

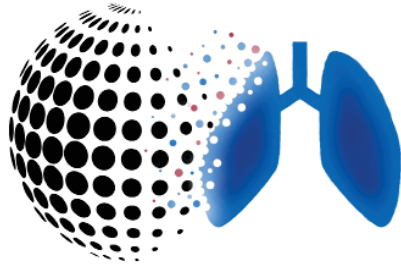
Effect of Hydrocortisone on Mortality in Patients with Severe Community-acquired Pneumonia

The REMAP-CAP Corticosteroid Domain Randomized Clinical Trial

The REMAP-CAP Investigators

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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

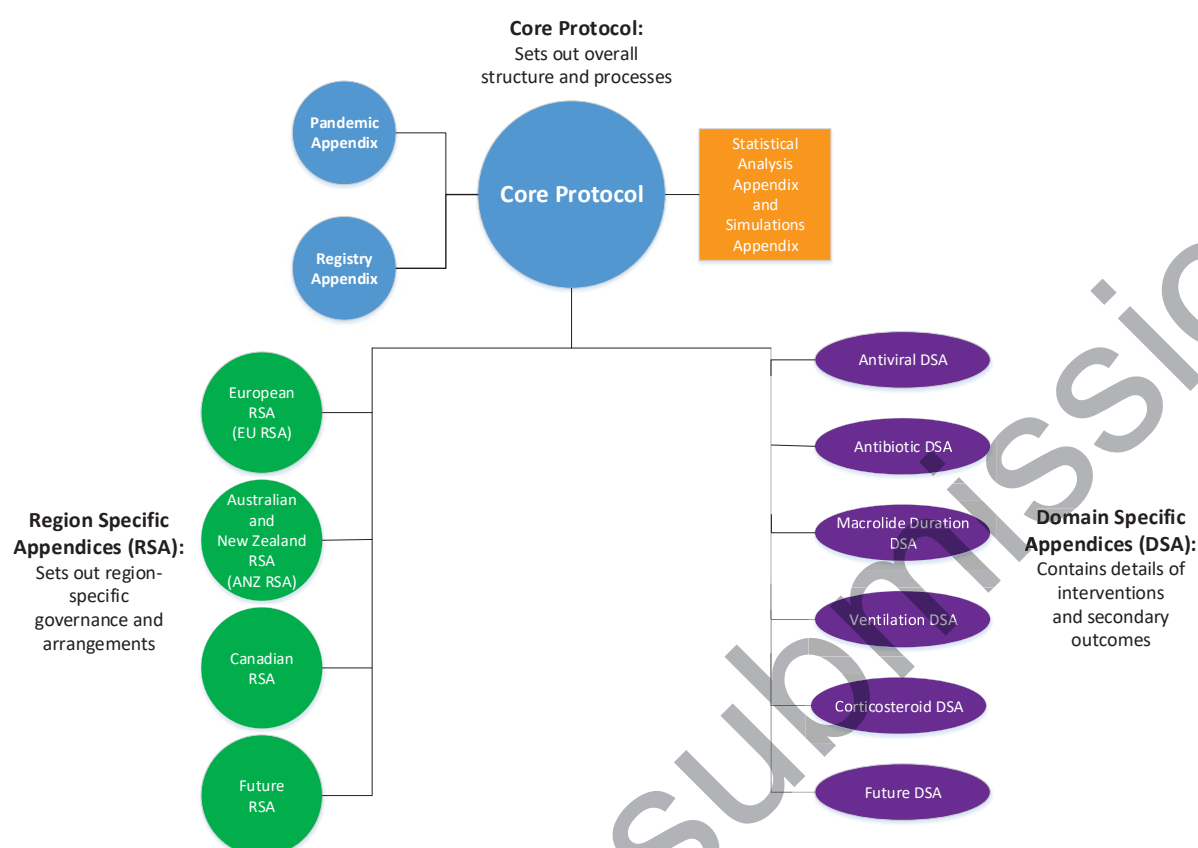
that a difference is detected or no that no difference is detected. However, when the conclusion of the statistical test is “no difference”, this could be that there truly is no meaningful difference, or that the result is indeterminate (i.e. it is possible that if more patients had been enrolled a clinically 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](https://clinicaltrials.gov/ct2/show/study/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

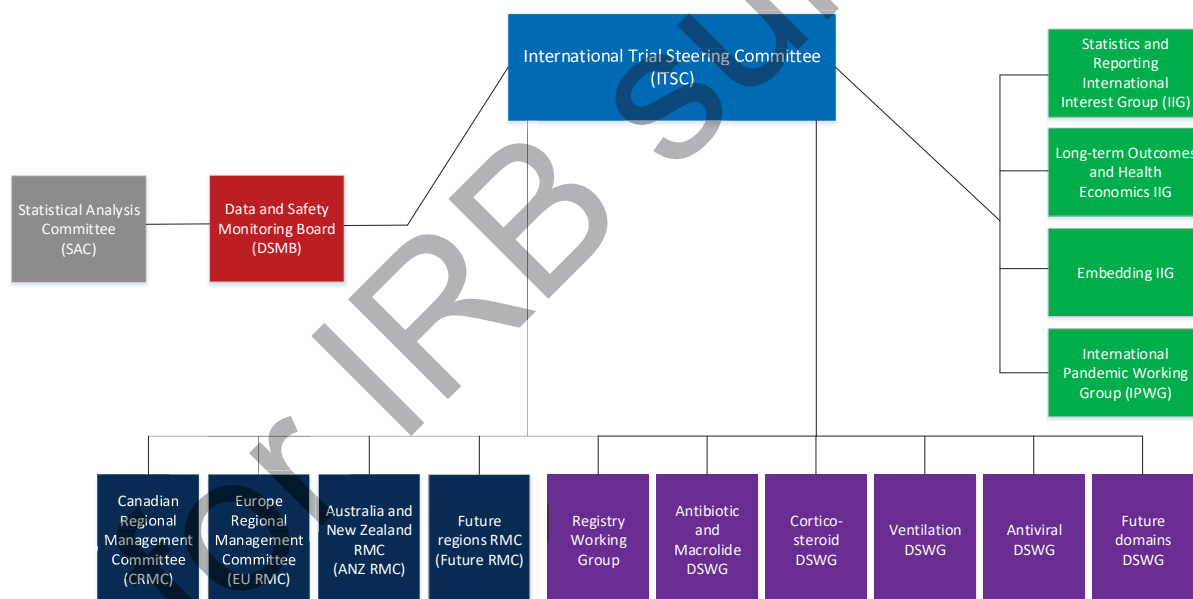
The study administration structure is designed to provide appropriate management of all aspects of the study, taking into account multiple factors including representation from regions that are participating in the trial, availability of skills and expertise related to trial conduct and statistical

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 determined by investigators in each region with membership listed in each RSA. Cross-representation between RMCs is strongly encouraged.

3.2.1. Responsibilities

The responsibilities of each RMC are:

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

3.3. *Domain-Specific Working Groups*

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

3.3.1. Responsibilities

The responsibilities of each DSWG are:

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

3.3.2. Members

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

3.4. *International Interest Groups*

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

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

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

3.4.1. Role

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

3.5. Sponsors

In relation to recruitment that occurs in:

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

3.5.1. Role of sponsor

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

3.5.2. Insurance

The provision of insurance is specified in each RSA.

4. INTERNATIONAL TRIAL STEERING COMMITTEE AUTHORIZATION

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

EU Executive Director
Marc Bonten

ANZ Executive Director
Steve Webb



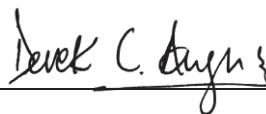
ANZ Deputy Director

Colin McArthur



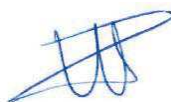
ITSC Member

Derek Angus



ITSC Member

Wilma van Bentum-Puijk



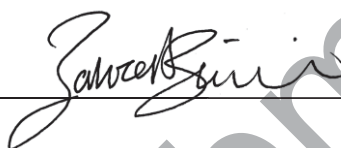
ITSC Member

Scott Berry



ITSC Member

Zahra Bhimani



ITSC Member

Frank Brunkhorst



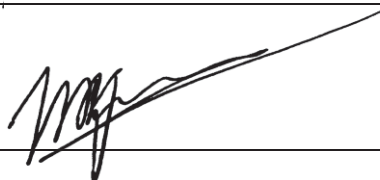
ITSC Member

Allen Cheng



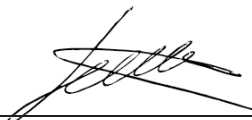
ITSC Member

Menno De Jong



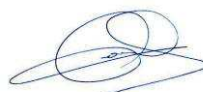
ITSC Member

Lennie Derde



ITSC Member

Herman Goossens



ITSC Member

Anthony Gordon



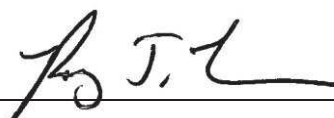
ITSC Member

Cameron Green



ITSC Member

Roger Lewis



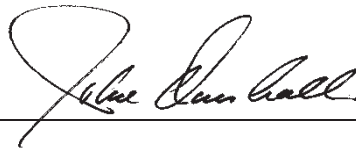
ITSC Member

Ed Litton



ITSC Member

John Marshall



ITSC Member

Shay McGuinness



ITSC Member

Srinivas Murthy



ITSC Member

Alistair Nichol



ITSC Member

Rachael Parke



ITSC Member

Jane Parker



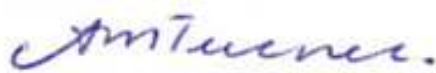
ITSC Member

Kathy Rowan



ITSC Member

Anne Turner



5. BACKGROUND & RATIONALE

5.1. Severe Community-Acquired Pneumonia

5.1.1. Introduction

This section, within the Core Protocol, provides background on the epidemiology, causes, treatment categories, and evidence base for the management of patients with severe community pneumonia. Detailed information regarding the rationale for specific interventions to which patients will be

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

5.1.2. Epidemiology

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

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

5.1.3. Standard care for patients with severe CAP

All patients admitted to an ICU with severe CAP will receive multiple different component therapies and many of these therapies will be administered concurrently. These therapies can be grouped into the following categories: treatment of the underlying infection (including antibacterial and antiviral

agents); the optional use of agents, such as corticosteroids, that modulate the host immune response to infection; and multiple supportive therapies that are used to manage organ systems that have failed or prevent complications of critical illness and its treatment ([Table 1](#)).

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

Examples of commonly used therapies that support failed organ systems or prevent the complications of critical illness and its treatment include oxygen therapy, invasive and non-invasive mechanical ventilation, intravenous fluid resuscitation, vasoactive drugs, dialysis, provision of nutrition, sedation, physiotherapy including mobilization, diuretic medications, suppression of gastric acid production, and mechanical or pharmacological interventions to prevent venous thromboembolism. The exact combination of supportive therapies is influenced by the spectrum of organ failures that occurs in any individual patient. (Dellinger et al., 2013)

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

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

	Nutrition
	Mobilization
	Sedation
	Venous thromboembolism prophylaxis
	Stress ulcer prophylaxis

5.1.4. Treatment guidelines

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

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

5.1.5. Variation in care and compliance with guidelines

Several observational studies report substantial variation in care with, for example, compliance with administration of antibiotics recommended by guidelines occurring in between 40% and 75% of patients. (Bodi et al., 2005, Frei et al., 2010, Lee et al., 2014, Shorr et al., 2006) These and other studies also report better clinical outcomes for patients who received antibiotics that were recommended by guidelines. (McCabe et al., 2009, Mortensen et al., 2004, Mortensen et al., 2005) However, it remains unclear if adherence to guideline recommendations is due to a direct causal link, or whether it is a surrogate for better quality care generally. There is also widely reported variation in compliance with many supportive therapies for patients with severe CAP, such as use of

low tidal volume ventilation, type of resuscitation fluid, and thresholds for the administration of transfusion for anemia. (Bellani et al., 2016, Finfer et al., 2010, Blood Observational Study Investigators of Anzics-Clinical Trials Group et al., 2010, Cecconi et al., 2015)

5.1.6. An unmet need for better evidence

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

5.2. *Influenza pandemics and emerging pathogens*

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

5.3. *Randomized Embedded Multifactorial Adaptive Platform Trials*

5.3.1. Generating clinical evidence

Angus has noted several problems encountered when generating robust clinical evidence, including barriers to conducting clinical trials, the generalizability of data from populations that are too broad or too narrow, the issue of equipoise especially when comparing different types of existing care, and

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

5.3.2. Underlying Principles of the Study Design

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

A conventional RCT (i.e. a non-platform trial) makes a wide range of assumptions at the time of design. These assumptions include the plausible size of the treatment effect, the incidence of the primary outcome, the planned sample size, the (typically, small number of) treatments to be tested, and that treatment effects are not influenced by concomitant treatment options. These assumptions are held constant until the trial completes recruitment and is analyzed. (Barker et al., 2009, Berry,

2012, Connor et al., 2013) Participants who are enrolled in a conventional RCT are not able to benefit from knowledge accrued by the trial because no results are made available until the trial completes. A REMAP uses five approaches to minimize the impact of assumptions on trial efficiency and also maximizes the benefit of participation for individuals who are enrolled in the trial. (Angus, 2015, Berry et al., 2015, Aikman et al., 2013, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016)

These design features are:

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

This creates a 'perpetual trial' with no pre-defined sample size, the objective of which is to define and continuously update best treatment over the life-time of the REMAP. The design aspects, including the risk of type I and type II error, are optimized prior to the commencement of the trial by the conduct of extensive pre-trial Monte Carlo simulations, modification of the trial design, and re-simulation in an iterative manner. The methods related to the application of the design features and the statistical analysis of this trial are outlined in the methods section of the protocol ([Section 7](#)).

The following sections describe the background, rationale, and potential advantages of each of the design features of a REMAP ([Section 5.3.4](#)).

5.3.3. Nomenclature

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

5.3.4. Randomization and Response Adaptive Randomization

The study will randomly allocate participants to one or more interventions, with each intervention nested within a domain. In this regard, a platform trial is no different to other forms of RCT in that randomization provides the basis for causal inference. However, unlike a conventional RCT, the proportion of participants who are randomized to each available intervention within a domain will

not be fixed. Rather, the trial will incorporate RAR. RAR utilizes random allocation with a weighted probability for each intervention, with the weighted probability being proportional to the extent to which similar participants recruited earlier in the trial benefited or not from each particular intervention. (Angus, 2015, Berry, 2012, Connor et al., 2013, Aikman et al., 2013, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016) RAR will result in participants in each particular stratum being randomized with greater probability to interventions that are performing better within that stratum. At the initiation of a new domain or when a new intervention is added to a domain the randomization proportion of all new interventions is balanced and only changes, with the application of RAR, that takes into account uncertainty about treatment effect so as to avoid excessive variability in proportions generated by RAR until sufficient sample size has accrued.

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

There are potential disadvantages associated with RAR. It is intended that participating sites and trial investigators will be blind to the RAR proportions. One disadvantage is that, for interventions that are provided without blinding, the treating clinicians may be able to draw inference about the RAR proportions and, as a consequence, draw inference about the interim standing of interventions that are being tested in the REMAP. This could have adverse consequences including that clinicians are influenced to not enroll participants within a domain but rather directly prescribe the treatment that

they believe to be doing better outside the trial. However, a number of factors mitigate this potential concern. First, it can be difficult to distinguish between patterns of sequential allocation status that are derived from fixed versus RAR. Second, extreme proportions will not be used (except where a Statistical Trigger but not a Platform Conclusion has been reached, see later). Finally, for many conditions, team-based management means that an individual clinician will directly observe only a small proportion of all participants enrolled within the trial at each participating site. Another disadvantage of RAR is that, under certain allocation rules, statistical power can be reduced. This concern is mitigated via pre-trial simulation to test the effects of different allocation rules. Furthermore, a REMAP that comprises multiple domains with multiple interventions within each domain will generally have higher, rather than lower, power as a consequence of the use of RAR. Finally, by deploying RAR rules to minimize the odds of exposure to inferior interventions, the design is intended to motivate embedding in clinical practice, thereby resulting in more rapid recruitment.

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

5.3.5. Embedding

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

'order set' for participants, including those orders that are determined by allocation status within the REMAP. While screening and recruitment for a REMAP can be conducted by research staff, it is not intended that recruitment should be dependent on research staff, particularly as such staff are typically only present during office hours. In addition to the facilitation of recruitment and high-fidelity delivery of the intervention, a further advantage is that the results of the trial can be translated rapidly within the ongoing REMAP so that all appropriate participants receive a treatment declared to be superior with continued allocation to that treatment option within the REMAP used to ensure implementation.

5.3.6. Multifactorial

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

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

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

5.3.7. Adaptive

5.3.7.1. *Frequent adaptive analyses*

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

5.3.7.2. *Analysis of data to reach conclusions*

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

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

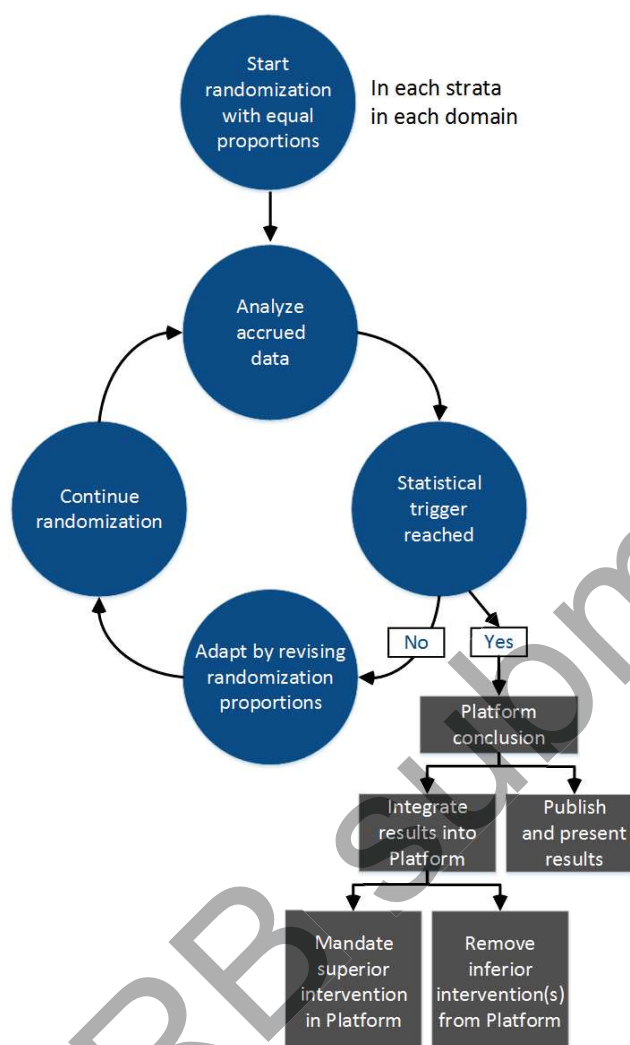
The algorithm by which a Platform Conclusion is reached is different for Statistical Triggers of superiority or inferiority, compared to those triggers that arise because of equivalence. Where the Statistical Trigger is for superiority or inferiority, so long as the DSMB is satisfied that the Statistical Trigger has been met validly, the default position is that the DSMB will declare this result as a Platform Conclusion. The only exception to this situation is if there is a need to evaluate potential interactions between treatments in different domains. In this circumstance the randomization

schedule will be adapted (all participants receive the superior intervention or randomization to one or more inferior interventions is removed) but Public Disclosure may be delayed until evaluation of the interaction is completed.

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

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

Figure 3: Adaptive Analyses



5.3.7.3. Probability thresholds

In this REMAP the pre-specified rules are that, at any adaptive analysis, an intervention will be declared “superior,” if it 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

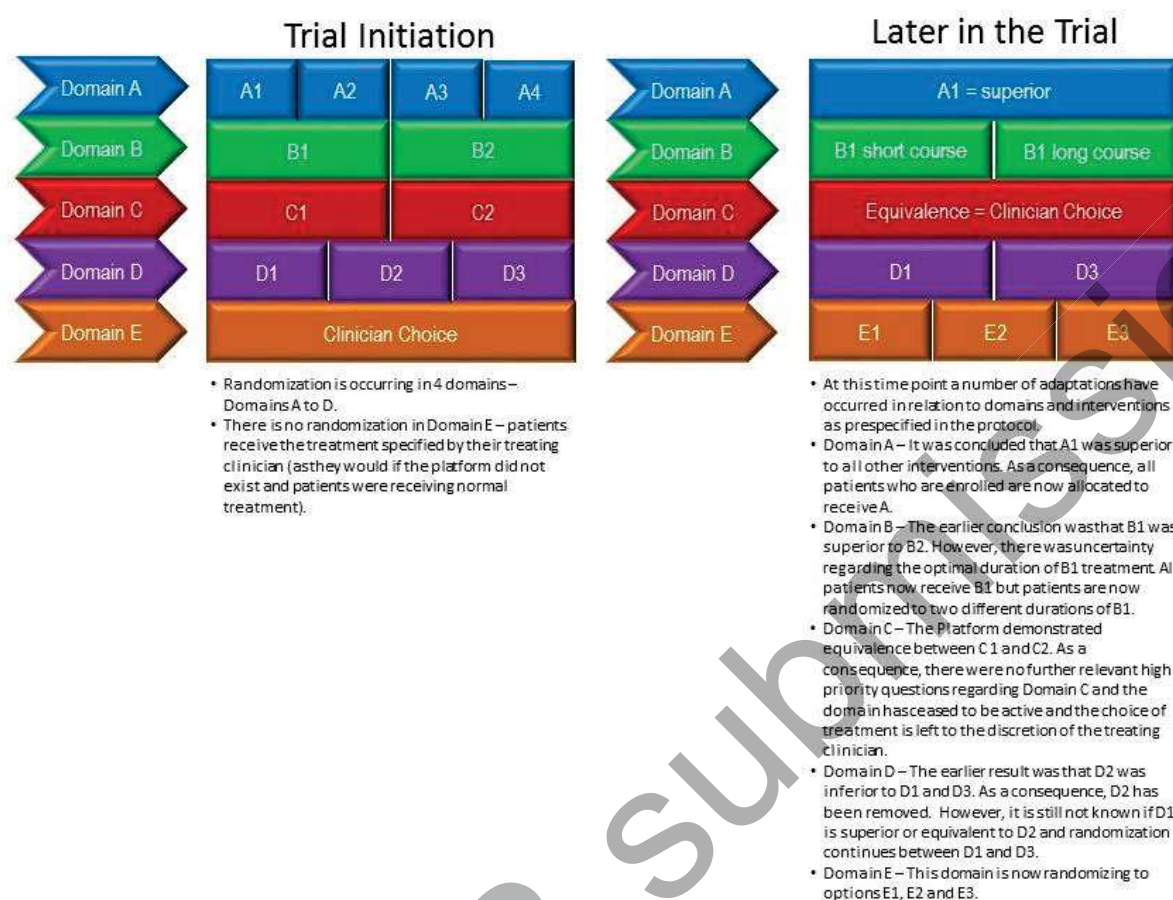
et al., 2013, Meurer et al., 2012, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016) An additional advantage is that dissemination of such results does not interrupt the conduct of the platform. In a single REMAP, there is no need for the “start-and-stop” periods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

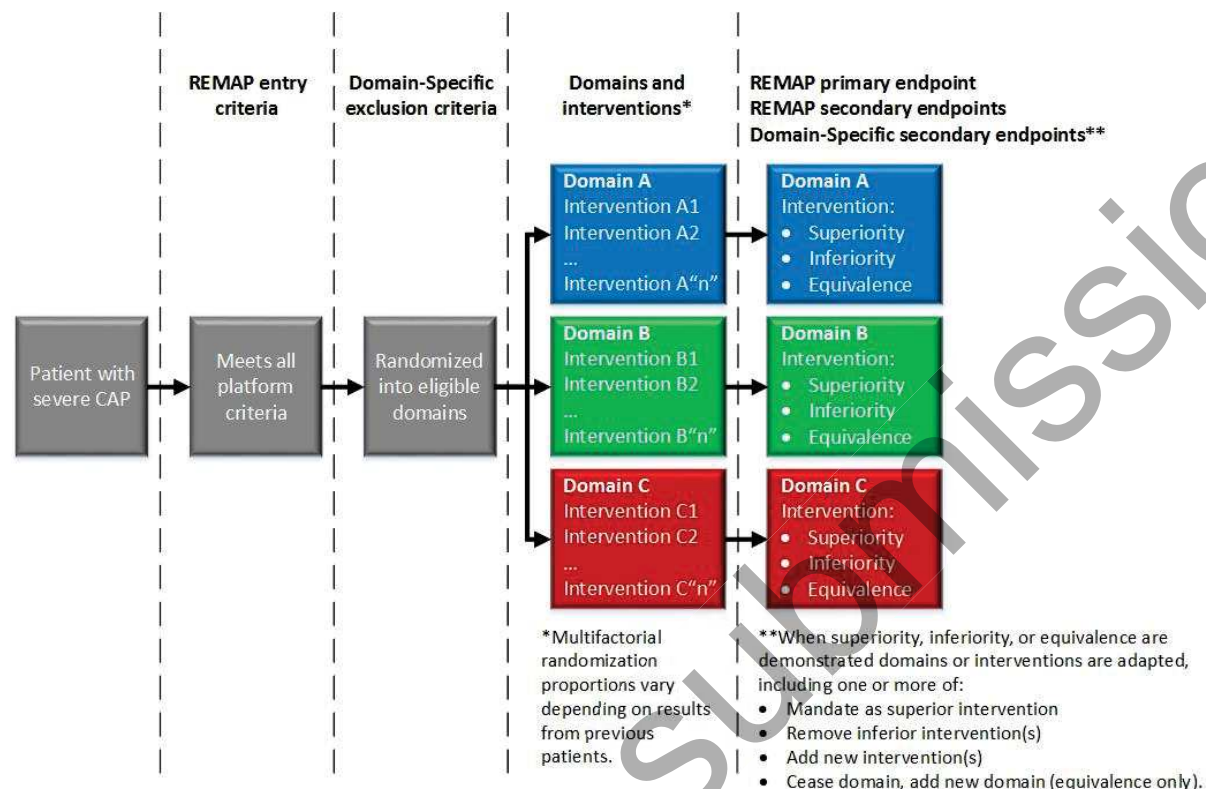
7. SUMMARY OF TRIAL DESIGN

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 subdivided 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, λ , 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 λ 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 λ parameter must be set, for each domain by domain pair.

In this REMAP, only three options are permitted with respect to specifying the λ parameter for each domain-domain pair. Firstly, λ 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, λ 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 λ 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 λ influences the initial amount of borrowing and the degree of borrowing as data accumulates. The value of λ 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 γ is specified in the model, in this REMAP the value of γ will be 0.075. The third choice is to allow no borrowing of the treatment-by-treatment interactions. This is equivalent to selecting a λ of infinity. This choice would be the most aggressive choice in estimating treatment-by-treatment interactions.

The λ 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

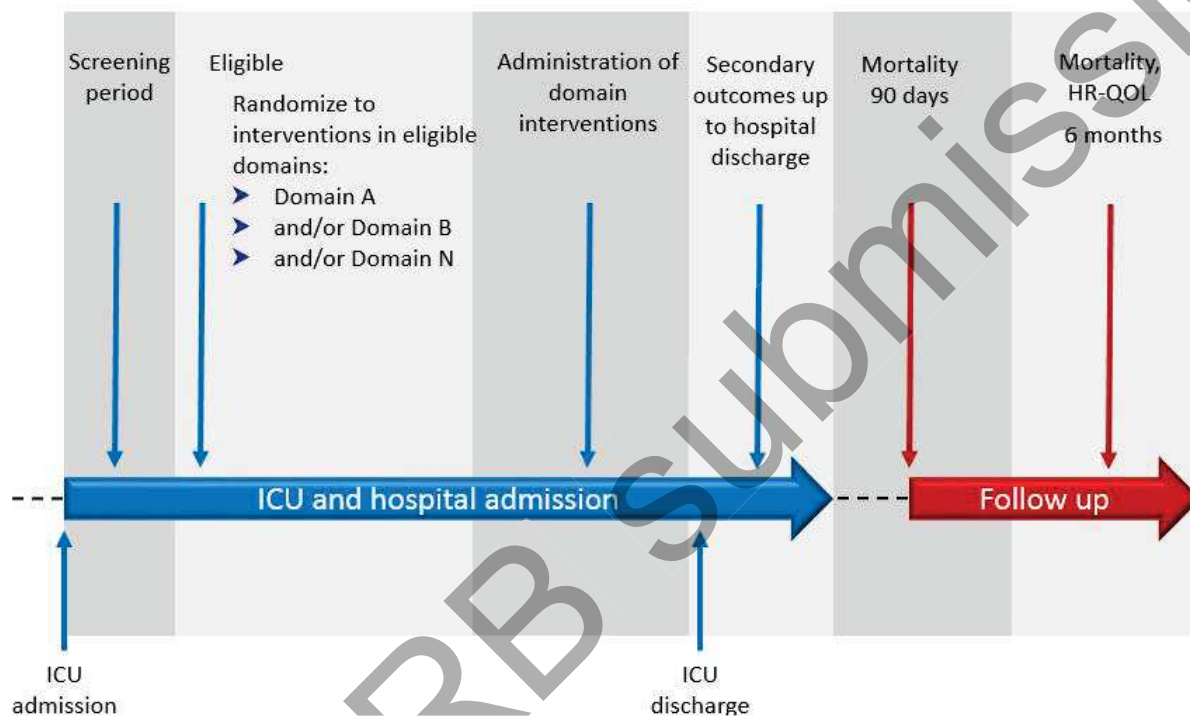
In each region or at the initiation of a new domain or both, the trial may consider commencing with only a small number of vanguard sites. The purpose of commencing the trial at vanguard sites is to learn about the effectiveness of different options for trial processes so that this information about

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.

10. REFERENCES

- ABEREGG, S. K., RICHARDS, D. R. & O'BRIEN, J. M. 2010. Delta inflation: a bias in the design of randomized controlled trials in critical care medicine. *Crit Care*, 14, R77.
- AIKMAN, K. L., HOBBS, M. R., TICEHURST, R., KARMAKAR, G. C., WILSHER, M. L. & THOMAS, M. G. 2013. Adherence to guidelines for treating community-acquired pneumonia at a New Zealand hospital. *J Pharm Pract Res*, 43, 272-275.
- ALMIRALL, J., BOLIBAR, I., VIDAL, J., SAUCA, G., COLL, P., NIKLASSON, B., BARTOLOME, M. & BALANZO, X. 2000. Epidemiology of community-acquired pneumonia in adults: a population-based study. *Eur.Respir.J.*, 15, 757-763.
- ALVAREZ-LERMA, F. & TORRES, A. 2004. Severe community-acquired pneumonia. *Curr.Opin.Crit Care*, 10, 369-374.
- ANGUS, D. C. 2015. Fusing Randomized Trials With Big Data: The Key to Self-learning Health Care Systems? *JAMA*, 314, 767-8.
- BARKER, A. D., SIGMAN, C. C., KELLOFF, G. J., HYLTON, N. M., BERRY, D. A. & ESSERMAN, L. J. 2009. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. *Clin.Pharmacol.Ther.*, 86, 97-100.
- BELLANI, G., LAFFEY, J. G., PHAM, T., FAN, E., BROCHARD, L., ESTEBAN, A., GATTINONI, L., VAN HAREN, F., LARSSON, A., MCAULEY, D. F., RANIERI, M., RUBENFELD, G., THOMPSON, B. T., WRIGGE, H., SLUTSKY, A. S., PESENTI, A., INVESTIGATORS, L. S. & GROUP, E. T. 2016. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA*, 315, 788-800.
- BERRY, D. A. 2012. Adaptive clinical trials in oncology. *Nat.Rev.Clin.Oncol.*, 9, 199-207.
- BERRY, S. M., CONNOR, J. T. & LEWIS, R. J. 2015. The platform trial: an efficient strategy for evaluating multiple treatments. *JAMA*, 313, 1619-1620.
- BHATT, D. L. & MEHTA, C. 2016. Adaptive Designs for Clinical Trials. *N Engl J Med*, 375, 65-74.
- BJERRE, L. M., VERHEIJ, T. J. & KOCHEN, M. M. 2009. Antibiotics for community acquired pneumonia in adult outpatients. *Cochrane.Database.Syst.Rev.*, CD002109.
- BLOOD OBSERVATIONAL STUDY INVESTIGATORS OF ANZICS-CLINICAL TRIALS GROUP, WESTBROOK, A., PETTILA, V., NICHOL, A., BAILEY, M. J., SYRES, G., MURRAY, L., BELLOMO, R., WOOD, E., PHILLIPS, L. E., STREET, A., FRENCH, C., ORFORD, N., SANTAMARIA, J. & COOPER, D. J. 2010. Transfusion practice and guidelines in Australian and New Zealand intensive care units. *Intensive Care Med*, 36, 1138-46.
- BODI, M., RODRIGUEZ, A., SOLE-VIOLAN, J., GILAVERT, M. C., GARNACHO, J., BLANQUER, J., JIMENEZ, J., DE LA TORRE, M. V., SIRVENT, J. M., ALMIRALL, J., DOBLAS, A., BADIA, J. R., GARCIA, F., MENDIA, A., JORDA, R., BOBILLO, F., VALLES, J., BROCH, M. J., CARRASCO, N., HERRANZ, M. A. & RELLO, J. 2005. Antibiotic prescription for community-acquired pneumonia in the intensive care unit: impact of adherence to Infectious Diseases Society of America guidelines on survival. *Clin.Infect.Dis.*, 41, 1709-1716.
- BURNS, K. E., CHANT, C., SMITH, O., CUTHBERTSON, B., FOWLER, R., COOK, D. J., KRUGER, P., WEBB, S., ALHASHEMI, J., DOMINGUEZ-CHERIT, G., ZALA, C., RUBENFELD, G. D. & MARSHALL, J. C. 2011. A Canadian Critical Care Trials Group project in collaboration with the international

- forum for acute care trialists - Collaborative H1N1 Adjuvant Treatment pilot trial (CHAT): study protocol and design of a randomized controlled trial. *Trials*, 12, 70.
- BYRNE, R. A. & KASTRATI, A. 2013. Unmet aspirations--where to now for catheter thrombectomy? *N Engl J Med*, 369, 1649-50.
- CAREY, L. A. & WINER, E. P. 2016. I-SPY 2--Toward More Rapid Progress in Breast Cancer Treatment. *N Engl J Med*, 375, 83-4.
- CECCONI, M., HOFER, C., TEBOUL, J. L., PETTILA, V., WILKMAN, E., MOLNAR, Z., DELLA ROCCA, G., ALDECOA, C., ARTIGAS, A., JOG, S., SANDER, M., SPIES, C., LEFRANT, J. Y., DE BACKER, D., INVESTIGATORS, F. & GROUP, E. T. 2015. Fluid challenges in intensive care: the FENICE study: A global inception cohort study. *Intensive Care Med*, 41, 1529-37.
- CONNOR, J. T., ELM, J. J. & BROGLIO, K. R. 2013. Bayesian adaptive trials offer advantages in comparative effectiveness trials: an example in status epilepticus. *J.Clin.Epidemiol.*, 66, S130-S137.
- COOK, D., LAUZIER, F., ROCHA, M. G., SAYLES, M. J. & FINFER, S. 2008. Serious adverse events in academic critical care research. *CMAJ*, 178, 1181-4.
- DELLINGER, R. P., LEVY, M. M., RHODES, A., ANNANE, D., GERLACH, H., OPAL, S. M., SEVRANSKY, J. E., SPRUNG, C. L., DOUGLAS, I. S., JAESCHKE, R., OSBORN, T. M., NUNNALLY, M. E., TOWNSEND, S. R., REINHART, K., KLEINPELL, R. M., ANGUS, D. C., DEUTSCHMAN, C. S., MACHADO, F. R., RUBENFELD, G. D., WEBB, S. A., BEALE, R. J., VINCENT, J. L., MORENO, R. & SURVIVING SEPSIS CAMPAIGN GUIDELINES COMMITTEE INCLUDING THE PEDIATRIC, S. 2013. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*, 41, 580-637.
- ECCLES, S., PINCUS, C., HIGGINS, B. & WOODHEAD, M. 2014. Diagnosis and management of community and hospital acquired pneumonia in adults: summary of NICE guidance. *BMJ*, 349, g6722.
- EUROPEAN MEDICINES AGENCY 2005. Guideline on the choice of the non-inferiority margin. In: COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP) (ed.). London.
- EWIG, S., WOODHEAD, M. & TORRES, A. 2011. Towards a sensible comprehension of severe community-acquired pneumonia. *Intensive Care Med*, 37, 214-223.
- FINFER, S., BELLOMO, R., BOYCE, N., FRENCH, J., MYBURGH, J. & NORTON, R. 2004. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N.Engl.J.Med.*, 350, 2247-2256.
- FINFER, S., LIU, B., TAYLOR, C., BELLOMO, R., BILLOT, L., COOK, D., DU, B., MCARTHUR, C., MYBURGH, J. & INVESTIGATORS, S. T. 2010. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. *Crit Care*, 14, R185.
- FREI, C. R., ATTRIDGE, R. T., MORTENSEN, E. M., RESTREPO, M. I., YU, Y., ORAMASIONWU, C. U., RUIZ, J. L. & BURGESS, D. S. 2010. Guideline-concordant antibiotic use and survival among patients with community-acquired pneumonia admitted to the intensive care unit. *Clin.Ther.*, 32, 293-299.
- HARRINGTON, D. & PARMIGIANI, G. 2016. I-SPY 2--A Glimpse of the Future of Phase 2 Drug Development? *N Engl J Med*, 375, 7-9.
- HUANG, D. T., ANGUS, D. C., MOSS, M., THOMPSON, B. T., FERGUSON, N. D., GINDE, A., GONG, M. N., GUNDEL, S., HAYDEN, D. L., HITE, R. D., HOU, P. C., HOUGH, C. L., IWASHYNA, T. J., LIU, K. D., TALMOR, D. S., YEALY, D. M., COMMITTEE, R. P. & THE, N. I. H. N. P. N. I. 2016. Design

and Rationale of the Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) Trial for Acute Respiratory Distress Syndrome. *Ann Am Thorac Soc*.

INSTITUTE OF MEDICINE 2013. *Best Care at Lower Cost: The Path to Continuously Learning Health Care in America*, Washington D.C, The National Academies Press.

LEE, J. S., NSA, W., HAUSMANN, L. R., TRIVEDI, A. N., BRATZLER, D. W., AUDEN, D., MOR, M. K., BAUS, K., LARBI, F. M. & FINE, M. J. 2014. Quality of care for elderly patients hospitalized for pneumonia in the United States, 2006 to 2010. *JAMA Intern.Med.*, 174, 1806-1814.

LEROY, O., SANTRE, C., BEUSCART, C., GEORGES, H., GUERY, B., JACQUIER, J. M. & BEAUCAIRE, G. 1995. A five-year study of severe community-acquired pneumonia with emphasis on prognosis in patients admitted to an intensive care unit. *Intensive Care Med.*, 21, 24-31.

LIM, W. S., BAUDOUIN, S. V., GEORGE, R. C., HILL, A. T., JAMIESON, C., LE, J., I, MACFARLANE, J. T., READ, R. C., ROBERTS, H. J., LEVY, M. L., WANI, M. & WOODHEAD, M. A. 2009. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax*, 64 Suppl 3, iii1-55.

MANDELL, L. A., WUNDERINK, R. G., ANZUETO, A., BARTLETT, J. G., CAMPBELL, G. D., DEAN, N. C., DOWELL, S. F., FILE, T. M., JR., MUSER, D. M., NIEDERMAN, M. S., TORRES, A. & WHITNEY, C. G. 2007. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*, 44 Suppl 2, S27-S72.

MCCABE, C., KIRCHNER, C., ZHANG, H., DALEY, J. & FISMAN, D. N. 2009. Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: playing by the rules. *Arch Intern Med* 169, 1525-1531.

MEURER, W. J., LEWIS, R. J. & BERRY, D. A. 2012. Adaptive clinical trials: a partial remedy for the therapeutic misconception? *JAMA*, 307, 2377-2378.

MORTENSEN, E. M., RESTREPO, M., ANZUETO, A. & PUGH, J. 2004. Effects of guideline-concordant antimicrobial therapy on mortality among patients with community-acquired pneumonia. *Am J Med*, 117, 726-731.

MORTENSEN, E. M., RESTREPO, M. I., ANZUETO, A. & PUGH, J. 2005. The impact of empiric antimicrobial therapy with a beta-lactam and fluoroquinolone on mortality for patients hospitalized with severe pneumonia. *Crit Care*, 10, R8.

MUSER, D. M., ROIG, I. L., CAZARES, G., STAGER, C. E., LOGAN, N. & SAFAR, H. 2013. Can an etiologic agent be identified in adults who are hospitalized for community-acquired pneumonia: results of a one-year study. *J Infect*, 67, 11-8.

MUSER, D. M. & THORNER, A. R. 2014. Community-acquired pneumonia. *N.Engl.J.Med.*, 371, 1619-1628.

PARK, J. W., LIU, M. C., YEE, D., YAU, C., VAN 'T VEER, L. J., SYMMANS, W. F., PAOLONI, M., PERLMUTTER, J., HYLTON, N. M., HOGARTH, M., DEMICHELE, A., BUXTON, M. B., CHIEN, A. J., WALLACE, A. M., BOUGHEY, J. C., HADDAD, T. C., CHUI, S. Y., KEMMER, K. A., KAPLAN, H. G., ISAACS, C., NANDA, R., TRIPATHY, D., ALBAIN, K. S., EDMISTON, K. K., ELIAS, A. D., NORTHFELT, D. W., PUSZTAI, L., MOULDER, S. L., LANG, J. E., VISCUSI, R. K., EUHUS, D. M., HALEY, B. B., KHAN, Q. J., WOOD, W. C., MELISKO, M., SCHWAB, R., HELSTEN, T., LYANDRES, J., DAVIS, S. E., HIRST, G. L., SANIL, A., ESSERMAN, L. J., BERRY, D. A. & INVESTIGATORS, I. S. 2016. Adaptive Randomization of Neratinib in Early Breast Cancer. *N Engl J Med*, 375, 11-22.

RHODES, A., EVANS, L. E., ALHAZZANI, W., LEVY, M. M., ANTONELLI, M., FERRER, R., KUMAR, A., SEVRANSKY, J. E., SPRUNG, C. L., NUNNALLY, M. E., ROCHWERG, B., RUBENFELD, G. D., ANGUS, D. C., ANNANE, D., BEALE, R. J., BELLINGHAN, G. J., BERNARD, G. R., CHICHE, J. D.,

- COOPERSMITH, C., DE BACKER, D. P., FRENCH, C. J., FUJISHIMA, S., GERLACH, H., HIDALGO, J. L., HOLLENBERG, S. M., JONES, A. E., KARNAD, D. R., KLEINPELL, R. M., KOH, Y., LISBOA, T. C., MACHADO, F. R., MARINI, J. J., MARSHALL, J. C., MAZUSKI, J. E., MCINTYRE, L. A., MCLEAN, A. S., MEHTA, S., MORENO, R. P., MYBURGH, J., NAVALES, P., NISHIDA, O., OSBORN, T. M., PERNER, A., PLUNKETT, C. M., RANIERI, M., SCHORR, C. A., SECKEL, M. A., SEYMOUR, C. W., SHIEH, L., SHUKRI, K. A., SIMPSON, S. Q., SINGER, M., THOMPSON, B. T., TOWNSEND, S. R., VAN DER POLL, T., VINCENT, J. L., WIERSINGA, W. J., ZIMMERMAN, J. L. & DELLINGER, R. P. 2017. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med*, 43, 304-377.
- RUGO, H. S., OLOPADE, O. I., DEMICHELE, A., YAU, C., VAN 'T VEER, L. J., BUXTON, M. B., HOGARTH, M., HYLTON, N. M., PAOLONI, M., PERLMUTTER, J., SYMMANS, W. F., YEE, D., CHIEN, A. J., WALLACE, A. M., KAPLAN, H. G., BOUGHEY, J. C., HADDAD, T. C., ALBAIN, K. S., LIU, M. C., ISAACS, C., KHAN, Q. J., LANG, J. E., VISCUSI, R. K., PUSZTAI, L., MOULDER, S. L., CHUI, S. Y., KEMMER, K. A., ELIAS, A. D., EDMISTON, K. K., EUHUS, D. M., HALEY, B. B., NANDA, R., NORTHFELT, D. W., TRIPATHY, D., WOOD, W. C., EWING, C., SCHWAB, R., LYANDRES, J., DAVIS, S. E., HIRST, G. L., SANIL, A., BERRY, D. A., ESSERMAN, L. J. & INVESTIGATORS, I. S. 2016. Adaptive Randomization of Veliparib-Carboplatin Treatment in Breast Cancer. *N Engl J Med*, 375, 23-34.
- SHORR, A. F., BODI, M., RODRIGUEZ, A., SOLE-VIOLAN, J., GARNACHO-MONTERO, J. & RELLO, J. 2006. Impact of antibiotic guideline compliance on duration of mechanical ventilation in critically ill patients with community-acquired pneumonia. *Chest*, 130, 93-100.
- SINGANAYAGAM, A., CHALMERS, J. D. & HILL, A. T. 2009. Severity assessment in community-acquired pneumonia: a review. *QJM*, 102, 379-388.
- SLIGL, W. I. & MARRIE, T. J. 2013. Severe community-acquired pneumonia. *Crit Care Clin.*, 29, 563-601.
- THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK 2000. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N.Engl.J.Med.*, 342, 1301-1308.
- U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES 2016. Non-inferiority clinical trials to establish effectiveness: guidance for industry. In: FOOD AND DRUG ADMINISTRATION (ed.).
- WARE, J. H. & ANTMAN, E. M. 1997. Equivalence trials. *N Engl J Med*, 337, 1159-61.
- WIERSINGA, W. J., BONTEN, M. J., BOERSMA, W. G., JONKERS, R. E., ALEVA, R. M., KULLBERG, B. J., SCHOUTEN, J. A., DEGENER, J. E., JANKNEGT, R., VERHEIJ, T. J., SACHS, A. P. & PRINS, J. M. 2012. SWAB/NVALT (Dutch Working Party on Antibiotic Policy and Dutch Association of Chest Physicians) guidelines on the management of community-acquired pneumonia in adults. *Neth.J.Med.*, 70, 90-101.
- WILKINSON, M. & WOODHEAD, M. A. 2004. Guidelines for community-acquired pneumonia in the ICU. *Curr.Opin.Crit Care*, 10, 59-64.
- WOODHEAD, M., BLASI, F., EWIG, S., GARAU, J., HUCHON, G., IEVEN, M., ORTQVIST, A., SCHABERG, T., TORRES, A., VAN DER, H. G., READ, R. & VERHEIJ, T. J. 2011. Guidelines for the management of adult lower respiratory tract infections--full version. *Clin.Microbiol.Infect.*, 17 Suppl 6, E1-59.
- WORLD HEALTH ORGANIZATION 2008. The Global burden of disease, 2004 update. Geneva, Switzerland: WHO Press.



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

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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 $d = 1, 2, \dots, D$. 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 $j = 1, \dots, J_d$ 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 $x_1, \dots, x_K$ 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 $s=1,\dots,S$.

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 not 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

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

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 $R = 1, \dots, R$ 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 $k = 1, \dots, K$, there is one term for every pairwise combination of $s = 1, \dots, S$ 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 ($s = 2, \dots, S$ 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 $T = 1, \dots, T$ where each represents an era, or a 13-week period of calendar time. The trial era in which the analysis is being conducted (the most current era) will be the referent and every other θ_T then represents the increase or decrease in mortality associated with calendar time since the start of the trial.

β_{d_j} are the terms that estimate the main effects of each intervention. There is one β_{d_j} term for each intervention in each domain. Intervention $j = 1$ in domain $d = 1$ is the referent and every other β_{d_j} estimates the relative increase or decrease in mortality associated with each other intervention in the trial.

γ_{kd_j} are the terms that estimate intervention by strata interactions. There is one term for every pairwise combination between the $k = 1, \dots, K$ strata in the trial and the $j = 1, \dots, J_d$ interventions across all $d = 1, \dots, D$ 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 mortality associated with an intervention when $g_k = 2$ (strata condition is "yes") versus when $g_k = 1$ (strata condition is "no").

$\delta_{jd'j'}$ are the terms that estimate the intervention by intervention interactions. There is one term for every pairwise combination between all the interventions $j = 1, \dots, J_d$ in one domain all interventions $j' = 1, \dots, J_{d'}$ 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 $c_R=1, \dots, C$. The parameter for each region is labeled v_R and is modeled hierarchically as:

$$[v_R] \sim N(\mu_{c_R}, \tau_{c_R}^2) \quad R = 2, \dots, N_R,$$

with hierarchical priors

$$[\mu_c] \sim N(0,1); [\tau_c^2] \sim IG(0.25,0.1), \text{ where } c=1,\dots,C.$$

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 0.20² 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 $d=1, \dots, D; j=1, \dots, J_d$ is considered the relative effect of each intervention. For identifiability, the effect for the first intervention within each domain is set to 0.

For some domains, there may be sets of interventions that are considered “nested”. For these nested interventions, the intervention effects are modeled hierarchically, which allows borrowing among the intervention effect estimates for the interventions within the nest. Each domain-specific appendix will specify which interventions, if any, will be considered nested for the model.

For all non-nested interventions, the intervention effects are given weak independent priors:

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

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

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

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,

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

which is described in the protocol as gamma = infinity. This prior spreads its mass over the real line.

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

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

which has a standard deviation of 0.15 (referred to as gamma = 0.15 in the protocol). This prior places most of its mass on small values, effectively shrinking the estimate of the interaction towards zero. For reference, on the log-odds scale (in which the parameter γ are) an effect of 0.15 is an odds-ratio of 1.16, which would make a probability of 0.20 increase to 0.225. This prior standard deviation value was selected by the ITSC in evaluating the model behavior versus possible scenarios.

7.7. *Intervention by intervention interactions*

It is anticipated that there may be interactions between some interventions, but that these would likely be relatively small.

For all two-way interaction parameters, three choices are available for modeling purposes. These choices are described in the protocol as the “lambda parameter” though they actually refer to choices for the standard deviation of the prior distribution for the interaction parameter. One of the following options will be pre-specified for each intervention-intervention pair:

- The model may force no interaction between a pair of interventions by setting the interaction parameter equal to zero. That is, $\delta_{d_j, d'_{j'}} = 0$ for the interaction between intervention j in domain d and intervention j' in domain d' (where $d \neq d'$). In the protocol, this option is written as $\text{lambda} = 0$.
- On the opposite extreme, the interaction term may be given a weak prior:

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

which is described in the protocol as $\text{lambda} = \text{infinity}$.

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

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

For reference, on the log-odds scale (in which the parameter δ are) an effect of 0.05 is an odds-ratio of 1.05, which would make a probability of 0.20 increase to 0.208. These prior values were selected by the ITSC in evaluating the model behavior versus possible scenarios.

8. STATISTICAL QUANTITIES

The following statistical quantities are used in the design of the trial. The posterior distribution of the model parameters is calculated using MCMC. The algorithm allows the generating of at least M (100,000) draws from the joint posterior distribution. The following posterior quantities are calculated during the MCMC algorithm. For each regimen, r , we define π_{r, g_k} as the relative

effectiveness of the regimen, for group g within strata k . Similarly, $\pi_{r,g_k}^{(m)}$ as the relative effectiveness of regimen r for group g within strata k , for the m th draw from the MCMC algorithm.

8.1. *Probability of Optimal Regimen*

Let $O_{g_k}(r)$ be the posterior probability that a regimen, r , is the optimal regimen for group g within strata k . For the $m=1, \dots, M$ draws from the posterior, the frequency of draws in which each unique regimen, r , is optimal in group g_k , is tracked. The frequency each regimen is optimal is the posterior probability that the regimen is the optimal regimen:

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

8.2. *Probability of Optimal Intervention*

While $O_{g_k}(r)$ tracks the posterior probability that a regimen is optimal, we also track the probability that an individual intervention is in the optimal regimen. We refer to the posterior probability an intervention j , from domain d , is in the optimal regimen for group g_k , as $\Lambda_{g_k}(d_j)$:

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

9. TRIAL ADAPTATION AND STOPPING CRITERIA AND GUIDELINES FOR INTERVENTIONS

The trial design is an adaptive perpetual platform trial design. The platform aspect of the trial refers to the fact that there will be multiple investigational interventions being simultaneously studied. The trial is designed to be perpetual and continue studying severe community-acquired pneumonia (severe CAP), with no designated end. The goals of the trial are to both treat patients effectively while also investigating the relative benefit of different interventions, within different groups of patients. The design is adaptive in that the key aspects of the trial will evolve in a pre-planned way based on accruing data.

First, there will be a starting status with regard to strata, domains, and the interventions within a domain. These aspects are expected to change during the course of the REMAP trial. Strata can be

added or removed. Similarly, domains can be added or removed, and interventions within the domains can be added or removed based on internal or external information. The trial design is generic in terms of the number of strata, domains, and interventions within a domain, so that the trial functions seamlessly, based on predefined rules, as the questions being evaluated within the trial evolve. Each section below describes aspects of the trial design that will evolve in a predetermined fashion based on accruing empirical information.

9.1. Data Sources

All patients in the perpetual trial will become a part of the accruing data in the trial. There will be a set of patients in the primary analysis population. All patients in the primary analysis population will remain in that population for as long as the trial is running.

9.2. Primary Analysis Population

The primary analysis population will consist of all patients that are randomized to at least one of the interventions and at least one intervention is revealed. The primary analysis population will be used for all efficacy endpoints and will be determined in accord with the intention to treat (ITT) principle and will comprise all randomized patients, analyzed by the regimen to which they were randomized and their stratum membership as determined at the time of randomization.

Other analysis populations may be used in supportive analyses of efficacy endpoints (when a Public Disclosure has been triggered) and in the analyses of domain-specific safety endpoints.

- A modified intention to treat (mITT) population, which will include only participants who received at least 1 dose of the allocated treatment (or similarly defined in the DSA for non-pharmacological interventions)
- A per protocol (PP) population, which will include only eligible patients who received the allocated intervention with no major protocol violations and where all outcomes were observed.

9.3. Adaptive Analyses

Adaptive analyses will be conducted frequently throughout the trial process. The first adaptive analysis will occur when there are a significant number of patients with 90-day outcome data. After that first adaptive analysis, they will be planned to be repeated monthly, perpetually, for the

remainder of the trial. Interim analyses may be skipped if, due to seasonal variations, enrollment is slow and little new information has accrued during the month. A regular time period (e.g. first of the month) will be selected and this will trigger the running of an adaptive analysis. These adaptive analyses will consist of all currently available data being analyzed according to the current trial model. Only data for patients reaching a 90-day window from time of randomization will be used in the analysis to avoid biases that may arise from differential timing of known failure compared with known success. The model run will be used to trigger allocation updates and possible Statistical Triggers (determining superiority, inferiority, and equivalence). These rules are presented in the following sections.

9.4. Allocation (Response Adaptive Randomization)

The allocation during the platform trial is adaptively set based on the accruing efficacy data. The data on the primary endpoint (mortality) will shape the randomization proportions for each regimen, within each stratum.

9.5. Initial randomization ratio

During the start to this trial there will be a period of time, the burn-in period, in which a response adaptive randomization scheme will be used with no new data. This response adaptive randomization will be based on initial prior parameters. Unless priors are selected favoring certain treatments within stratum these probabilities will be equal for each intervention.

9.6. Response Adaptive Randomization

After the burn-in period, RAR will be used for the allocation for each regimen. Allocation to the regimens will be allowed to vary across the patient groups defined by the strata. Patients will be enrolled in the trial and randomized to a regimen according the group they belong to within each strata. The randomization for each patient is based on the probability that each regimen is the optimal regimen for a patient within that patient strata, but balanced by the sample size already allocated to that regimen. This balancing creates better learning about the optimal regimen by allowing a less aggressive randomization to regimens that already have a larger number of patients allocated. We refer to this scheme as maximizing the information about the optimal regimen within a stratum.

The randomization for a patient in group g within strata k is proportional to

$$\rho_{r,g_k} \propto \sqrt{\frac{O_{g_k}(r)}{n_{r,g_k} + 1}}.$$

Where $O_{g_k}(r)$ is the probability that regimen r is optimal for patients in group g of strata k and n_{r,g_k} is the total number of patients in group g of strata k who have already been allocated to regimen r . Multiple normalizations are done to create the final randomization probabilities. The following steps are carried out.

1. Each randomization probability is normalized to sum to 1 by dividing by the sum of quantities over all regimens.
2. Any single intervention with a sum of probabilities across all regimens within a stratum less than 10% will be increased to sum to the floor randomization per intervention of 0.10. Note that a minimum randomization of 10% implies a maximum randomization probability of 90%
 - a. A nuisance parameter (φ) will be added to the odds ratio for each intervention that does not achieve at least a 10% randomization probability. The value of φ will be selected to create a minimum randomization probability of 10% for each intervention.

The result is a set of randomization probabilities for each regimen, for each group as defined by the strata.

9.7. Introduction of new interventions

While this REMAP is running, if a new intervention is started then the randomization will be “blocked” for the new intervention in order to guarantee an initial sample size. If there are J_d interventions in a domain after the new intervention is started, then a fixed allocation of $1/J_d$ will be used to allocate patients to the new intervention. The remaining $1 - \frac{1}{J_d}$ probability will be allocated to the other interventions using the RAR. This burn-in for each intervention will last until 25 patients have been allocated to the new intervention. At that point this restriction will be removed and adaptive randomization to all regimens will be carried out.

9.8. Intervention Efficacy Announcement / Conclusion

At each adaptive analysis the results of the relative efficacy of different interventions can trigger adaptive decision rules. These include Public Disclosure of the results, removal of interventions within strata, and deterministic allocation to interventions within strata. The following sections present the prospective rules for these adaptive decisions. The adaptive analyses will be carried out by the Statistical Analysis Committee (SAC).

9.9. Intervention Superiority

At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being the optimal intervention for a strata group, $\Lambda_{g_k}(d_j) > 0.99$, and there are at least 250 patients randomized to that intervention in that strata group, then that intervention, within that domain, will be deemed as being superior within that strata group, triggering a Public Disclosure. At that point, the remaining interventions in the domain will be halted for inferiority for that strata group. All future patients in that strata group will then be allocated to that superior intervention and randomized to interventions in the other domains. This will continue until new interventions are added to the domain that contains the superior intervention.

9.10. Intervention Inferiority

At any adaptive analysis, if a single intervention has less than a $0.01/(J_d-1)$ posterior probability of being the optimal intervention for a strata group $\Lambda_{g_k}(d_j) < 0.01$, then that intervention will be deemed as being inferior within that domain, for that strata group, triggering a report to the Data Safety and Monitoring Board (DSMB). The DSMB then makes a judgment on whether a Platform Conclusion has been reached and whether to trigger a Public Disclosure. If so, no additional patients in that strata group will be randomized to that intervention. When simultaneous superiority/inferiority occurs (for example when there are 2 interventions they are always simultaneous), then the result will be released as an intervention demonstrating superiority.

9.11. Intervention Equivalence

If the two interventions within the domain have at least a 90% posterior probability that the odds ratio comparing the two within any stratum is between 1/1.2, and 1.2, the two interventions will be considered equivalent for that stratum. This result will be communicated to the ITSC and they will

take the appropriate action (Public Disclosure, removal of one intervention, no action). There is no automatic adaptation when this occurs.

9.12. *Deviation from pre-specified analyses (contingency plans, non-convergence, testing model fit etc.)*

The SAC will monitor the model behavior, including numerical stability and scientific appropriateness. Simpler models will be constructed and evaluated determining any root cause issues, data issues, or inappropriate model fit. If any numeric instabilities can be fit in statistical numeric methods, these will be done by the SAC and the adjustments recorded and noted. If the model is deemed to provide an inappropriate fit then the SAC will inform the DSMB of appropriate adjustments which will be reported to the ITSC in a way that does not risk unblinding trial results. Possible adjustments could include:

1. If there are issues within an intervention for limited data the parameter for that intervention can be fixed for model stability.
2. If there is missing data on whether there were revelations of delayed reveals and/or state values then an ITT Model ignoring the changing states will be fit to explore the effects
3. A reasonable solution should technology fail or data issues arise would be to keep the randomization unchanged, fix the randomization for an intervention, or create equal randomization for all interventions/regimens.



Statistical Analysis Plan for fixed dose hydrocortisone for patients in whom pandemic infection is neither suspected nor proven (PINSNP)

Fixed dose hydrocortisone for non-pandemic pneumonia SAP Version 1.0 dated 5 February 2024

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1. FIXED DOSE HYDROCORTISONE FOR NON-PANDEMIC PNEUMONIA SAP VERSION

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

1.1. Version history

Version 1: Finalized on 5 February 2024.

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3. INTRODUCTION

This statistical plan for the analysis of fixed dose hydrocortisone in the non-pandemic stratum of the REMAP-CAP trial is an appendix to the Core protocol Statistical Analysis Plan (SAP). The general statistical approach is outlined in detail in the Core protocol SAP. This appendix provides specific details regarding the application of the general approach to the specific case in which we proposed to analyze the effect of fixed dose hydrocortisone in severe non-pandemic pneumonia. This analysis is being conducted because this intervention triggered the pre-set futility trigger ($<5\%$ probability of $\geq 20\%$ improvement in the odds of death at 90 days compared to control) within all unit of analyses made up of the shock and influenza strata, leading to cessation of enrolment as recommended by the Data Safety and Monitoring Board (DSMB).

REMAP-CAP explores multiple treatment domains by randomizing patients within multiple domains simultaneously. The adaptive platform trial was designed to produce modular results for individual interventions (compared to relevant control groups) or full domains upon reaching platform conclusions. When a predefined statistical trigger is met, the results are unblinded, analyzed based on a pre-specified plan, and made public. This document prespecifies the analyses to be conducted and reported on the unblinded data. The unblinded data will be for all patients eligible for fixed dose hydrocortisone who were randomized to fixed dose hydrocortisone or control interventions in the Corticosteroid Domain within the severe state non-pandemic stratum (pandemic infection neither suspected nor proven - PINSNP).

The authors of this document are blinded to all individual data other than: a.) prior publicly disclosed results for other domains and interventions, and; b.) correspondence from the DSMB attesting to the fact that the statistical trigger for futility has been reached for fixed dose hydrocortisone in all four units of analyses made up of shock and influenza strata. The primary analysis for this SAP will be conducted when the patient last randomized before closing of the fixed dose hydrocortisone arm reaches 90 days of follow-up (completion of the primary endpoint).

4. DESIGN CONSIDERATIONS

REMAP-CAP is designed with a Bayesian analysis as the primary analysis method for the trial. There is one overarching Bayesian hierarchical model, prespecified in the Core protocol SAP, driving all adaptations, statistical triggers, and result summaries. That primary statistical analysis model will be used to report the primary results for the effect of fixed dose hydrocortisone in the PINSNP stratum.

The Domain Specific Appendix specified the primary analysis populations based on three analytic patient strata (with “strata” defined at time of randomization into the domain and considered to be non-dynamic). The three domain-specific strata included: (1) age (children vs. adults); (2) source of infection (influenza vs. non-influenza pneumonia); and (3) shock (present or absent at enrollment). At the time of closure of randomization to the fixed dose hydrocortisone intervention, no children had yet been enrolled and therefore this analytic stratum is not considered (all patients are in the adult stratum). However, the other two analytic strata are included (as per, and as defined in, the Core Protocol and Corticosteroid Domain-specific Appendix). Although the domain also specified units of analysis based on illness severity (moderate/noncritically ill vs. severe/critically ill), moderately ill patients were not eligible for the fixed dose hydrocortisone intervention and therefore this stratum is not considered herein (all patients are severe). The analyses herein pertain only to the fixed dose hydrocortisone group (the only closed intervention in this domain), and the analysis of all ongoing interventions in this domain will be considered in a future SAP. The primary analysis will report the effect of hydrocortisone compared to no hydrocortisone in each unit of analysis defined by influenza and shock strata.

5. UNBLINDING

REMAP-CAP has multiple domains to which patients can be randomized and multiple interventions within domains. During the time that severe state PINSNP patients have been eligible for fixed dose hydrocortisone, 2 other active interventions have been available within the Corticosteroid domain: fixed dose dexamethasone and shock-dependent hydrocortisone. Only data for patients who were randomized to control or fixed dose hydrocortisone will be unblinded. No data on patients randomized to the other interventions in the Corticosteroid domain or on the effect of other interventions that are still being evaluated in other domains will be unblinded. However, the primary analysis will be conducted by the independent and unblinded Statistical Analysis Committee (SAC), using all available information required for the primary model (including information to which only the SAC and DSMB are unblinded). Secondary analyses will be conducted on the unblinded data set (fixed dose hydrocortisone vs. control) by investigators who are blinded to information about other interventions and domains. These analyses are identified below.

6. INTERVENTIONS

There are two arms (interventions) analyzed herein:

1. No corticosteroids assigned (control)

2. Fixed dose hydrocortisone (active comparator)

No interaction effects with other interventions within other domains will be evaluated.

7. DISEASE STATES

There are two disease states (**moderate** and **severe**) in REMAP-CAP. However, as noted above only severe state patients were eligible for the fixed dose hydrocortisone intervention, and therefore this analysis is restricted to patients in the severe state.

8. ANALYSIS POPULATION

1. REMAP-CAP severe state non-pandemic (PINSNP) pneumonia intent-to-treat (ITT) population. This population includes all patients randomized to at least one domain in the PINSNP stratum. This analysis population is used for the primary analysis.
2. Hydrocortisone specific ITT. This population consists of non-pandemic (PINSNP) pneumonia patients randomized to either fixed dose hydrocortisone or control. This analysis population is used for secondary analyses.
3. Hydrocortisone eligible ITT. This population consists of non-pandemic (PINSNP) pneumonia patients eligible for both control and fixed dose hydrocortisone and randomized to either fixed dose hydrocortisone or control. This analysis population is used for sensitivity analyses and descriptive summaries of endpoints that are not analyzed.

Each of these analysis populations will include only the patients randomized on or before 6 December 2023 (date that enrollment into the fixed dose hydrocortisone intervention was closed).

9. ENDPOINTS

The following endpoints will be analyzed, displayed graphically, and summarized through descriptive statistics. Section 15 below itemizes which specific endpoints will be analyzed in which specific populations.

1. Primary endpoint: 90-day mortality

- A dichotomous endpoint of all-cause mortality at 90-days.
- The primary analysis will analyze landmark mortality. In addition, Kaplan Meier curves will be generated to illustrate when deaths occurred with the accompanying hazard ratio estimated from a secondary analysis of mortality up to day 90 as a time-to-event endpoint.

2. ICU mortality, censored at 90 days

- A dichotomous endpoint of death in ICU up to 90 days. ICU mortality is defined as any death in the ICU within the same hospital admission.
3. **ICU length of stay, censored at 90 days**
 - A time-to event endpoint of leaving the ICU alive. If a patient is known to leave and then return to the ICU within 14 days of discharge, the intervening days while on the ward will be counted as ICU days.
 - Patients that die in the ICU will be considered to have 90-days of follow-up with no discharge event (i.e., the worst possible outcome).
 - Patients still in the ICU at data snapshot will be censored.
 4. **Ventilator-free days (VFD), censored at 28 days**
 - VFD will be calculated by counting the number of days that the participant is not ventilated.. If the participant is discharged alive from hospital, the remainder of days censored at 28 days are counted as ventilator-free days. In hospital mortality through day 90 is considered a -1 (worst outcome).
 5. **Organ-support free days (OSFD), censored at 28 days**
 - OSFD is an ordinal endpoint with in-hospital mortality through day 90 as the worst outcome. The organ support considered is cardiovascular (vasopressor/inotrope support) and respiratory support, calculated through 28 days.
 6. **Progression to intubation and mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or death**
 - A dichotomous endpoint of whether a patient progresses to intubation and mechanical ventilation, ECMO or death in hospital. This endpoint is defined for patients that are not on mechanical ventilation or ECMO at baseline.
 7. **Proportion of intubated patients who receive a tracheostomy, censored at 28 days**
 - This endpoint will be summarized descriptively only.
 8. **Hospital length of stay, censored at 90 days**
 - A time-to event endpoint of leaving the hospital alive.
 - Patients that die in-hospital will be considered to have 90-days of follow-up with no discharge event (i.e., the worst possible outcome).
 - Patients still in the hospital at data snapshot will be considered censored.
 9. **Destination at time of hospital discharge (home, rehabilitation hospital, nursing home or long-term care facility, or another acute hospitalization)**
 - This endpoint will be summarized descriptively only.

10. Readmission to the index ICU during the index hospitalization in the 90 days following enrollment

- This endpoint will be summarized descriptively only.

11. At least one serious adverse event (SAE)

- The proportion of patients with at least one SAE will be reported and analyzed.

10. GRAPHICAL DATA SUMMARIES

1. All ordinal endpoints will be plotted using stacked cumulative bar plots and cumulative probability plots.
2. All time-to-event endpoints will be plotted using Kaplan-Meier plots. Positive clinical event outcomes will be plotted as the cumulative rate of event, and negative events will be plotted as the cumulative event-free rate.

11. DESCRIPTIVE STATISTICS

1. Ordinal endpoints will be summarized by the cumulative frequency of each outcome. The 25th, 50th, and 75th percentiles will be summarized.
2. Dichotomous endpoints will be summarized by the proportion in each category.
3. Time-to-event outcomes will be summarized by the 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles from the Kaplan-Meier estimates, as available.

12. BASELINE CHARACTERISTICS

The following demographics will be summarized across arms: age, sex, BMI, ethnicity, APACHE II score (measured from hospital admission to randomization), suspected and confirmed influenza infection, preexisting conditions, baseline use of high-frequency nasal oxygenation, non-invasive ventilation, invasive mechanical ventilation, ECMO, vasopressors/inotropes, renal replacement therapy, and miscellaneous physiological values and inflammatory biomarker laboratory values.

13. COMPLIANCE

The compliance to steroid use over the first seven days will be summarized descriptively as follows:

- Proportion for whom we have dosing information for study day 1 thru 8
- Proportion who received at least one dose
- Additional proportion who received an alternative systemic steroid
- Proportion who received no steroid

- Proportion who received first dose HC before midnight on first day
- Median duration and IQR of HC therapy and of any systemic steroid therapy

Use of corticosteroids in the control arm over the first seven days will be summarized descriptively as follows:

- Proportion for whom we have medication inventory for study day 1 thru 8
- Proportion who received any hydrocortisone
- Proportion who received any systemic steroid
- Median duration and IQR of systemic steroids

14. ANALYTIC APPROACH

Each inferential analysis will be done using a Bayesian model. Some default frequentist methods are used for exploration and description. A summary of the analyses methods is provided below.

The protocol permitted fixed borrowing (shrinkage) between the analytic populations. Accordingly, treatment effects were estimated for the treatment in each stratum by combining all analytic groups into a single Bayesian hierarchical model, but allowing sharing of information between analysis groups through the use of a shrinkage parameter in the model. This effect averages treatment effects across groups and may increase power within a single group depending on the findings from other groups.

14.1. Analytic Approach for Primary Endpoint and Secondary Dichotomous Endpoints

A Bayesian cumulative logistic regression model will be used for the primary endpoint and for each dichotomous secondary outcome. The model will specify the “event” as the negative outcome and be parameterized so that an odds-ratio <1 implies benefit to patients. The model is the standard logistic link function model:

$$\log \left(\frac{\pi}{1 - \pi} \right) = \alpha + [factors]$$

References will be made to the factors in the model and their prior distribution. Full details of the model are specified in the Current State of the Statistical Model: Non-Pandemic Model Version 3.1.

The model has factors for:

- Strata and state effects
- Each global site, nested within country
- Age; ≤40, 41-65, 66-75, 76+
- Sex

- Time; 13-week buckets of time working backwards from the last enrolled patient
- For each domain, an effect for being randomized to the domain
- For each domain, an effect for being ineligible for the domain
- An effect for each intervention within each domain
- Specified interactions in the model between interventions and strata
- Specified interactions in the model between interventions across domains

The analysis uses the following rules:

- All sites within a country that have <5 patients randomized will be combined into a single site within that country.
- Time buckets with <5 randomized subjects in a state may be combined with the more recent neighboring bucket for that state.

The model will be referenced with certain model assumptions for sensitivity analyses. For example, the “time effects” in the model could be assumed to be 0.

14.1.1. Analytic Approach for Sensitivity Analyses of the Primary Outcome

Several sensitivity analyses will be included. First, the primary outcome will be analyzed within each analysis population without the use of statistical borrowing – estimating independent treatment effects for each analytic stratum. Second, the primary outcome will be analyzed within each analysis population estimating a single effect of hydrocortisone compared to no hydrocortisone. Finally, the effect of fixed dose hydrocortisone will be examined using only patients eligible for both fixed dose hydrocortisone and control (not just those eligible for this domain), as specified as the third analysis population (Hydrocortisone eligible ITT). Given that there were no intervention-specific exclusion criteria in this domain, this analysis population is likely to resemble the original analysis population, primarily differing based on sites participating in the domain but not participating in the fixed dose hydrocortisone or control interventions. The specified analysis models adjust for site as a factor. Nevertheless, this sensitivity analysis is included.

14.2. Analytic Approach for Secondary Ordinal Endpoints

Ordinal outcomes will be analyzed using Bayesian cumulative logistic models. The model is structured so that an odds-ratio <1 implies clinical benefit to be consistent with the primary endpoint. The model assumes a proportional effect of treatment across the scale of the ordinal outcome. The model includes all factors specified for the primary analysis model and the same prior distributions, if applicable. The reference probabilities of observing each ordinal outcome will be modeled with a non-

informative Dirichlet prior with total weight of 1 with equal weight across all modeled ordinal categories.

14.3. Analytic Approach for Secondary Time-To-Event Endpoints

All inferential time-to-event analyses will be done using a Bayesian piecewise exponential model. The Bayesian time-to-event model is intended to mirror a Cox proportional hazards model, with the underlying hazard rate modeled with a piecewise exponential model. The underlying hazard will be modeled with a hazard rate for each 10-day period in the model. The prior distribution for the hazard rate for each day is a gamma distribution with 1 day of exposure and a mean equal to the total exposure divided by the total number of events. This prior is intended to have little weight but to provide numerical stability to the model. Each factor is incorporated as a proportional hazard rate through an additive linear model of the log-hazard. The default prior for each factor is the same as for the log-odds in the ordinal model, if applicable. If other non-specified variables are added to the model, then a normal distribution with mean 0 and standard deviation 10 will be utilized.

14.4. Markov Chain Monte Carlo (MCMC) Model Stability

The Bayesian models have many parameters and there may be risk of poor model stability, including convergence and mixing behavior of the MCMC sampler. These instabilities may be based on sparse data on the outcome or covariates. The statisticians running the model may make changes that do not affect the overall interpretation but provide reliable model diagnostics and scientific rigor. Any alterations will be noted. For treatment effects estimated in groups with small sample sizes or low event rates, we will report the effect, if possible, from the analysis model and care will be taken as to not overinterpret the effect.

14.5. Model Outputs

The standard model outputs for each treatment effect will be the mean, standard deviation, median, and 95% credible intervals (all credible intervals will be equal-tailed intervals, so 95% credible intervals will range from the 2.5th percentile to the 97.5th percentile of the posterior distribution). For the dichotomous endpoints, the odds-ratio will be summarized. For the ordinal endpoints, the odds-ratios will be summarized. For the time-to-event endpoints, the hazard ratios will be summarized. For consistency, all models will be parameterized so that an odds-ratio or hazard-ratio less than 1 indicates clinical benefit (and a posterior probability of $\geq 99\%$ that the odds ratio < 1 is assumed to be statistically significant). Futility is defined as $< 5\%$ posterior probability of a $\geq 20\%$ reduction in the odds of death at 90 days.

14.6. Exploratory Analyses

Exploratory analyses after unblinding will not be considered inferential and no p-values or posterior probabilities will be presented. Any post-hoc exploratory analyses may use the following methods (with a frequentist or Bayesian inference):

1. Dichotomous proportions will be compared using logistic regression summarizing the odds-ratio and 95% confidence intervals. Differences between proportions will be summarized using observed differences and normal approximations for the 95% credible intervals.
2. Ordinal endpoints will be compared using a cumulative proportional odds model with summaries of the odds-ratio, 95% confidence intervals, and Wilcoxon tests for robustness against a lack of proportional odds.
3. Time-to-Event analyses will utilize a Cox proportional hazards model or piecewise exponential model, summarizing the hazard ratios and 95% confidence intervals.
4. Continuous endpoints will compare means with 95% confidence intervals based on two-sample t-test procedures.

15. SPECIFIC PROSPECTIVE ANALYSES

The specific prospective analyses are summarized in the table and described in detail below.

#	Status	Population	Endpoint	Other
1	Primary	REMAP-CAP PINSNP severe state ITT	90-day mortality	Includes all interventions and pre-specified interactions.
2	Sensitivity	REMAP-CAP PINSNP severe state ITT	90-day mortality	Estimates an overall/pooled treatment effect for hydrocortisone (i.e., no interaction modeled between steroid domain interventions and strata)
3	Sensitivity	REMAP-CAP PINSNP severe state ITT	90-day mortality	Prior on interaction between intervention and strata is weakened to $N(0, 1^2)$
4	Sensitivity	Hydrocortisone eligible ITT	90-day mortality	Restricted to hydrocortisone eligible controls
5	Sensitivity	Hydrocortisone specific ITT	90-day mortality	Pre-specified prior on intervention by strata effects
6	Sensitivity	Hydrocortisone specific ITT	90-day mortality	Estimates an overall treatment effect for hydrocortisone (i.e., no interaction modeled between steroid domain interventions and strata)

7	Sensitivity	Hydrocortisone specific ITT	90-day mortality	Prior on interaction between intervention and strata is weakened to $N(0, 1^2)$
8	Sensitivity	Hydrocortisone eligible ITT	90-day mortality	Estimates an overall treatment effect for hydrocortisone (i.e., no interaction modeled between steroid domain interventions and strata)
9	Sensitivity	Hydrocortisone eligible ITT	90-day mortality	Prior on interaction between intervention and strata is weakened to $N(0, 1^2)$
10	Secondary	Hydrocortisone specific ITT	ICU mortality	Dichotomous analysis
11	Secondary	Hydrocortisone specific ITT	ICU length of stay	Time-to-event analysis
12	Secondary	Hydrocortisone specific ITT	Ventilator-free days	Ordinal analysis
13	Secondary	Hydrocortisone specific ITT	Organ support-free days	Ordinal analysis
14	Secondary	Hydrocortisone specific ITT	Hospital length of stay	Time-to-event analysis
15	Secondary	Hydrocortisone specific ITT	90-day mortality	Time-to-event analysis.
16	Subgroup	Hydrocortisone specific ITT	90-day mortality	Source of infection (influenza or not)
17	Subgroup	Hydrocortisone specific ITT	90-day mortality	Source of infection confirmed (influenza confirmed or not)
18	Subgroup	Hydrocortisone specific ITT	90-day mortality	Baseline shock (present or not)
19	Subgroup	Hydrocortisone specific ITT	90-day mortality	Baseline ventilation (ventilated vs not)
20	Primary Safety Analysis	Hydrocortisone specific ITT	Serious adverse events per patient	Time effects removed from model.

15.1. Reporting of Analysis Results

For each analysis model, the following summaries will be reported when applicable:

Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 41-65				
Age 66-75				
Age 76+				
Female				
Time Bucket 1				
...				
Time Bucket k-1				
Hydrocortisone (vs control)				
Main effect of subgroup				
Fixed dose hydrocortisone by subgroup				

15.2. Graphical summaries

The following graphical summaries will be provided for all endpoints:

- Population: Hydrocortisone specific ITT
- Endpoint: all endpoints
- Factors: Fixed dose hydrocortisone and no corticosteroid interventions

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Rijnstate ziekenhuis Arnhem: Robert Jan Hassing, Frances Greven, Danique Huijbens, Harald Verheij,
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UMC Groningen: Karina Meijer, Douwe Postma, Karen Thedinga

UMC Leiden: Evert de Jonge, Jeanette Wigbers, Michael del Prado

UMC Utrecht: Marc Bonten, Jelle Haitsma Mulier, Emma Rademaker, Anna Linda Peters, Birgit
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ZGT Almelo: Bastiaan Wittekamp, Bart Grady, Ellen Platenkamp, Herma Harberink, Chantal Dibbelink

Ziekenhuis Gelderse Vallei Ede: Sjoerd van Bree, Marianne Bouw-Ruiter, Margreet Osinga, Arthur van
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New Zealand:

Auckland City Hospital, Cardiothoracic and Vascular ICU: Shay McGuinness, Rachael Parke,
Magdalena Butler, Keri-Anne Cowdrey, Alix Gray, Brittany Mason, Melissa Robertson, Laura
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Auckland City Hospital, DCCM: Colin McArthur, Thomas Hills, Eamon Duffy, Caroline O'ConnorYan
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O'Connor, Lauren West

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Stacey Morgan, Tara Burke

Middlemore Hospital: Tony Williams, Susan Morpeth, Rima Song, Dinuraj Girijadevi, Vivian Lai, Sarah
Lui, Tina Mwembani

North Shore Hospital: Robert Everitt, Sarah Bridges, Hina Karim

Rotorua Hospital: Ulrike Buehner, Erin Williams

Tauranga Hospital: Jonathan Chen, Amanda Miller, Caroline Abbott

Waikato Hospital: Pranesh Jogia, Robert Martynoga, Kara Trask, Amelia Butler, Jessica Newlands,
Kelly Henderson

Wellington Regional Hospital: Paul Young, Eden Lesona, Leanlove Navarra, Kirsha Delaney, Joy
Marmol, Reece Latino, Shan Qiu, Odessa David, Nina Roberts

Whangarei Hospital: Ralph Fuchs, Bridget Lambert

Taranaki Base Hospital: Jonathan Albrett, Carolyn Jackson, Simon Kirkham

Dunedin Hospital: Pawel Twardowski, Alisha Da Silva, Christina Kumate

Portugal:

Hospital de Abrantes: Nuno José Teodoro Amaro dos Santos Catorze, Tiago Nuno Alfaro Lima Pereira,
Ricardo Manuel Castro Ferreira, Joana Margarida Pereira Sousa Bastos, Teresa Margarida
Oliveira Batista

Romania:

"Dr. Victor Babes" Clinical Hospital of Infectious and Tropical Diseases Bucharest: Simin Aysel
Florescu, Delia Stanciu, Corneliu Popescu, Mihaela Florentina Zaharia, Alma Gabriela Kosa,
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Saudi Arabia:

King Abdulaziz Medical City- Riyadh: Yaseen M Arabi, Eman Al Qasim, Lolowa Alswaidan, Mohamed
M Hegazy, Hatim Arishi, Ali Al Amri, Samah Y AlQahtani, Brintha Naidu, Haytham Tlayjeh,
Sajid Hussain, Farhan Al Enezi, Sheryl Ann Abdukahil

Serbia:

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Slovenia:

University Medical Centre Maribor: Andrej Markota, Žiga Kalamar, Franc Svenšek, Martin Marinšek, Jure Fluher, Katja Jerenec, Barbara Kit, Iris Živko, Matija Peneš, Bor Daković

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Hospital del Mar: Rosana Muñoz-Bermúdez, Clara Vilà-Vilardell, Purificación Pérez-Terán, Aleix Granado Garcia, Judith Marin-Corral, Anna Salazar Degracia, Francisco Parrilla Gómez, Maria Isabel Mateo López, Purificación Pérez-Terán, Clara Vilá, Judit Bigas, Irene Dot Jordana, Cristina Climent Company, Lucia Picazo Moreno, María Acer Puig

Reina Sofia University Hospital: Rafael León López, Jorge Rodríguez-Gómez, Sheila Cárcel, Rosario Carmona, Carmen de la Fuente, Marina Rodriguez, Julian de la Torre Cisneros

Hospital Regional Universitario de Málaga: Manuel Enrique Herrera Gutiérrez, Carolina Joya Montosa, Alvaro Valverde Montoro.

Hospital Universitario de Jerez: Ángel Estella, Manuel Ángel Gracia Romero

Hospital Universitario Reina Sofia: Eduardo Aguilar Alonso, Rafael López, Jorge Rodríguez-Gómez, Carmen de la Fuente, Julian de la Torre Cisneros, Rodrigo Rayo Castillo, Paula Buendia

University Hospital Marques de Valdecilla: Borja Suberviola Cañas, Alfredo Del Moral de Diego

Ramon y Cajal University Hospital: Maria Cruz Soriano Cuesta, Aaron Blandino Ortiz, Marina Lopez Olivencia, Ana Villaclaras Pacheco, Eduardo Morales Soribas, Itziar Pozuelo Echegaray, Noemí Paredes de Dios, José Márquez Alonso, Loreto López Vergara, Luis Jaramillo Valarezo.

Switzerland:

University Hospital Zurich: Pedro D. Wendel-Garcia, Philipp K. Buehler, Eva-Maria Kleinert

Singapore:

National University Hospital: Matthew Cove, Ryanna Koh, John Soong, Paul Tambyah

Ng Teng Fong General Hospital: Faheem Ahmed Khan, Manasa Sachin

Tan Tock Seng Hospital: Sharlene Ho, Yeo He Ping, Ser Hon Puah

United Kingdom:

Aberdeen Royal Infirmary: Callum Kaye, Amanda Coutts, Lynn MacKay;

Addenbrooke's Hospital: Charlotte Summers, Petra Polgarova, Neda Farahi, Eleonore Fox, Katherine Bongaerts. Peter Featherstone, Anthony Ng, David Sapsford;

Alder Hey Children's NHS Foundation Trust: Stephen J McWilliam, Daniel B Hawcutt, Laura Rad, Laura O'Malley, Jennifer Whitbread, Dawn Jones, Rachael Dore, Paula Saunderson;

Alexandra Hospital Redditch: Olivia Kelsall, Nicholas Cowley, Laura Wild, Jessica Thrush, Hannah Wood, Karen Austin;

Altnagelvin Hospital: Adrian Donnelly, Martin Kelly, Naoise Smyth, Sinéad O'Kane, Valerie Mortland, Diane Mackey, Simon Galbraith, Breda Robinson, Declan McClintock, Majella Warnock, Ryan Campbell, Edmund McCallion;

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Barnet Hospital: Rajeev Jha, Michael Kalogirou, Christine Ellis, Vinodh Krishnamurthy, Aibhilin O'Connor, Saranya Thurairatnam;

Basildon University Hospital: Dipak Mukherjee, Agilan Kaliappan, Mark Vertue, Anne Nicholson, Joanne Riches, Gracie Maloney, Lauren Kittridge, Amanda Solesbury, Angelo Ramos;

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Angharad Williams, Emma Thomas, Rhys Davies, Matt Wise, Daniel Law;

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Roceld Rojo, Phoebe Coghlan, Joanna Smee, Gareth Barker;

Chesterfield Royal Hospital: Euan Mackay, Rheanna Smith, Peter Hickey, Edward Harris, Abigail
Forsyth, Holly Bladdon, Nerys Winnard, Jon Cort, Amanda Whileman, Thomas Spencer, Nick
Spittle, Sarah Beavis, Anand Padmakumar, Katie Dale, Joanne Hawes, Emma Moakes, Rachel
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The Christie NHS Foundation Trust: Vidya Kasipandian, Amit Patel, Suzanne Allibone, Roman Mary-
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Arachchige, Melissa Hartley, Sam Balls-Burgess, Jack Bloomfield, Lok Hin Lui, Bethany
Plummer, Jennifer Shu Ki Lok;

Countess of Chester Hospital: Peter Bamford, Andrew Reid, Kathryn Cawley, Maria Faulkner,
Charlotte Pickering;

Croydon University Hospital: Ashok Sundar Raj, Georgios Tsinaslanidis, Reena Nair Khade, Gloria
Nwajei Agha, Rose Nalumansi Sekiwala;

Cumberland Infirmary: Tim Smith, Chris Brewer, Jane Gregory;

Darlington Memorial Hospital: James Limb, Amanda Cowton, Julie O'Brien, Kelly Postlethwaite;

Derriford Hospital: Nikitas Nikitas, Colin Wells, Helen McMillan, Liana Stapleton, Bethan Stowe,
Kayleigh Spencer;

East Kent Hospitals (Queen Elizabeth the Queen Mother Hospital): Ana Alegria, Salah Turki, Tarek
Elsefi, Nikki Crisp, Louise Allen;

East Lancashire Hospitals NHS Trust (Royal Blackburn Hospital): Nicholas Truman, Matthew Smith,
Shuan Morgan, Janice Hartley, Srikanth Chukkambotla, Victoria Taylor, Debbie Sutton, Darren
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Grange University Hospital: Tamas Szakmany, Shiney Cherian, Gemma Williams, Christie James, Abby Waters, Hasham Almeshhedani, Natalie Duric, Robert Jesty, Catriona Spiers;

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Leicester Royal Infirmary: Hafiz R Qureshi, Neil Flint, Sarah Nicholson, Sara Southin, Andrew Nicholson, Amardeep Ghattaoraya;

Lewisham and Greenwich NHS Trust: Daniel Harding, Sinead O'Halloran, Amy Collins, Emma Smith, Estefania Trues;

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Liverpool Heart and Chest Hospital: Craig Wilson, Zuhra Surti;

Luton and Dunstable University Hospital: Loku Chamara Warnapura, Ronan Agno, Prasannakumari Sathianathan, Deborah Shaw, Nazia Ijaz, Adam Spong, Suganya Sabaretnam, Dean Burns, Eva Lang, Margaret Louise Liverpool Tate;

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Manchester Royal Infirmary: Jonathan Bannard-Smith, Richard Clark, Kathrine Birchall, Joanne Henry, Fiona Pomeroy, Rachael Quayle, Katharine Wylie, Anila Sukuraman, Maya John, Sindhu Sibin;

Medway Maritime Hospital: Arystarch Makowski, Beata Misztal, Syeda Haider, Angela Liao, Rebecca Squires;

Milton Keynes University Hospital: Richard Stewart, Teena Babu, Esther Mwaura, Louise Mew, Lynn Wren, Felicity Williams, Sara-Beth Sutherland, Rashmi Rebello, Kiranjit Bharaj, Atique Rehman;

Mid & South Essex NHS Foundation Trust: Aneta Oborska, Abdul Kayani, Selver Kalchko-Veyssal, Rajalakshmi Orath Prabakaran, Bernard Hadebe;

Musgrove Park Hospital: Richard Burgess, Richard Innes, Richard Burgess, Benjamin Plumb, William Rutherford, Thanseela Mahenkutty, Richard Bufton, Patricia Doble, Libby Graham, Charmaine Shovelton, Tessa Deans, Rebecca Purnell, Ashly Thomas;

Nevill Hall Hospital: Vincent Hamlyn, Nancy Hawkins, Anna Roynon-Reed, Sean Cutler, Sarah Lewis;

Newham University Hospital: Juan Martin Lazaro, Tabitha Newman, James Hand, Karen Smallshaw, Ausra Zdanavidiene;

Ninewells Hospital: Pauline Austin, Susan Chapman, Louise Cabrelli;

Norfolk and Norwich University Hospital: Simon Fletcher, Jurgens Nortje, Deirdre Fottrell-Gould, Georgina Randell, Katie Stammers, Gail Healey, Marta Goncalves Pinto, Zarah Brown, Karen

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Northampton General Hospital: Mohsin Zaman, Einas Elmahi, Andrea Jones, Kathryn Hall;

Northern General Hospital, Sheffield: Gary H Mills, Ajay Raithatha, Kris Bauchmuller, Kim Ryalls, Kate Harrington, Helen Bowler, Jas Sall, Richard Bourne, Alice Howell, Claire Jarman, Rosemary Kirk, Alison Lye;

Northumbria Healthcare Trust: Charlotte Bomken, Mari Kilner, Jessica Reynolds, Bryan Yates;

Northwick Park Hospital NHS Trust: Jamie Gross, Natalie Massey, Olumide Adebambo, Matilda Long, Kiran Tony;

North Manchester General Hospital: Zoe Borrill, Tracy Duncan, Andrew Ustianowski, Alison Uriel, Ayaa Eltayeb, Jordan Alfonso, Samuel Hey, Joanne Shaw, Claire Fox, Gabriella Lindergard, Bethan Charles, Bethany Blackledge, Karen Connolly, Jade Harris;

North Middlesex University Hospital: Jeronimo Moreno Cuesta, Kugan Xavier, Dharam Purohit, Munzir Elhassan, Anne Haldeos, Rachel Vincent, Marwa Abdelrazik, Samuel Jenkins, Arunkumar Ganesan, Rohit Kumar, David Carter, Dhanalakshmi Bakthavatsalam, Alasdair Frater, Malik Tahir Saleem, Daanyaal Madarbukus;

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Pilgrim Hospital Boston: Manish Chhablani, Gunjan Phalod, Amy Kirkby, Simon Archer, Kimberley Netherton;

Princess Royal Hospital: Denise Skinner, Jane Gaylard, Julie Newman;

Princess of Wales Hospital: Sonia Sathe, Lisa Roche, Ellie Davies;

Poole Hospital: Henrik Reschreiter, Julie Camsooksai, Sarah Patch, Sarah Jenkins, Charlotte Humphrey, Emma Langridge;

Queen Alexandra Hospital Portsmouth: David Pogson, Steve Rose, Helen Claridge, Shenu George, Zoe Daly, Lutece Brimfield, Angie Nown;

Queen Elizabeth Hospital, Birmingham: Dhruv Parekh, Colin Bergin, Michelle Bates, Christopher McGhee, Daniella Lynch, Khushpreet Bhandal, Kyriaki Tsakiridou, Amy Bamford, Lauren

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Queen's Hospital, Romford: Mandeep-Kaur Phull, Abbas Zadi, Tatiana Pogreban, Lace Rosaroso, Neale O'Brien, Elisa Visentin;

Queens Medical Centre and Nottingham City Hospital: Daniel Harvey, Benjamin Lowe, Megan Meredith, Anju Thomas, David Ford, Sophie Lubbock, Alexandra McCoy, Lucy Ryan, Amy Clark, Martin Dent, Alexandra Gibbins, Theerata Haghi, Treasa Joseph, Lucy Morris, Cecilia Peters, Julia Sampson, Catherine Walton, DREEM Research Team;

The Rotherham NHS Foundation Trust: Anil Hormis, Rachel Walker, Jake Warrington, Dawn Collier, Sarah Kimpton, Susan Oakley, Cheryl Graham, Victoria Maynard;

Royal Alexandra Hospital: Kevin Rooney, Natalie Rodden, Nicola Thomson, Phillip Henderson, Susan Currie, Izabela Orlikowska, Deborah McGlynn, Lynn Abel, Lisa Gemmell, Radha Sundaram, James Hornsby;

Royal Berkshire Hospital: Andrew Walden, Liza Keating, Matthew Frise, Nicola Jacques, Parminder Bhuie, Sabi Gurung Rai, Shauna Bartley;

Royal Bournemouth and Christchurch Hospitals: Martin Schuster-Bruce, Sally Pitts, Rebecca Miln, Laura Purandare, Luke Vamplew;

Royal Brompton Hospital: Brijesh Patel, Debra Dempster, Mahitha Gummadi, Natalie Dormand, Shu Fang Wang;

Royal Cornwall NHS Trust: Michael Spivey, Sarah Bean, Karen Burt, Lorraine Moore, Fiona Hammonds, Carol Richards, Rachel Chapman, Thomas Cornell;

Royal Devon and Exeter NHS Foundation Trust: Christopher Day, Letizia Zitter, Sarah Benyon;

Royal Glamorgan Hospital: Jayaprakash Singh, Ceri Lynch, Lisa Roche, Justyna Mikusek, Bethan Deacon, Keri Turner;

Royal Gwent Hospital: Evelyn Baker, John Hickey, Shreekant Champanerkar, Lindianne Aitken, Lorraine LewisProsser, Christie James;

Royal Hallamshire Hospital, Sheffield: Gary H Mills, Norfaizan Ahmad, Matt Wiles, Jayne Willson, Alice Howell, Claire Jarman, Rosemary Kirk, Alison Lye, Ajay Raithatha, Jas Sall;

Royal Hampshire Hospitals: Irina Grecu, Jane Martin, Caroline Wrey Brown, Ana-Marie Arias, Emily Bevan, Samantha Westlake, Denise Griffin, Laura Payne, Rachel Bryant, Roisin Kelly, Tatiana Dunn, Bindu Anil, Rajani Sreejith, Hayley Cousins, Helen Wood, Janet Green, Emma Levell;

Royal Infirmary of Edinburgh: Thomas H Craven, David Hope, Lucy McDonald, Lauren Callender, Maggie Wishart, Mia Amamio, Scott Simpson, Katie Doverman, Jo Singleton, Sarah Clark, Corrienne McCulloch, Simon Biddie, Sophie Birch, Kate Britton, Lucy Marshall, Manu Shankar-Hari;

Royal Liverpool University Hospital: Ingeborg D Welters, David Oliver Hamilton, Karen Williams, Victoria Waugh, David Shaw, Suleman Mulla, Alicia Waite, Jaime Fernandez Roman, Maria Lopez Martinez, Brian Johnston, Robert Ayee, Stephanie Beresford, Laura Medhurst;

Royal London Hospital: Zudin Puthuchear, Timothy Martin, Filipa Santos, Ruzena Uddin, Maria Fernandez, Fatima Seidu, Alastair Somerville, Mari-Liis Pakats, Salma Begum, Tasnin Shahid, Priya Dias, Ruzena Uddin;

The Royal Free Hospital: Sanjay Bhagani, Mark De Neef, Sara Mingo Garcia, Amitaa Maharajh, Aarti Nandani, Jade Dobson, Gloria Fernando, Christine Eastgate, Keith Gomez, Zakee Abdi, Glykeria Pakou;

The Royal Marsden NHS Foundation Trust: Kate Colette Tatham, Shaman Jhanji, Ethel Black, Arnold Dela Rosa, Ryan Howle, Ravishankar Rao Baikady;

The Royal Oldham Hospital: Redmond P Tully, Andrew Drummond, Joy Dearden, Grainne O'Connor, Michelle Mulcahy, Chloe Rishton, Jennifer Kujacz, Carole Blessen, Jennifer E Philbin, Sheila Munt;

The Royal Wolverhampton NHS Trust (New Cross Hospital): Shameer Gopal, Jagtar- Singh Pooni, Saibal Ganguly, Andrew Smallwood, Stella Metherell;

Royal Papworth Hospital: Alain Vuylsteke, Charles Chan, Saji Victor, COVID Research Team, Papworth Hospital;

Royal Stoke Hospital: Ramprasad Matsa, Minerva Gellamucho, Michelle Davies, Christopher Thompson, Nehal Patel, Susan Brammer, Lucy Bailey, Elisa Sernicola;

Royal Surrey County Hospital: Ben Creagh-Brown, Cheryl Marriot, Armored Salberg, Louisa Zouita, Sarah Stone, Natalia Michalak-Glinska, Sinead Donlon, Shelia Mtuwa, Irving Mayangao, Jerik Verula, Dorota Burda, Celia Harris, Emily Jones, Paul Bradley, Esther Tarr, Lesley Harden, Charlie Piercy, Eleanor Smith;

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Sherwood Forest Hospitals NHS Foundation Trust: Valli Ratnam, Mandy Gill, Jill Kirk, Sarah Shelton;

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Southmead Hospital: David Arnold, Ed Moran, Jade King, Kate Helliker, Maisie Borrill, Louise Solomon, Matt Thomas, Ruth Worner, Beverley Faulkner, Emma Gendall, Kati Hayes, Hayley Blakemore, Borislava Borislavova, Kerry Smith, Deanna Stephens;

St. Bartholomew's Hospital: Colin Hamilton-Davies, Carmen Chan, Celina Mfuko, Hakam Abbass, Vineela Mandadapu;

St. George's Hospital: Susannah Leaver, Maria Thanasi, Vince Ventura, Maria Maiz Cordoba, Kamal Patel, Sarah Farnell-Ward, Romina Pepermans Saluzzio, Sam Rawlins, Christine Sicat, Edna Fernandes;

St. Mary's Hospital: Anthony Gordon; Sara Perez Guillotin, Dorota Banach, Ziortza Fernández de Pinedo Artaraz, Leilani Cabrerros, Jenny Wong, Anita Gurung, Amal Mohammed, Eleanor Jepson, Victoria Latham;

St. Peter's Hospital, Chertsey: Ian White, Maria Croft, Nicky Holland, Rita Pereira, Maia Aquino, Teri Chin, Victoria Frost, Karen Wells;

Stepping Hill Hospital, Stockport: Ahmed Zaki, David Johnson, Hywel Garrard, Suzy Collins, Rebecca Mills, Claire Tibke, Vera Juhasz, Susan Hopkins, Louise Brown, Abigail Pemberton;

Sunderland Royal Hospital: Alistair Roy, Anthony Rostron, Vaileious Lostarakos, Carina Dowson, Lindsey Wood, Nadia Elkaram, Charlotte Caroline, Claire Gimour, Jennifer Henderson, Rebecca Young, Sarah Cornell;

Swansea Bay University Health Board (Morriston Hospital): Suresh Pillai, Rachel Harford, Helen Ivatt, Debra Evans, Suzanne Richards, Eilir Roberts, James Bowen, James Ainsworth, Marie Williams;

The Great Western Hospital: Malcolm Watters;

The Queen Elizabeth Hospital King's Lynn: Gayathri Wijewardena;

Torbay and South Devon NHS Foundation Trust: Angela Foulds, Adam Revill;

Ulster Hospital: Chris Murray, Fred McElwaine, Jen Elder, Pdraig Headley, John McCaffrey, Samantha Hagan, Vicki Adell, Emma Gibson;

United Lincolnshire NHS Trust: Russell Barber, Anette Hildrith, Gunjan Phalod, Stephanie Barker, Susan Butler, Olesya Francis, Claire Hewitt, Kelvin Lee, Maryanne Okubanjo, Andrew Sloan, Silvia Tavares;

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Supplemental methods

Inclusion and exclusion criteria

REMAPCAP platform Inclusion 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

REMAPCAP Platform Exclusion criteria

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

Corticosteroid Domain Specific Inclusion criteria

1. Patient is aged ≥ 28 days old (corrected gestational age)
2. If in the Moderate State, patient is receiving some form of supplemental oxygen (simple facemask, low or high flow nasal oxygen, or non-invasive ventilation)

Corticosteroid Domain Specific Exclusion criteria

1. Known hypersensitivity to any corticosteroid
2. 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* or COVID-19 pneumonia
3. If in the Severe State, more than 24 hours have elapsed since ICU admission; if the patient has already been assigned a treatment in another domain in the Moderate State, exclusion will occur if more than 24 hours has elapsed since commencement of sustained organ failure support in an ICU.
4. The treating clinician believes that participation in the domain would not be in the best interests of the patient

Corrective action plan following incorrect labeling of patients

On February 23rd, 2024, it was identified that there was a coding error for 28 participants randomized between the 'fixed course hydrocortisone' and 'no corticosteroid' arms of the non-pandemic stratum of the Corticosteroid Domain at participating sites in Europe prior to March 2020. This error resulted in the reverse allocation status being recorded for these participants in an export sent from one of the REMAP-CAP database providers to trial statisticians.

These miscoded data were used in a single adaptive analysis in August 2021, and impacted the subsequent response adaptive randomization (RAR) proportions for this domain. The exact impact on randomization proportions is difficult to quantify. However for participants without COVID-19 randomized to the Corticosteroid Domain between the interim analysis performed in August 2021 and the occurrence of a statistical trigger for this domain in November 2023, there was increased likelihood of being assigned to the 'fixed-course hydrocortisone' intervention. In November 2023, 'fixed-course hydrocortisone' was found to be futile in comparison to the 'no corticosteroid' control.

After conducting an internal investigation, we are confident that this error:

- Did not result in the incorrect allocation for these participants being recorded in the study database itself, or being shown to research teams at participating sites
- Did not impact the coding of allocations for any other participants in the trial
- Did not impact the coding of allocations that the affected participants received in any other domains
- Did not impact the validity of the Platform Conclusion for the Corticosteroid Domain that was reached in November 2023
- Has not impacted any of the results published from REMAP-CAP to date
- Did not affect parallel safety reporting to the Data Safety Monitoring Board
- Is now resolved with processes in place (see below)

The coding error was identified on February 23, 2024, and there was extensive review of the existing code for other potential errors, with none identified. Regulators were notified within 30 days of identifying the error.

Preventive actions have been put in place across the platform.

- Data management for REMAP-CAP Platform transitioned to a central 'Data Coordination Centre' (ICNARC, UK) in 2022, providing centralized data management with enhanced processes for data processing. This replaced a process by which exports were sent directly from multiple data providers to trial statisticians.
- Any updates to specification documents for exports to trial statisticians are overseen by the Data Coordination Centre in collaboration with trial statisticians, reducing the risk of miscommunication between multiple parties.
- Procedures and work instructions implemented in 2023 at Data Coordination Centre to ensure that any updates to code are checked by multiple experienced data managers. These include, but not limited to: 'Receiving and Importing Exports from Data Providers'; 'Merged Database'; and 'Generating Data Exports'
- Policies implemented to mitigate the impact of alterations to randomization proportions:
 - Caps on randomization proportions, limiting extreme deviation from balanced randomization, implemented in 2023.
 - Significant delays between conducting interim analyses will result in a reversion to balanced randomization ratios to avoid prolonged periods where disproportionate randomization allocation may occur, implemented in 2024.

Supplemental results

Platform Exclusions (see Figure 1)

Patients excluded from the REMAP-CAP platform	7,257
Randomized to the Platform within the last 90 days	30
No signs and symptoms of a lower respiratory tract infection	266
No radiological evidence of new onset infiltrates of infective origin	466
In-patient within the previous 30 days	765
Resident of a nursing home or long-term care facility	234
Community-acquired pneumonia not the primary reason for admission	1066
Exceeded platform eligibility time windows	2613
No qualifying organ support in ICU	1429
Death deemed to be imminent and inevitable	388
Other	0

STable 1. Analyses in the subset of patients randomized at sites offering both hydrocortisone and control

90-day mortality	Hydrocortisone (n=339)				Control (n=116)			
Sensitivity analysis restricting primary model to this subset								
Vasopressor-dependent shock	Yes	Yes	No	No	Yes	Yes	No	No
Influenza	Yes	No	Yes	No	Yes	No	Yes	No
# patients evaluated/ Total #	19/19	143/145	9/11	160/164	3/3	54/54	5/5	54/54
Deaths n (%)	4 (21.1)	27 (18.9)	1 (11.1)	29 (18.1)	0 (0)	7 (13)	1 (20)	4 (7.4)
Analysis with borrowing								
Median adjusted OR (95% CrI)	1.60 (0.68-3.88)	1.61 (0.72-3.69)	1.60 (0.67-3.88)	1.60 (0.72-3.74)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Mean adjusted OR (SD)	1.76 (0.82)	1.76 (0.77)	1.76 (0.84)	1.76 (0.79)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Probability of superiority, %	11.9	14	15	13.1	-	-	-	-
Probability of harm, %	85	86.9	86	88.1	-	-	-	-
Probability of >20% reduction in odds of death, %	6.5	5.2	6	7.2	-	-	-	-
Sensitivity analysis without borrowing to generate Independent treatment effects for each stratum								
Median adjusted OR (95% CrI)	1.25 (0.18-8.25)	1.72 (0.67-4.70)	1.11 (0.15-7.81)	1.51 (0.57-4.45)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Mean adjusted OR (SD)	2.03 (2.55)	1.98 (1.08)	1.87 (2.53)	1.81 (1.10)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Probability of superiority, %	41.9	12.5	45.8	20	-	-	-	-
Probability of harm, %	58.1	87.5	54.2	80	-	-	-	-
Probability of >20% reduction in odds of death, %	35	6.5	39.2	11.4	-	-	-	-
Sensitivity analysis generating a pooled treatment effect across strata								
Median adjusted OR (95% CrI)	1.55 (0.75-3.63)				1 (Reference)			
Mean adjusted OR (SD)	1.71 (0.76)				1 (Reference)			
Probability of superiority, %	14.4				-			
Probability of harm, %	85.6				-			
Probability of >20% reduction in odds of death, %	4.4				-			

Model restricted to patients randomized to receive either fixed duration hydrocortisone or hydrocortisone control. The model adjusts for age, sex, site (nested within country), domain ineligibility, randomization within each domain, strata (vasopressor dependent shock versus no vasopressor dependent shock and influenza versus no influenza), disease state (not on invasive mechanical ventilation, ventilated but not severely hypoxic, or ventilated and severely hypoxic) and time epochs. Odds ratios (OR) < 1 indicate improved outcomes. SD denotes standard deviation. CrI denotes Credible Interval.

STable 2. Pathogens causing community acquired pneumonia

	All patients randomized to hydrocortisone or control		Subset randomized at sites offering hydrocortisone and control	
	Hydrocortisone (n=536)	Control (n=122)	Hydrocortisone (n=339)	Control (n=116)
No pathogen isolated, n/total(%)	278/532 (52.2)	71/119 (59.7)	166/336 (49.4)	65/113 (57.5)
Bacterial pathogen isolated, n/total(%) ¹	221/532 (41.5)	44/119 (37)	145/336 (43.2)	44/113 (38.9)
Streptococcus pneumoniae	110/532 (20.7)	24/119 (20.2)	66/336 (19.6)	23/113 (20.4)
Staphylococcus aureus	25/532 (4.7)	4/119 (3.4)	14/336 (4.2)	3/113 (2.7)
Streptococcus agalactiae	1/532 (0.2)	0/119 (0)	1/336 (0.3)	0/113 (0)
Streptococcus pyogenes	10/532 (1.9)	2/119 (1.7)	6/336 (1.8)	2/113 (1.8)
Escherichia coli	7/532 (1.3)	3/119 (2.5)	5/336 (1.5)	3/113 (2.7)
Klebsiella spp	7/532 (1.3)	2/119 (1.7)	7/336 (2.1)	2/113 (1.8)
Pseudomonas aeruginosa	5/532 (0.9)	0/119 (0)	3/336 (0.9)	0/113 (0)
Acinetobacter spp	4/532 (0.8)	2/119 (1.7)	4/336 (1.2)	2/113 (1.8)
Burkholderia pseudomallei	4/532 (0.8)	0/119 (0)	4/336 (1.2)	0/113 (0)
Haemophilus influenzae	11/532 (2.1)	4/119 (3.4)	6/336 (1.8)	4/113 (3.5)
Moraxella catarrhalis	2/532 (0.4)	0/119 (0)	1/336 (0.3)	0/113 (0)
Legionella spp	38/528 (7.2)	6/119 (5)	31/335 (9.3)	6/113 (5.3)
Mycoplasma spp	13/520 (2.5)	2/116 (1.7)	7/328 (2.1)	2/110 (1.8)
Chlamydophila spp	3/510 (0.6)	0/114 (0)	0/321 (0)	0/108 (0)
Viral pathogen isolated, n/total (%) ²	57/531 (10.7)	12/119 (10.1)	38/335 (11.3)	11/113 (9.7)
Influenza A	33/531 (6.2)	7/119 (5.9)	22/335 (6.6)	6/113 (5.3)
Influenza B	6/531 (1.1)	1/119 (0.8)	5/335 (1.5)	1/113 (0.9)
SARS-CoV-2	8/520 (1.5)	2/107 (1.9)	5/324 (1.5)	2/101 (2)
Respiratory Syncytial Virus (RSV)	9/516 (1.7)	1/115 (0.9)	7/328 (2.1)	1/109 (0.9)
Other coronavirus	6/513 (1.2)	2/116 (1.7)	1/322 (0.3)	2/110 (1.8)
Both viral and bacterial pathogens isolated, n/total(%)	25/531 (4.7)	8/119 (6.7)	13/335 (3.9)	7/113 (6.2)
Influenza / Streptococcus pneumoniae	5/531 (0.9)	2/119 (1.7)	3/335 (0.9)	1/113 (0.9)
Influenza / Staphylococcus aureus	5/531 (0.9)	2/119 (1.7) ⁴	3/335 (0.9)	2/113 (1.8) ⁴
Influenza / Streptococcus pyogenes	3/531 (0.6)	2/119 (1.7)	2/335 (0.6)	2/113 (1.8)
Influenza / other bacterial pathogen	3/531 (0.6)	0/111 (0)	1/335 (0.3)	0/105 (0)
SARS-CoV-2 / Streptococcus pneumoniae	5/531 (0.9)	0/111 (0)	2/335 (0.6)	0/105 (0)
RSV / bacterial pathogen	4/531 (0.8) ⁵	1/119 (0.8)	2/335 (0.6)	1/113 (0.9)
Other	0/531 (0)	1/119 (0.8)	0/335 (0)	1/113 (0.9)
Other pathogen isolated, n/total(%) ³	2/532 (0.4)	1/118 (0.8)	0/336 (0)	1/112 (0.9)
Tuberculosis	2/532 (0.4)	1/118 (0.8)	0/336 (0)	1/112 (0.9)

¹ 24 patients (n=19, Hydrocortisone; n=5, Control) had co-isolation of bacterial pathogens (n=11, Hydrocortisone; n=5, Control) when restricted to sites offering hydrocortisone and control)

² 6 patients (n=5, Hydrocortisone; n=1, Control) had co-isolation of viral pathogens (n=3, Hydrocortisone; n=1, Control) when restricted to sites offering hydrocortisone and control)

³ including cryptococcus, pneumocystis, non-tuberculous mycobacteria, nocardia, mucorales

⁴ 2 patients with multiple bacterial pathogens isolated (Haemophilus influenzae / Mycoplasma spp)

⁵ 2 patients with multiple viral pathogens isolated (both other coronavirus)

Data Sharing Statement

Question	Authors' Response
Will the data collected for your study be made available to others?	Yes
Would you like to offer context for your decision?	—
Which data?	De-identified patient data set
Additional information about data	—
How or where can the data be obtained?	info@remapcap.org
When will data availability begin?	April 1st 2025
When will data availability end?	January 31 2029
Will any supporting documents be available?	—
Which supporting documents?	—
Additional information about supporting documents	—
How or where can supporting documents be obtained?	—
When will supporting documents availability begin?	—
When will supporting documents availability end?	—
To whom will data be available?	Data will be available to researchers on request subject to sponsor restrictions
For what type of analysis or purpose?	Research
By what mechanism?	After approval of a proposal, with investigator support
Any other restrictions?	—
Additional information	—