure, password protected web based CRF designed by SPIRAL Web Solutions Ltd., in New Zealand, using a server located in Australia. All allocations and all other data collected in the trial will be entered into a secure, password protected web based CRF designed by WP8 of PREPARE, ResearchOnline 2, Located in the Netherlands. Each subject will be allocated a unique trial number that is used as the common identifier in both databases. Data management and transfer will comply with GDPR requirements in the country in which a site is located. The Project Managers and the coordinating center will coordinate data entry and data management.

10.8. *Trial group linkage / participation*

The participation of established trial networks is recognized as one method for facilitating high quality trial conduct. The COMBACTE network will facilitate the identification of suitable sites to participate in the trial.

In the United Kingdom (UK), The Intensive Care National Audit & Research Centre (ICNARC) and Imperial College London will jointly coordinate the identification and participation of suitable sites.

In Germany, the Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin (DGIIN) / Center for Sepsis Control & Care (CSCC) network will facilitate the identification and participation of suitable sites.

Additional networks that are based in Europe will be approached to determine their interest in contributing as partners to the study.

10.9. *Site start up and initiation*

A site initiation teleconference or visit will be conducted before site activation; at least 1 routine monitoring visit will be conducted during the recruitment period; and a close out visit. Additional monitoring visits will be planned based on patient inclusion rate or indication. Email and telephone communication will supplement site visits.

Standardized procedures will be in place to educate sites on the trial and trial procedures before site initiation. These include printed material, face-to-face start up meetings, webinars, and on-line study materials.

10.10. *Quality assurance and monitoring*

10.10.1. Quality assurance

As described in the Core Protocol Section 8.11.

10.10.2. Monitoring

The study will use a monitoring plan that is developed on a risk-based approach, as described by the Netherlands Federation of University Medical Centres (NFU). Details can be found in the monitoring plan.

A representative of the UMC Utrecht or a local representative at request of the UMC Utrecht will monitor the study. Monitoring will be conducted by quality control reviews of protocol compliance, data queries and safety reporting.

A monitoring report will be prepared following each visit and reviewed by the management committee 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 monitor for these visits during the course of the study and at the completion of the study as needed.

10.11. *Safety reporting*

Safety reporting will occur as outlined in the Core Protocol Section 8.13.

All Serious Adverse Events (SAE) will be recorded in the electronic Case Report Form (eCRF) and intermittently monitored by the Sponsor. Complications of the underlying critical illness and its treatment do not require specific SAE reporting as the trial endpoints are designed to measure the vast majority of events. These will be monitored by the sponsor both centrally and on-site through sourced data verification. However, any SAE that is considered by the site-investigator to be attributable to a study intervention or study participation should be reported as detailed below. For sites in Europe, all SAEs must be reported immediately to the coordinating center (UMC Utrecht) via email (prepare_icu@umcutrecht.nl) within a maximum of 24-hours of the investigators becoming aware of the event. Personal data must be pseudonymized before transmission using the randomization number of the person concerned.

Only SAEs that occur between randomization and hospital discharge censored at day 90 need to be recorded.

The investigator should notify the Institutional / EC of the occurrence of the serious adverse event in accordance with local requirements.

Web address www.researchonline.org

Contact phone numbers for SAE advice:

UMC Utrecht	+31 (0) 6 27 74 44 77

10.12. *Contraceptive advice*

If any trial drugs require specific contraceptive advice in this trial population, the details will be provided in the relevant Domain Specific Appendix and the relevant Summary of Patient Characteristics referred to.

11.ETHICAL CONSIDERATIONS

11.1. *Ethical and regulatory issues*

The trial will be conducted in accordance with EU and national legislation relevant in each European country. Research ethics and regulatory authorities' approvals will be obtained prior to the start of the study at each institution from the responsible local or national IRB and relevant CA. It is the principal investigator's responsibility to ensure that all conditions for approval of the study are met and that amendments to the protocol, or trial design, including new domain specific appendices or serious adverse events are also reported to the IRB as required by that committee and all relevant regulatory authorities.

12.MODIFICATIONS SPECIFIC TO A NETWORK IN EUROPE

12.1. *Introduction*

This section identifies any issue that is different within a specific network in Europe to vary the protocol in that network from what is specified elsewhere in this RSA or the Core Protocol or both.

12.2. *Network Germany (NET-GER)*

12.2.1. Recruitment numbers

The initial planned enrollment in NET-GER will be 600 participants.

12.2.2. Repeat enrollment

A patient who has been enrolled previously in REMAP-CAP is not eligible for re-enrolment in any second or subsequent episode of CAP.

12.2.3. Process for obtaining consent

As outlined in Core Protocol and in the Antibiotic and Corticosteroid DSAs, some interventions specified in this REMAP meet the requirement for emergency indication (§ 41 para. 2 Arzneimittelgesetz (AMG)) that apply to patients who are unable to consent for themselves and, if necessary, without a declaration of consent from the legal representative.

The process for establishing participation in Germany for a patient who is not competent to consent is outlined below.

Wherever possible, a presumed will of the patient has to be asked for (contact close relatives or existing legal representative). The legal representative is asked for consent. The legal representative is a person with participant's power of attorney or a person appointed by the court.

If consent cannot be obtained directly from a legal representative or the legal representative is unavailable, a patient's inability to consent and the urgency of participating in the study must be confirmed by an independent consultant physician. Once this is established by the independent consultant physician, a patient may then be enrolled. To be eligible as an independent consultant physician, the physician must not have any involvement with the trial, must not hold an appointment at the institution that is conducting the trial and must not be a member of the team that is providing care to the patient. The consultant independent physician must document the relevant findings and conclusions in writing.

If a patient is enrolled by a determination by an independent consultant physician, the patient's legal representative must be approached to ask for a subsequent declaration of consent or a legal representative has to be appointed by the court.

It is the responsibility of the site investigator to identify promptly a suitable person to act as the legal representative and if required submit an application to the appropriate court as soon as possible after randomization. The legal representative can withdraw the participant from the trial at any time. However, data collected before this time will continue to be available and utilized in the analysis of the trial.

When an enrolled participant regains competency, their participation should be explained and an opportunity provided to the participant to provide their ongoing consent. The patient can withdraw from participation from the trial at any time. However, data collected before this time will continue to be available and utilized in the analysis of the trial.

Patients or their legal representatives can withdraw their consent at any time and without giving reasons and can cancel participation in the study. In such a case, the patient is asked to state the reason for termination, but is advised that this is not necessary to do so. Information as to when and in which study arm a patient was randomized as well as the withdrawal of their consent and time of withdrawal must be documented. In this situation, the patient must also be informed that stored data may be further used, if necessary, to:

- determine the effects of the medicinal product to be tested; and
- ensure that the legitimate interests of the participant are not prejudiced.

12.2.4. (Serious) Adverse Events

Contrary to the Core Protocol 8.13, the following applies to Germany without exception:

12.2.4.1. Definitions

According to GCP-V § 3 (31), an Adverse Event (AE) is any adverse event that occurs to a subject who has been administered an investigational product and is not necessarily causally related to that treatment. According to ICH-GCP, these may be signs of disease (including e.g. abnormal laboratory values), diseases or symptoms associated with the use of an investigational product. This is independent of whether the event is causally related to the investigational product or not.

According to GCP-V § 3 (31), a Serious Adverse Event (SAE) or a Serious Adverse Reaction (SAR) is any adverse event or adverse reaction that is fatal, life-threatening, requires hospitalization or prolongation of treatment, results in permanent or serious disability or disability, or results in congenital anomaly or birth defect.

12.2.4.2. Documentation and Reporting

The documentation and notification obligations according to GCP-V §12 (4) - (6) shall be strictly observed.

All adverse non-serious and serious events must be recorded completely with the study data, regardless of whether a causal relationship with the investigational drug or the study procedures can be assumed. All events that are not documented as part of the endpoint capture must be documented using the AE form of the eCRF.

Medical or surgical procedures are not documented as AEs, but rather the disease that led to the necessary intervention. Daily variations in the clinical picture as well as the usual progression of severe CAP are not listed as AEs. Diseases that already exist before inclusion in the study are not considered an AE, but an accompanying disease (documented in medical history). The clinically relevant worsening of a pre-existing condition that is not associated with severe CAP is considered an adverse event. A measure to treat a pre-existing condition that was planned prior to inclusion in the study is not considered an adverse event.

For AEs, a description (medical term), start, end, causality, measures for handling the investigational drug and the event as well as the outcome are documented. Each AE must be checked for the criteria of an SAE and, if necessary, the SAE reporting procedure must be followed (see Section 10.11.).