

# 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 1 dated 7 November 2016

## TABLE OF CONTENTS

<b>1.</b>	<b>ABBREVIATIONS AND GLOSSARY .....</b>	<b>7</b>
<b>1.1.</b>	<b>Abbreviations .....</b>	<b>7</b>
<b>1.2.</b>	<b>Glossary .....</b>	<b>9</b>
<b>2.</b>	<b>INTRODUCTION.....</b>	<b>13</b>
<b>2.1.</b>	<b>Synopsis .....</b>	<b>13</b>
<b>2.2.</b>	<b>Protocol Structure .....</b>	<b>14</b>
2.2.1.	Core Protocol.....	15
2.2.2.	Domain-Specific Appendices.....	16
2.2.3.	Region-Specific Appendices .....	16
2.2.4.	Statistical Analysis Appendix and Simulations Appendix .....	17
2.2.5.	Current versions of Protocol Documents.....	17
2.2.6.	Version History .....	18
<b>2.3.</b>	<b>Lay Description.....</b>	<b>18</b>
<b>2.4.</b>	<b>Trial registration.....</b>	<b>19</b>
<b>2.5.</b>	<b>Funding of the trial .....</b>	<b>19</b>
<b>3.</b>	<b>STUDY ADMINISTRATION STRUCTURE .....</b>	<b>19</b>
<b>3.1.</b>	<b>International Trial Steering Committee .....</b>	<b>20</b>
3.1.1.	Responsibilities.....	20
3.1.2.	Members .....	21
3.1.3.	Contact Details .....	22
<b>3.2.</b>	<b>Regional Management Committees .....</b>	<b>22</b>
3.2.1.	Responsibilities.....	22
<b>3.3.</b>	<b>Domain-Specific Working Groups.....</b>	<b>22</b>
3.3.1.	Responsibilities.....	22
3.3.2.	Members .....	23
<b>3.4.</b>	<b>International Interest Groups.....</b>	<b>23</b>
3.4.1.	Role.....	23
<b>3.5.</b>	<b>Sponsors .....</b>	<b>23</b>
3.5.1.	Role of sponsor.....	23
3.5.2.	Insurance.....	23
<b>4.</b>	<b>INTERNATIONAL TRIAL STEERING COMMITTEE AUTHORIZATION .....</b>	<b>24</b>
<b>5.</b>	<b>BACKGROUND &amp; RATIONALE.....</b>	<b>25</b>

<b>5.1. Severe Community-Acquired Pneumonia .....</b>	<b>25</b>
5.1.1. Introduction .....	25
5.1.2. Epidemiology.....	25
5.1.3. Standard care for patients with severe CAP .....	26
5.1.4. Treatment guidelines .....	27
5.1.5. Variation in care and compliance with guidelines .....	28
5.1.6. An unmet need for better evidence.....	28
<b>5.2. Influenza pandemics and emerging pathogens .....</b>	<b>29</b>
<b>5.3. Randomized Embedded Multifactorial Adaptive Platform Trials.....</b>	<b>29</b>
5.3.1. Generating clinical evidence .....	29
5.3.2. Underlying Principles of the Study Design .....	30
5.3.3. Nomenclature .....	31
5.3.4. Randomization and Response Adaptive Randomization .....	31
5.3.5. Embedding .....	33
5.3.6. Multifactorial.....	33
5.3.7. Adaptive .....	34
5.3.8. Nesting of the REMAP within a Registry .....	39
5.3.9. Platform.....	40
<b>6. OBJECTIVES.....</b>	<b>40</b>
<b>6.1. Primary objective .....</b>	<b>40</b>
<b>6.2. Secondary objectives .....</b>	<b>41</b>
<b>7. SUMMARY OF TRIAL DESIGN .....</b>	<b>41</b>
<b>7.1. Introduction .....</b>	<b>41</b>
<b>7.2. Nomenclature .....</b>	<b>42</b>
<b>7.3. Study setting and participating regions .....</b>	<b>42</b>
<b>7.4. Eligibility criteria.....</b>	<b>43</b>
7.4.1. REMAP Inclusion Criteria.....	44
7.4.2. REMAP Exclusion Criteria .....	44
7.4.3. Domain-Specific Exclusion criteria .....	45
<b>7.5. Interventions.....</b>	<b>45</b>
7.5.1. Domain-Specific Information .....	45
7.5.2. Treatment allocation and Response Adaptive Randomization.....	45
7.5.3. Adaptation of Domains and Interventions.....	47

<b>7.6. Endpoints</b>	<b>47</b>
7.6.1. Primary Endpoint	48
7.6.2. Secondary Endpoints	48
<b>7.7. Bias Control</b>	<b>49</b>
7.7.1. Randomization	49
7.7.2. Allocation concealment	49
7.7.3. Blinding of treatment allocation	49
7.7.4. Blinding of outcome adjudication	50
7.7.5. Follow up and missing data	50
<b>7.8. Principles of Statistical Analysis</b>	<b>50</b>
7.8.1. Preface	50
7.8.2. Introduction	50
7.8.3. Target populations (strata and states) and implications for evaluation of treatment-treatment interactions	51
7.8.4. Bayesian Statistical modeling	55
7.8.5. Statistical Handling of Ineligible Participants	57
7.8.6. Intervention Superiority Statistical Trigger	58
7.8.7. Intervention Inferiority Statistical Trigger	59
7.8.8. Intervention Equivalence Statistical Trigger	59
7.8.9. Action when a Statistical Trigger is achieved	59
7.8.10. Analysis set for reporting	60
7.8.11. Simulations and statistical power	61
<b>7.9. Co-enrolment with other trials</b>	<b>61</b>
<b>7.10. Cooperation between the REMAP and other trials with overlapping populations or interventions</b>	<b>62</b>
<b>7.11. Registry of non-randomized patients</b>	<b>62</b>
<b>7.12. Criteria for termination of the trial</b>	<b>62</b>
<b>8. TRIAL CONDUCT</b>	<b>63</b>
<b>8.1. Site time-lines</b>	<b>63</b>
8.1.1. Initiation of participation at a site	63
8.1.1. Vanguard sites	63
<b>8.2. Summary of time-lines for recruited participants</b>	<b>64</b>
<b>8.3. Recruitment of participants including embedding</b>	<b>64</b>
8.3.1. Embedding	64

8.3.2.	Participant recruitment procedures at participating units .....	65
<b>8.4.</b>	<b>Treatment allocation .....</b>	<b>65</b>
<b>8.5.</b>	<b>Delivery of interventions .....</b>	<b>66</b>
8.5.1.	Treatment allocation and protocol adherence at participating units.....	66
<b>8.6.</b>	<b>Unblinding of allocation status.....</b>	<b>66</b>
<b>8.7.</b>	<b>Criteria for discontinuation of a participant in the trial .....</b>	<b>66</b>
<b>8.8.</b>	<b>Concomitant care and co-interventions .....</b>	<b>67</b>
<b>8.9.</b>	<b>Data collection .....</b>	<b>67</b>
8.9.1.	Principles of data collection .....	67
8.9.2.	Variables to be collected .....	67
8.9.3.	Data required to inform Response Adaptive Randomization .....	69
8.9.4.	Blinding of outcome assessment .....	70
<b>8.10.</b>	<b>Data management .....</b>	<b>70</b>
8.10.1.	Source Data .....	70
8.10.2.	Confidentiality .....	70
<b>8.11.</b>	<b>Quality assurance and monitoring.....</b>	<b>70</b>
8.11.1.	Plans for improving protocol adherence and complete data .....	70
8.11.2.	Data Monitoring .....	71
<b>8.12.</b>	<b>Data safety and monitoring board.....</b>	<b>71</b>
<b>8.13.</b>	<b>Safety monitoring and reporting .....</b>	<b>72</b>
8.13.1.	Principles .....	72
8.13.2.	Definition.....	72
8.13.3.	Reporting Procedures for Serious Adverse Events .....	73
8.13.4.	Attribution of serious events to study interventions.....	73
8.13.5.	Attribution of a death to study interventions or study participation .....	74
<b>9.</b>	<b>GOVERNANCE AND ETHICAL CONSIDERATIONS .....</b>	<b>74</b>
<b>9.1.</b>	<b>Management of participating sites and trial coordination .....</b>	<b>74</b>
<b>9.2.</b>	<b>Ethics and regulatory issues .....</b>	<b>74</b>
9.2.1.	Guiding principles.....	74
9.2.2.	Ethical issues relevant to this study .....	74
9.2.3.	Approvals.....	76
<b>9.3.</b>	<b>Protocol modifications.....</b>	<b>76</b>
9.3.1.	Amendments.....	76

<b>9.4. Confidentiality</b> .....	<b>77</b>
<b>9.5. Declarations of interest</b> .....	<b>77</b>
<b>9.6. Post-trial care</b> .....	<b>77</b>
<b>9.7. Communication</b> .....	<b>78</b>
9.7.1. Reporting.....	78
9.7.2. Communication of trial results.....	78
<b>9.8. Publication policy</b> .....	<b>78</b>
<b>9.9. Data access and ownership</b> .....	<b>78</b>
9.9.1. Data ownership .....	78
9.9.2. Access to Data .....	78
<b>9.10. Consent form</b> .....	<b>79</b>
<b>10. REFERENCES</b> .....	<b>80</b>

## TABLE OF TABLES

Table 1: Potential targets of interventions to reduce mortality in patients with CAP .....	27
Table 2: Features of a REMAP that contribute to advantages of the design.....	40

## TABLE OF FIGURES

Figure 1: Protocol Structure.....	15
Figure 2: REMAP-CAP Organization Chart .....	20
Figure 3: Adaptive Analyses .....	35
Figure 4: REMAP Evolution Over Time.....	38
Figure 5: REMAP Structure.....	42
Figure 6: Study Procedures .....	64

## 1. ABBREVIATIONS AND GLOSSARY

### 1.1. *Abbreviations*

ANZ	Australia and New Zealand
APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	Acute Respiratory Distress Syndrome
CAP	Community-Acquired Pneumonia
CRF	Case Report Form
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
eCIS	Electronic Clinical Information System
eCRF	Electronic Case Report Form
EU	European
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
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
ITT	Intention-To-Treat
LOS	Length of Stay
MCMC	Markov Chain Monte Carlo
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
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
Severe CAP	Severe Community-Acquired Pneumonia
SOPs	Standard Operating Procedures
VFD	Ventilator Free Days
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 contains 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.

**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 being studied 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 contains all information about the trial specific to the conduct of the trial in that region. Each region will have its own regional-specific appendix. 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 Region-Specific Appendix (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 sub-group of patients within the REMAP that is used as a unit of analysis within a Bayesian statistical model for analysis of treatment effect and for RAR. A state is a set of mutually exclusive categories, defined by characteristics of a patient, that are dynamic in that they can change for a single patient, at different time-points, during the patient's participation in the REMAP.

**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 provides 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 strata but may be reached for, the same intervention, in more than one strata at the same adaptive analysis.

**Stratum** A stratum is a sub-group of patients within the REMAP that is used as a unit of analysis within a Bayesian statistical model for analysis of treatment effect and for RAR. The criteria that define a stratum must be present at or before the time of enrolment.

SUPERSEDED

## 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 community-acquired pneumonia (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 2 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 the occurrence of death during the index hospital admission censored 60-days from the date of enrolment.

**Methods:** The study will enrol 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 the occurrence of death during the index hospital admission censored 60-days from the date of enrolment. There will also be both general and domain-specific secondary outcome measures.

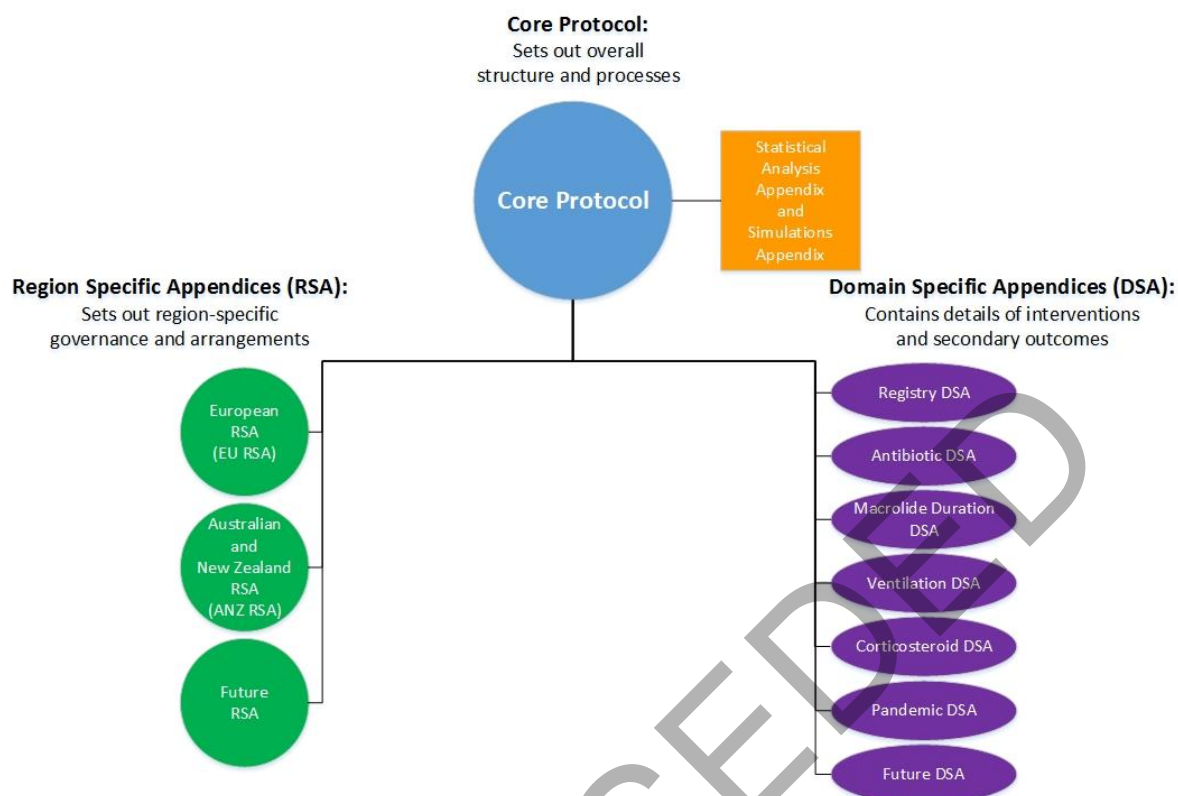
In a conventional trial, enrolment continues until a pre-specified sample size is obtained, at which time enrolment ceases, and the trial data are analyzed to obtain a result. The possible results are that a difference is detected or no that no difference is detected, but within the results defined as “no difference”, this result can be interpreted as being 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-specific 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 presently 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) 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, multiple DSAs, multiple RSAs, a Statistical Analysis Appendix and a Simulations Appendix.

### 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 modification to a DSA will be subject of a separate ethics application for approval. 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 publically accessible document on the study website.

#### 2.2.5. Current versions of Protocol Documents

At any one time there will be the same current version of the Core Protocol, in all regions, with accompanying RSAs and DSAs that change over time.

The current versions of all documents that comprise this protocol are:

- REMAP-CAP Core Protocol Version 1, dated 7 November 2016 (this document)
- Region-Specific Appendices
  - European Region-Specific Appendix Version 1, dated 7 November 2016
  - Australia and New Zealand Region-Specific Appendix Version 1, dated 7 November 2016
- Domain-Specific Appendices
  - Antibiotic Domain-Specific Appendix Version 1, dated 7 November 2016
  - Corticosteroid Domain-Specific Appendix Version 1, dated 7 November 2016
  - Macrolide Duration Domain-Specific Appendix Version 1, dated 7 November 2016

- Ventilation Domain-Specific Appendix, to be finalized
- Registry Domain-Specific Appendix, to be finalized
- Statistical Analysis Appendix Version 1, dated 7 November 2016

#### 2.2.6. Version History

Version 1: Approved by the ITSC on 7 November 2016

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

## **2.4. Trial registration**

This is a single trial, conducted in multiple regions, but will, as a minimum, be registered in 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.

Funding is being sought for other regions and countries.

## **3. STUDY ADMINISTRATION STRUCTURE**

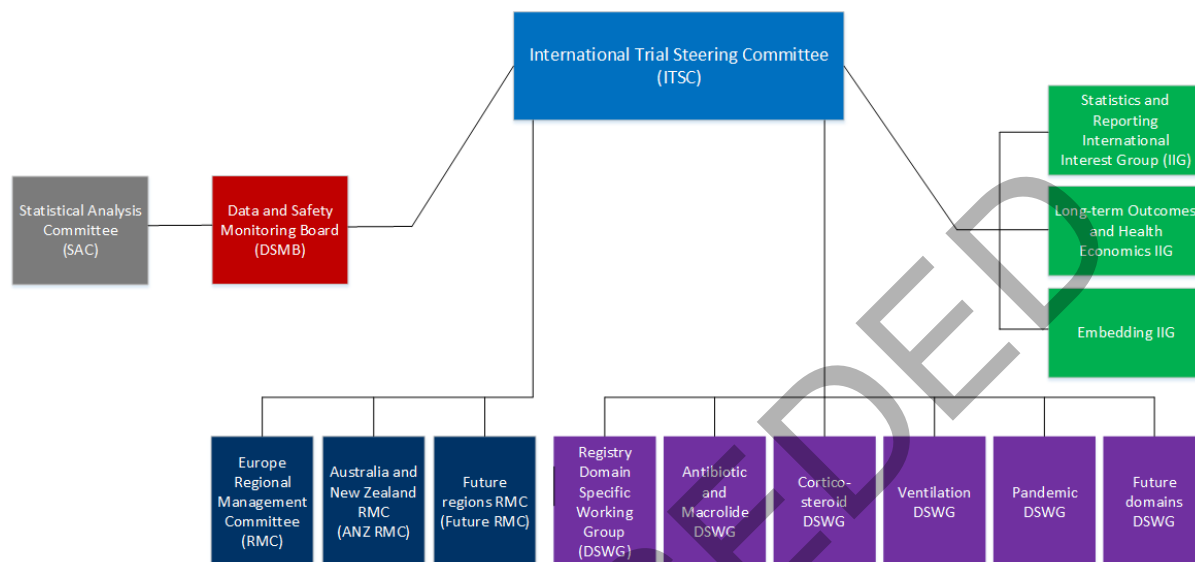
The study administration structure is designed to provide appropriate management of all aspects of the study, taking into account multiple factors including representation from regions that are participating in the trial, availability of skills and expertise related to trial conduct and statistical analysis,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

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

Dr. Scott Berry, President and Senior Statistical Scientist of Berry Consultants, member ITSC and Executive Director of International Statistics Interest Group (ISIG)

Professor Marc Bonten, European Executive Director and Chair European RMC

Professor Allen Cheng, Chair Antibiotic Domain and Macrolide Duration DSWG

Dr. Lennie Derde, European trial physician

Professor Herman Goossens, PI for PREPARE

Dr. Ed Litton, member ITSC

Dr. Colin McArthur, Australian and New Zealand (ANZ) Deputy Executive Director and Chair Registry DSWG

Dr. Shay McGuinness, Chair Australian and New Zealand RMC

Professor Alistair Nichol, member ITSC and Chair Ventilation DSWG

Ms. Genevieve O'Neill, Australian Project Manager

Dr. Rachael Parke, member ITSC

Professor Steve Webb, Australian and New Zealand Executive Director

### 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)

### 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.

In relation to recruitment that occurs in Australia the sponsor is Monash University.

In relation to recruitment that occurs in New Zealand the sponsor is the Medical Research Institute of New Zealand.

### 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,

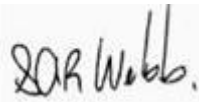
**EU Executive Director**

Marc Bonten



**ANZ Executive Director**

Steve Webb



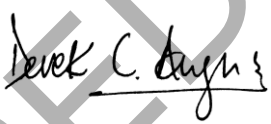
**ANZ Deputy Director**

Colin McArthur



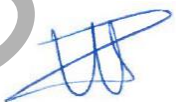
**ITSC Member**

Derek Angus



**ITSC Member**

Wilma van Bentum-Puijk



**ITSC Member**

Scott Berry



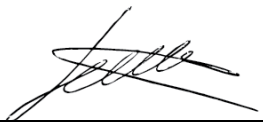
**ITSC Member**

Allen Cheng




**ITSC Member**

Lennie Derde



**ITSC Member**

Herman Goossens



**ITSC Member**

Ed Litton

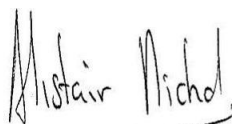




**ITSC Member**  
Shay McGuinness



**ITSC Member**  
Alistair Nichol



**ITSC Member**  
Genevieve O'Neill



**ITSC Member**  
Rachael Parke



## 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 specialised 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 4<sup>th</sup> 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 in low and middle income countries CAP. (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 aetiology 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 mobilisation, 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 13 of 113 in the Surviving Sepsis Campaign Guidelines. (Dellinger et al., 2013) 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 anaemia. (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 aetiological 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.

## **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 generalisability 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 enrolment 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, maximises 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 maximises 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 analysed. (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 minimise the impact of assumptions on trial efficiency and also maximises 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 optimised 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 enrol 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 enrol 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 enrolment 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 sites 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 randomized 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.

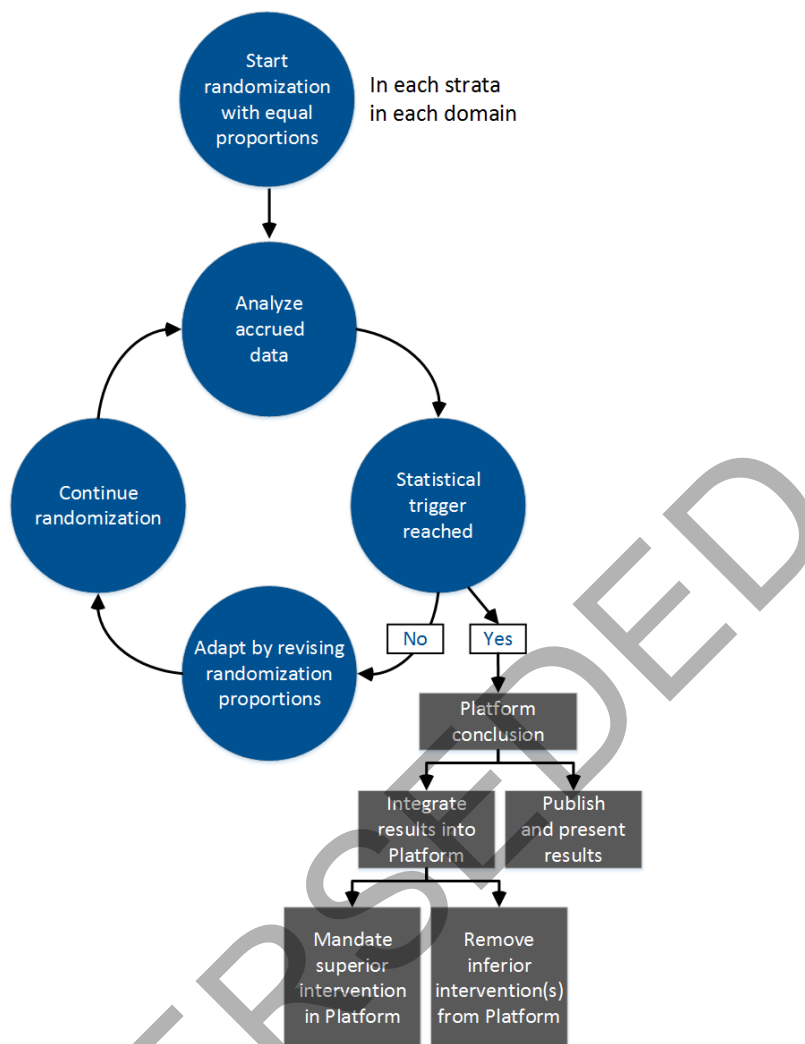
The occurrence of a Statistical Trigger is communicated immediately to the trial DSMB by the SAC. The DSMB has primary responsibility for determining if a Statistical Trigger should lead to a Platform Conclusion. The declaration of a Platform Conclusion results in the removal of inferior intervention from randomisation 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 randomisation 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 or to allow additional accrual to narrow the margin of equivalence (for example where health economic issues are relevant).

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 each stratum*. 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 of 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 enrolment 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

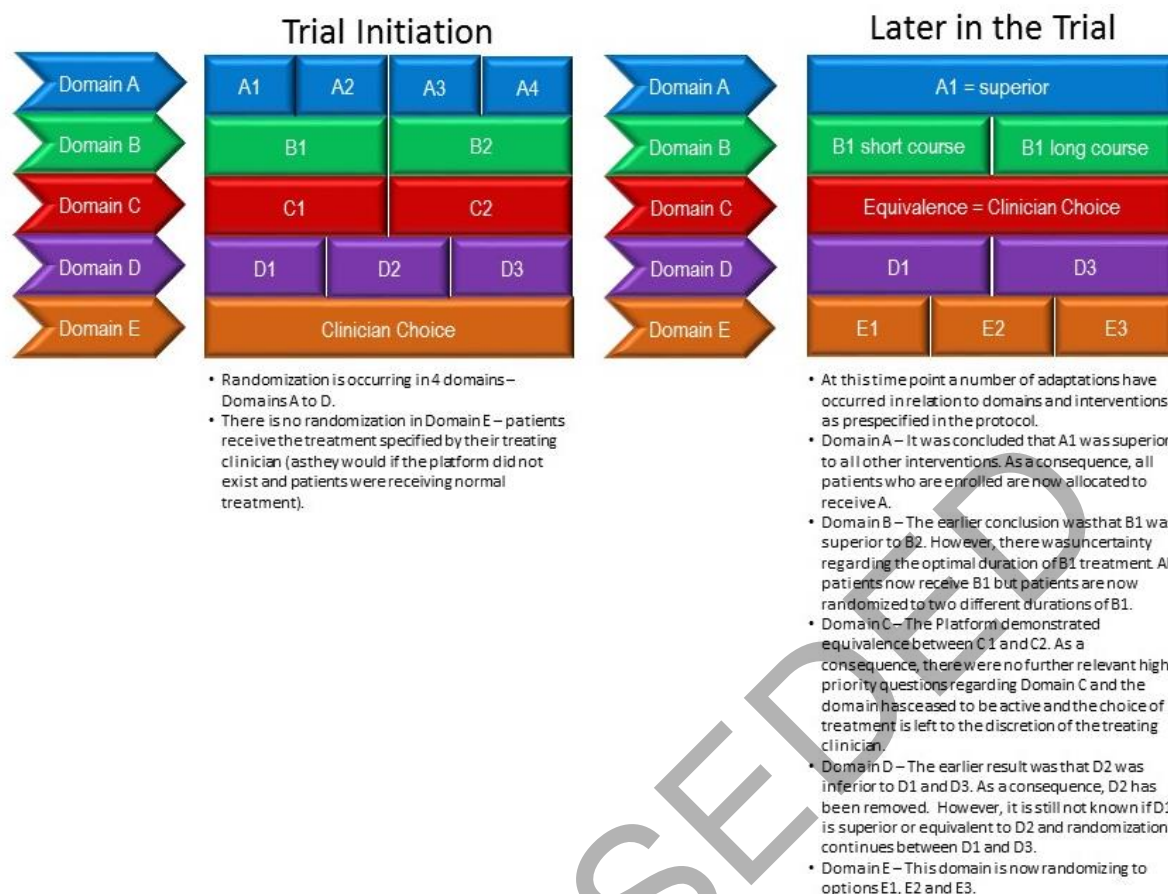
al., 2016, Rugo et al., 2016) An additional advantage is that dissemination of such results does not interrupt the conduct of the platform. In a single REMAP, there is no need for the “start-and-stop” periods that would typically occur under the alternative approach of multiple separate trials. These “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 available sample	Safety of trial participants	Avoidance of trial down-time	Fusion of clinical research with clinical care	Determination of optimal treatment for the disease	Self-learning healthcare system
Multifactorial	X		X	X	X	
Response Adaptive Randomization		X		X		X
Embedding				X		X
Frequent adaptive analyses	X	X			X	
Sub-group analysis	X	X			X	
Evaluation of interaction		X			X	
Substitution of new interventions	X		X		X	

## 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 the occurrence of death during the index hospital admission censored 60-days from the date of enrolment.



## **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 60-days, organ failure free days (OFFDs) censored at 60-days, other endpoints as indicated for specific domains, and, where feasible or specified in a DSA, survival at 1 year, health related quality of life (HRQoL) assessed after 1 year using the EQ5D and disability assessed after 1 year using the World Health Organization Disability Assessment Schedule (WHODAS).

## **7. SUMMARY OF TRIAL DESIGN**

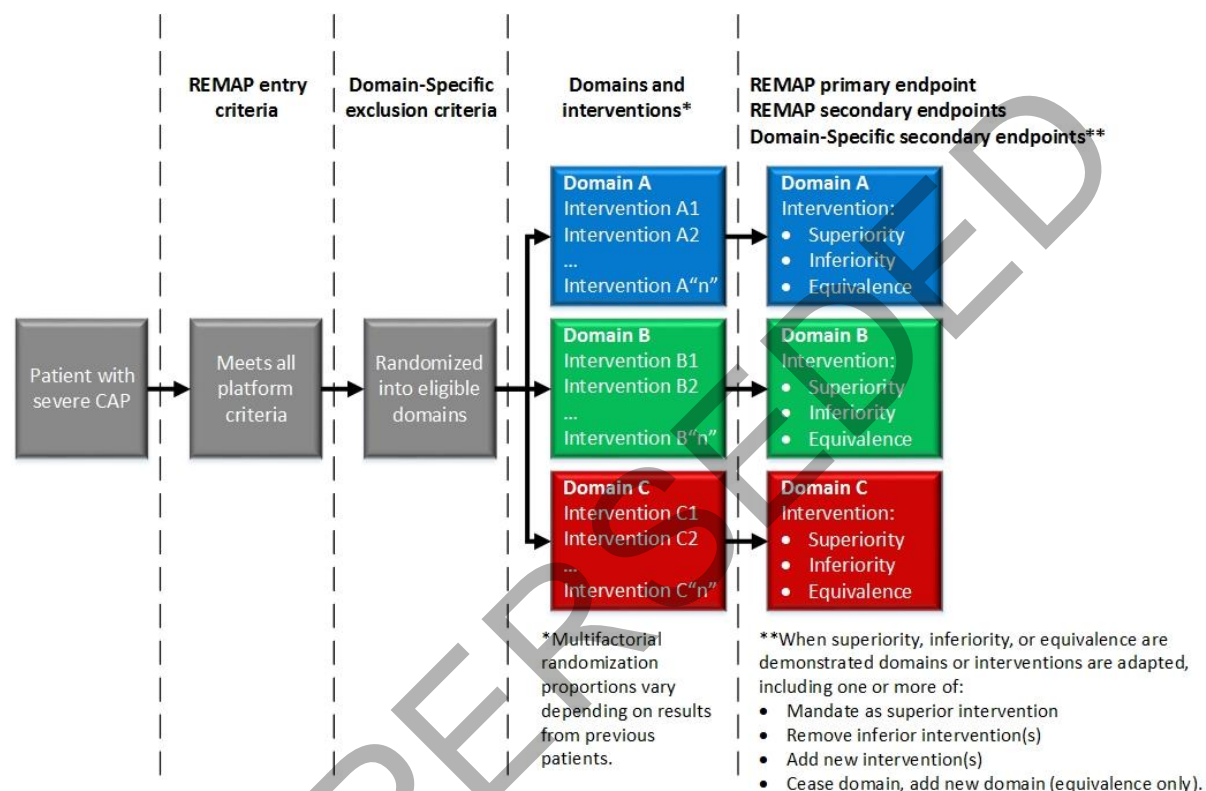
### **7.1. Introduction**

This is a REMAP that aims to test many interventions in a number of domains with the primary outcome being the occurrence of death during the index hospital admission censored 60-days from the date of enrolment. 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 will 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 higher dependency unit and is able to provide non-invasive

ventilation and continuous administration of vasoactive medications. 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 trial will be launched in the following regions:

- Europe, with funding from a European Union FP7 grant FP7-HEALTH-2013-INNOVATION-1, grant number 602525, to support the enrolment of 4000 participants. This funding terminates in 2019.
- Australia and New Zealand. In Australia the project has received funding from a NHMRC Project Grant (APP1101719), to support the enrolment of 2000 participants. This funding terminates in December 2020, although some extension may be feasible. In New Zealand the project has received funding from a HRC Programme Grant (16/631), to support the enrolment of 800 participants. This funding terminates in November 2021.

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. The current regions are:

- Europe
- Australia and New Zealand

#### **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 randomisation within the REMAP. The other level is that, once eligible for inclusion within the REMAP, additional 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
- none of the Domain-Specific exclusion criteria present

As such, the “inclusion criteria” for being eligible for a domain are that the patient is eligible for the REMAP. The only exception to this is that for inclusion with the Registry Domain, in which patients do not necessarily receive any randomised intervention within the REMAP, that the inclusion criteria for the registry 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 randomisation 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 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 consolidation (in patients with pre-existing radiological changes, evidence of new infiltrate)
2. Requiring 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, has 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 or inevitable during this hospital admission 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 60-days

### 7.4.3. Domain-Specific Exclusion criteria

Each domain may have additional, domain-specific exclusion criteria. Patients who fulfill the Overall REMAP Eligibility Criteria will be assessed for enrolment 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 the 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 60 days of follow-up from the time of enrolment. Although outcome may be known before 60 days (death in hospital or discharge alive from 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 60 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. Randomisation to remaining interventions would likely continue at those sites until the superior intervention is available at those sites.

## **7.6. Endpoints**

The primary outcome for this REMAP will apply to all domains. Secondary outcomes generic to all Domains are provided in this Core Protocol below. Secondary outcomes specific to individual domains are provided in the relevant DSAs.

### 7.6.1. Primary Endpoint

The primary endpoint for all domains will be the occurrence of death during the index hospital admission censored 60-days from the date of enrolment.

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 60 days after enrolment are coded as being alive.

### 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 60-days;
- ICU LOS;
- VFDs censored at 60-days;
- OFFDs censored at 60-days;
- Proportion of intubated participants who receive a tracheostomy censored at 60-days;
- Proportion of intubated participants who require re-intubation censored at 60-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 enrolment 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 60-days are counted as ventilator- or organ failure-free days.

Hospital outcomes:

- Hospital LOS censored 60-days after enrolment;
- Destination at time of hospital discharge;



- Readmission to the index ICU during the index hospitalization in the 60-days following enrolment;

Post-hospital 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 1 year after enrolment
- HRQoL at 1 year after enrolment using the EQ5D
- Disability status measured at 1 year after enrolment using the WHODAS

## **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 randomisation 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 in-hospital mortality censored at 60-days is not subject to ascertainment bias. Wherever possible, central 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. No imputation will be made for missing data in the statistical analysis with regard to the determination of RAR, Statistical Triggers and Platform Conclusions.

### **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 analyse 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, or if two or more

interventions are equivalent, in comparison to all other interventions within the domain 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 strata and the eligibility criteria 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 is modeled as possibly varying in the different stratum in the REMAP.

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 strata 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, 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-treatment 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 enrolment and at other times after enrolment 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 enrolment 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 a recognized element in Platform Trials.

Second, within this REMAP, there is interest in studying different domains that are relevant for a target population or defined disease state that, while it may be present at the time of enrolment for some participants, may only occur after enrolment 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 defines 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 enrolment or may develop after the time of enrolment.

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 enrolment, requires the use of models that take into account that the likelihood of entering the state after enrolment 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 is 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 are referred to as strata. The covariate is classified in to mutually exclusive and exhaustive sets for analysis of treatment effect, as well as for defining separate RAR. The criteria that define a stratum must be present at or before the time of enrolment.

The simplest structure for strata is a single dichotomous stratum variable, which divides participants in the REMAP into two strata. More complex arrangements are possible, such as a single stratum variable that is ordinal or two (or more) dichotomous stratum 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 stratum 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, essentially targeting certain

strata to specific domains. Each single stratum is the smallest unit for the RAR and is specified separately for each stratum. The *a priori* defined strata that are used for determination of results and for RAR may be changed during the life of the REMAP as knowledge is accumulated and, if this occurs, will result in amendment of one or both of the Core Protocol and DSAs.

#### 7.8.3.3. 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.

#### 7.8.3.4. 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 enrolment or later) at which administration of the allocated intervention is commenced.

At the time of enrolment, all participants, are randomized to one intervention in every domain for which the participant is eligible for at enrolment 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 enrolment).

For participants, who at the time of enrolment 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 not eligible at the time of enrolment but might become eligible for a domain, if their state changes, there are two options regarding the revealing of the

participants allocation status. One option is that the allocation status is revealed if and only if later eligibility occurs and is revealed at the time that eligibility occurs. This is referred to as Randomization with Delayed Reveal. The other option is, the randomization status is revealed at the time of enrolment but the intervention is only administered if and when eligibility occurs. This is referred to as Randomization with Immediate Reveal and Delayed Initiation.

Randomization with Immediate Reveal and immediate Initiation allows for the analysis to enact an intent-to-treat approach to the intervention assignment. When analysis is done in this way, it is possible to evaluate interactions between treatments in different domains that share that stratum.

Alternatively, 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 enrolment. 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 enrolment. Participants who are randomized within such a domain, at time of enrolment, 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 Immediate Reveal and Delayed Initiation within a stratum. For such participants, their allocation status is revealed at the time of enrolment but the intervention is only initiated after the time of enrolment if and when criteria that define domain eligibility are achieved. As such, this can be conceptualized as randomization to plan to commence an intervention later in the course of a participant's illness, if and when it is appropriate to do so. Participants in this category are analyzed within baseline stratum in an intent-to-treat 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.

#### 7.8.3.5. *Current strata and states*

At the launch of this REMAP, the default strata are defined, at the time of enrolment, by:

- Shock, defined in 2 categories, present or absent, with present defined as the patient is receiving continuous infusion of intravenous vasoactive medications at the time of enrolment for the treatment of hypotension, or suspected or proven shock, or both

At the launch of this REMAP, 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  $\geq 200$ , and participants who are receiving invasive mechanical ventilation and have a P:F ratio of  $<200$ .

The domains to which each strata or state applies together with the relationship between the timing of domain eligibility and the revealing of allocation status and what treatment-treatment interactions will be evaluated are specified in each DSA.

#### 7.8.3.6. *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 and are not used in determination of a Statistical Trigger or RAR. Such analysis will only be conducted following the determination of a Platform Conclusion.

#### 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 or equivalence of the interventions (known as a posterior probability distribution) within a 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. If this were to occur it would 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.

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 country in which a participant is treated, changes in outcome that occur over time (era), stratum and state at enrolment (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 or state (where eligibility is defined by a state) is analyzed separately but the model captures the commonalities across such sub-groups. Additionally, 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. The results of these analyses are used to achieve the primary objective of the trial which is to determine the effectiveness of interventions, 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 (intervention-intervention 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 enrol 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 specify that the only available intervention should be provided to the participant but this is so as to reinforce trial processes associated with successful embedding.

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 a stratum, then that intervention will be deemed as being superior to all other interventions in that domain in that stratum. 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 stratum, then that intervention will be deemed as being inferior for that stratum. If superiority and inferiority were to be discovered simultaneously (for example when there are 2 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 have at least a 0.90 probability of being within a pre-specified delta for the primary endpoint (by default a delta of 3% for mortality is utilized) for a stratum then these interventions will be deemed as being equivalent. The DSA may define different levels of delta. This Statistical Trigger 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

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.

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 remaining interventions in the domain in that stratum 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).

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 stratum. 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.

If two or more interventions are deemed as being equivalent, 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. A combination of the primary analysis and any secondary analyses will be used to determine if the interventions that are equivalent should continue to be randomized (for example if results for clinically relevant secondary endpoints are indeterminate or future interactions are of interest) or if randomization should cease (for example if results for clinically relevant secondary endpoints indicate superiority or if there are health economic implications from the deeming of two or more interventions as equivalent). If randomization is ceased, all participants will then be allocated to any remaining interventions in the domain (while still being randomized to interventions from other domains) until any new interventions are added to the domain. If randomization is ceased, 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 automatic adaptation when equivalence is deemed to have occurred.

#### 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 in conjunction with the adaptive analysis that 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 60 days of follow up or because data for a participant who has completed 60 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.

### **7.9. Co-enrolment with other trials**

Co-enrolment of participants in other research studies, including interventional trials, is strongly encouraged. The principle is that co-enrolment 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-enrolment 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-enrolment 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-enrolment will lie with the RMC. In all circumstances the ITSC and RMCs should liaise regarding decisions about co-enrolment. Decisions regarding co-enrolment 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 DSA.

### **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:

- Funding or other necessary support is no longer available
- 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

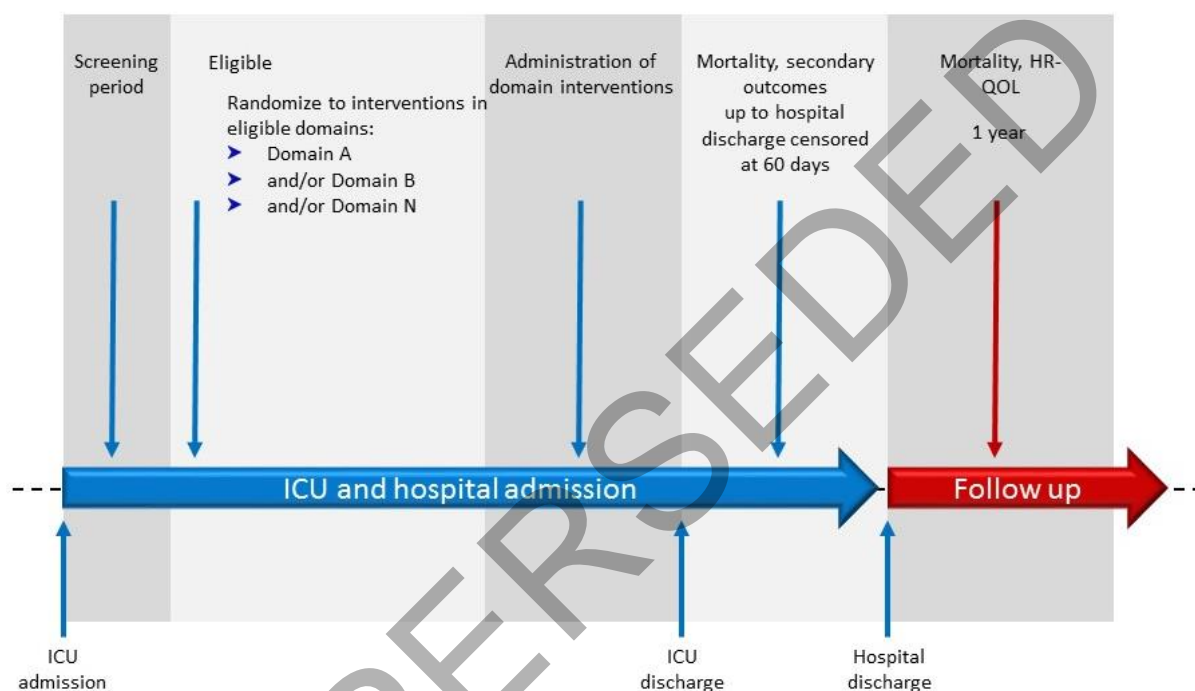
In each region or at the initiation of a new domain or both, the trial may consider commencing with only a small number of vanguard sites. The purpose of commencing the trial at vanguard sites is to

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 randomisation 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 enrolment, 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. 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.

*8.9.2.1. Baseline and required for randomization*

- Overall REMAP Inclusion / exclusion check list
- Domain-specific exclusion checklist
- Administration of intravenous vasoactive medications

*8.9.2.2. Baseline but not required for randomization*

- Demographic data (date of birth, age, sex, estimated body weight and height)
- Date and time of hospital admission
- Date and time of first ICU admission
- Source of ICU admission
- Components of Acute Physiology and Chronic Health Evaluation (APACHE) II score
- Intervention allocation status within domains and randomization number

*8.9.2.3. Daily from randomization until discharge from ICU or Day-60 whichever comes first*

- Occurrence of administration of vasopressors/inotropes
- Administration of dialysis
- Administration of invasive or non-invasive ventilation
- One or more episodes of extubation or de-cannulation
- Time of extubation or decannulation, if occurred on that day
- Reintubation or recannulation
- Mean arterial pressure
- 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

*8.9.2.6. Post-hospital outcome data*

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

- Survival status at 1 year
- HRQoL measured by EQ-5D
- Disability status measured by WHODAS at 1 year

*8.9.2.7. Process-related outcomes*

- Time from index hospital admission to ICU admission
- Time from ICU admission to randomization
- Co-interventions
- Compliance with allocated treatment

*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
  - a. Unique trial-specific number
  - b. Intervention for each revealed domain
  - c. Strata
    - i. Shock or no shock
2. Outcome
  - a. be the occurrence of death during the index hospital admission censored 60-days from the date of enrolment
  - b. For each enrolled domain, whether the participant received the intervention to which they were randomized

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 hospital discharge or death and within 67-days of enrolment into the REMAP if the participant is alive and in hospital on at 60-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 summarised 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 sites 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 enrolment 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.

### **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 enrolment but before 60-days but during admission to the ICU in the index hospital 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 evaluations 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. For all interventions, caution should be exercised in attributing a death to a trial intervention unless a clear causal link between a study intervention and death can be identified and described.

## 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 enrolment 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 will be informed of their enrolment as soon as practicable after regaining competency, provided with information regarding the trial, and provided with the opportunity for continued participation in the study. 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, informed consent form(s) and participant and/or authorised 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 randomisation 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 publically 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 authorised 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

- 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., TBOUL, 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.
- 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. & BEUCAIRE, 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.
- 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.
- 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.