



PROTOCOL SUMMARY

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

Protocol Summary Version 3 dated 11 September 2019

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1. ABBREVIATIONS

ANZ RMC	Australian and New Zealand Region Management Committee
ANZ RSA	Australian and New Zealand Regional-Specific Appendix
CAP	Community-Acquired pneumonia
CRE	Carbapenem Resistant Enterobacteriaceae
CRE	Case Report Form
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
eCRF	Electronic Case Report Form
ESBL	Extended Spectrum Beta-Lactamase
Eu RMC	Europe Regional Management Committee
Eu RSA	Europe Region-Specific Appendix
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HRC	Health Research Council
HRQoL	Health Related Quality of Life
ICU	Intensive Care Unit
IIG	Internationally Interest Group
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
IV	Intravenous
LOS	Length of Stay
MDR	Multi-Drug Resistant
mg	Milligrams
MRO	Multi-Resistant Organisms
MRSA	Methicillin-Resistant Staphylococcus Aureus
NHMRC	National Health and Medical Research Council
OFFDs	Organ Failure Free Days
PREPARE	Platform for European Preparedness Against (Re-)emerging Epidemics
RAR	Response-Adaptive Randomization

RCC	Regional Coordinating Center
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia
RMC	Regional Management Committee
RSA	Region-Specific Appendix
SAC	Statistical Analysis Committee
SAE	Serious Adverse Event
severe CAP	Severe Community-Acquired Pneumonia
SOPs	Standard Operating Procedures
VFDs	Ventilator Free Days
VRE	Vancomycin Resistant Enterococci
WHODAS	World Health Organization Disability Assessment Schedule

2. INTRODUCTION

The aim of this protocol summary is to provide an overview of the key novel aspects of the study including the modular components of the protocol and the rationale and benefits of the study design. In operational terms, this study is very similar to a conventional clinical trial, with the trial making attempts, wherever possible, to manage complexity with in-built centralized trial processes. The trial objectives, eligibility criteria, outcome measures, conduct, data management, governance and ethical considerations are also summarized below. This document will be updated periodically as the trial undergoes pre-specified adaptations.

3. PROTOCOL STRUCTURE

The structure of this protocol is modular because this trial is highly adaptive and is intended to allow the trial to evolve over time. The modules consist of the Core Protocol, Region-Specific Appendices (RSAs), Domain-Specific Appendices (DSAs), a Statistical Analysis Appendix and a Simulations Appendix ([see Figure 1](#)). This Simulations Appendix is an operational document and not part of the formal trial protocol. Refer to Core Protocol Section 2.

The Core Protocol contains all information that is generic to the trial, including the background and rationale for studying severe community-acquired pneumonia (severe CAP), the research approach, the trial design and conduct, the overall trial governance structures, and ethical considerations.

Region-Specific Appendix each region will have its own RSA containing all information about the trial specific to the conduct of the trial in that region. A region is defined as a country or collection of countries with study sites for which a Regional Management Committee (RMC) is responsible.

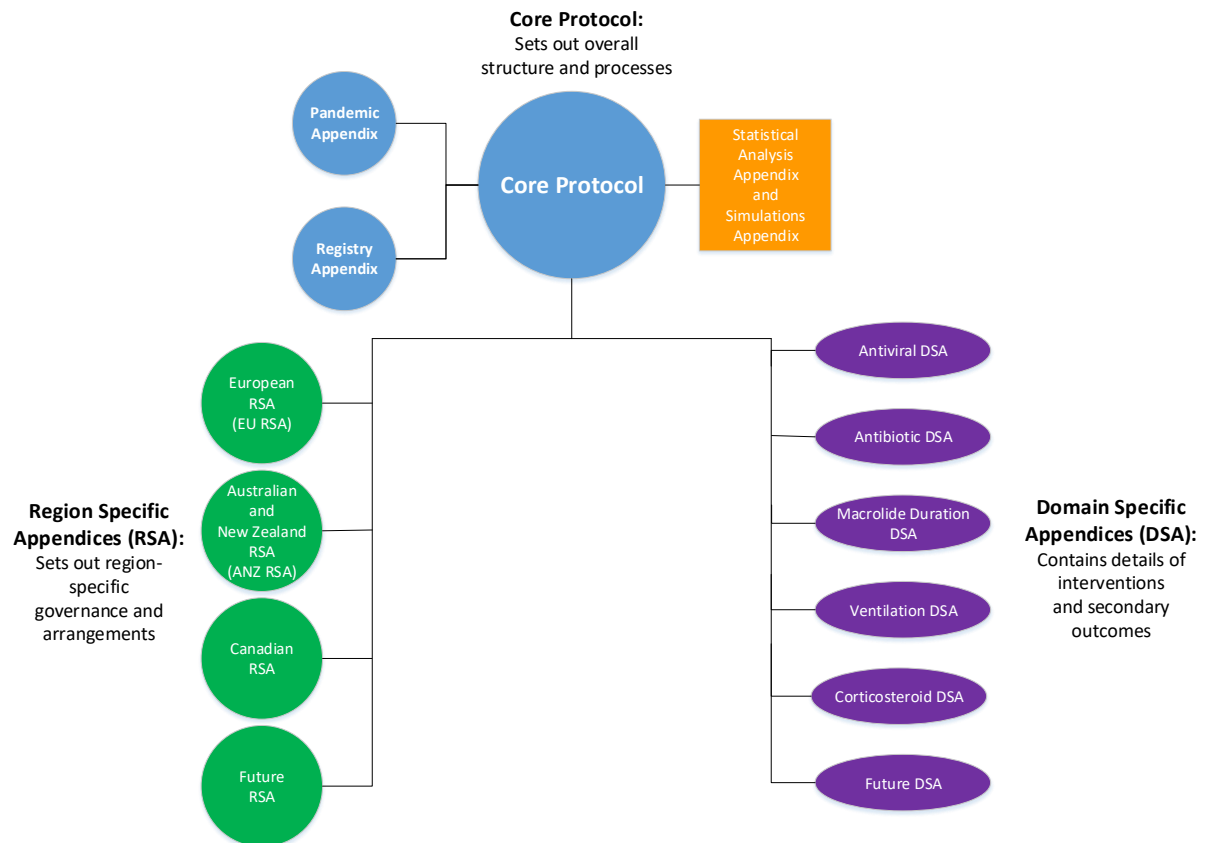
Domain-Specific Appendices contain the information about the interventions, which are nested within a domain (a specific set of competing alternative and mutually exclusive interventions within a common clinical mode). Each DSA includes domain-specific eligibility, features of the interventions and how they are delivered, and any additional endpoints and data collection that are not covered in the Core Protocol. At any one time, there are likely to be several domains to which a REMAP-CAP participant is assessed for eligibility (e.g. a Corticosteroid Domain in which randomization is to intravenous (IV) hydrocortisone or no IV hydrocortisone and an IV Antibiotic Domain in which randomization is to one of several possible IV antibiotic interventions).

The Statistical Analysis and Simulations Appendices contain the underlying assumptions for the statistical analyses and detailed descriptions of how they will be conducted. The Statistical Analysis and Simulation Appendices will change overtime, as trial adaptation occurs in accordance with the domain and intervention trial adaptations. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).

The Registry Appendix outlines a dataset collected for all adult patients admitted to participating ICUs for CAP, including patients who are randomized in REMAP-CAP. The registry utilizes retrospective collection of existing clinical data and routine healthcare and administrative data collected by linkage to existing healthcare-related registries and administrative sources. The registry appendix may not be operational in all countries and regions. The registry provides information on characteristics and outcome of patients who may have been eligible for randomization but were not randomized and provides a source of information on long-term outcome for all patients with CAP. There are no interventions specified in association with participation in the registry component.

Figure 1 displays the components of the protocol and their relationship.

Figure 1: Protocol Structure (Figure 1 in Core Protocol)



4. PROTOCOL SUMMARY VERSION

The version of the Protocol Summary is in this documents header and on the cover page.

4.1. Version History

Version 1: Approved by the ITSC on 21 November 2016

Version 1.1: Approved by the ITSC on 09 May 2017

Version 2: Approved by the ITSC on 15 January 2018

Version 3: Approved by the ITSC on 11 September 2019

5. PROTOCOL DOCUMENTS VERSIONS

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 3, dated 10 July 2019
- Region-Specific Appendices
 - European Region-Specific Appendix Version 3, dated 23 August 2019
 - Australia and New Zealand Region-Specific Appendix Version 3, dated 24 August 2019
 - Canadian Region-Specific Appendix Version 2, dated 5 July 2019
- Domain-Specific Appendices
 - Antibiotic Domain-Specific Appendix Version 3, dated 10 July 2019
 - Corticosteroid Domain-Specific Appendix Version 3, dated 12 July 2019
 - Macrolide Duration Domain-Specific Appendix Version 3, dated 10 July 2019
 - Antiviral Domain-Specific Appendix Version 1, dated 10 July 2019
 - Ventilation Domain-Specific Appendix, to be finalized
- Statistical Analysis Appendix Version 3, dated 24 August 2019
- Registry Appendix Version 1, dated 11 September 2019

6. ADMINISTRATION

6.1. Funding

The trial is currently funded in Europe (FP7 grant FP7-HEALTH-2013-INNOVATION-1, grant number 602525), within The Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE) consortium, sponsor is University Medical Centre Utrecht). In Australia the trial has been funded by the National Health and Medical Research Council (NHMRC) (grant number APP1101719), sponsor is Monash University, Melbourne. In New Zealand the trial has been funded by the Health Research Council (HRC) of New Zealand (grant number 16/631, Medical Research Institute of New Zealand, Wellington). In Canada, the trial has been funded by the Canadian Institute of Health Research, Strategy for Patient-Orientated Research (CIHR-SPOR) Innovative Clinical Trials Program Grant (No. 158584), the sponsor is Unity Health, Toronto.

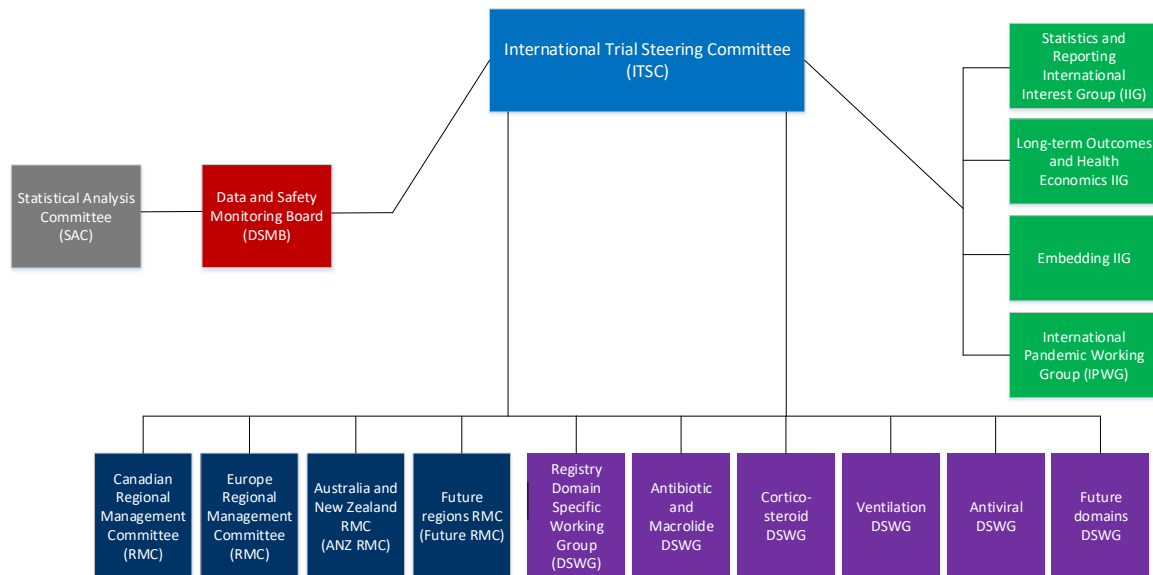
Funding is being sought for other regions and countries. Refer to Core Protocol Section 2.5.

6.2. Administrative Structure

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 (IIG) 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. Refer to Core Protocol Section 3.

Figure 2: REMAP-CAP Organization Chart (Figure 2 in Core Protocol)



6.3. 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.

Refer to Core Protocol Section 2.4.

7. BACKGROUND

7.1. Significance

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 CAP 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 CAP commonly but it is not known if one antibiotic strategy is best or whether all suitable antibiotic

strategies have similar levels of effectiveness. Using current conventional clinical trials methods to assess the efficacy of treatments for pneumonia, in a series of separate and sequential trials would take an inordinate length of time to study and it would not be possible to evaluate interactions between treatment options. Refer to Core Protocol Section 5.

7.2. *Design features of a REMAP:*

In comparison to a conventional trial, this trial combines a number of novel design features and has been termed a Randomized, Embedded, Multifactorial Adaptive Platform trial (REMAP). These features are designed to enhance the efficiency of trial conduct, generate new knowledge more quickly, and improve outcome for participants within the trial. The design features are explained fully in the Core Protocol Section 5.3, include:

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

The benefits of a REMAP, compared to a conventional trial, include:

- avoiding indeterminate results
- concluding an answer to a question when sufficient data have accrued (not when a pre-specific sample is reached)
- utilizing already accrued data to increase the likelihood that patients within the trial are randomized to treatments that are more likely to be beneficial
- evaluates multiple questions simultaneously
- evaluates heterogeneity of treatment effects in defined subgroups
- can evaluate the interaction between interventions in different domains.
- incorporates interventions found to be superior into standard care within the REMAP for future patients
- is intended to be perpetual (or at least open-ended), substituting new questions in series as initial questions are answered
- can be adapted in a timely fashion in the event of a future epidemic of a respiratory pathogen to evaluate the most relevant treatment options.

8. OBJECTIVES

The primary objective of this REMAP is, for adult patients with severe CAP who are admitted to an ICU, to identify the effect of a range of interventions to improve outcome as defined by all-cause mortality at 90 days. Refer to Core Protocol Section 6.1.

The secondary objectives (Core Protocol Section 6.2) are to determine the effect of interventions on:

- ICU mortality censored at 90 days
- ICU length of stay (LOS) censored at 90 days
- hospital LOS censored at 90 days
- ventilator free days (VFDs) censored at 28 days
- organ failure free days (OFFDs) censored at 28 days
- domain-specific endpoints
- survival at 6 months
- health related quality of life (HRQoL) using the EQ5D and disability assessed using the World Health Organization Disability Assessment Schedule (WHODAS) assessed after 6 months (at some, but not all, participating sites)

9. TRIAL DESIGN

The trial will recruit only participants who are admitted to an ICU. The eligibility criteria for the REMAP are applied at two levels. One level is that there are inclusion and exclusion criteria that determine eligibility for randomization within the REMAP. The other level is that, once eligible for inclusion within the REMAP, additional criteria are applied that are specific to each 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 and domain-specific criteria are met. Patients who are not eligible for one or more domains can still be enrolled in the other domains for which they are eligible. Refer to Core Protocol Section 7.4.

9.1. Sample size

The REMAP has funding currently to allow recruitment of up to 7,100 patients, comprising 4,000 patients in Europe, 2,000 patients in Australia, 800 patients in New Zealand, and 300 patients in

Canada. Additional funding locations are submitted or planned in other locations and further funding applications in the initial regions are intended.

9.2. REMAP Inclusion Criteria

To participate in this trial, a patient must meet both of the following criteria:

1. Adult patient admitted to an ICU for acute severe CAP within 48 hours of hospital admission with
 - a. symptoms or signs or both that are consistent with lower respiratory tract infection (for example, acute onset of dyspnea, cough, pleuritic chest pain) AND
 - b. Radiological evidence of new onset infiltrate of infective origin (in patients with pre-existing radiological changes, evidence of new infiltrate)
2. Up to 48 hours after ICU admission, receiving organ support with one or more of:
 - a. Non-invasive or invasive ventilatory support;
 - b. Receiving infusion of vasopressor or inotropes or both

Refer to Core Protocol Section 7.4.1.

9.3. REMAP Exclusion Criteria

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

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

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.

Refer to Core Protocol Section 7.4.2.

9.4. Domain specific entry criteria

The domain-specific entry criteria are summarized in the tables for each domain located later in this document ([Section 12](#)).

9.5. Primary Endpoint

The primary endpoint for all domains will be all-cause mortality at 90 days. Refer to Core Protocol Section 7.6.1.

9.6. Secondary Endpoints

Secondary endpoints will include ICU and in-hospital outcomes, and post-hospital outcomes including survival, HRQoL and Disability status at 6 months after enrollment and additional domain-specific endpoints. Refer to Core Protocol Section 7.6.2 and DSAs.

9.7. Criteria for termination of the trial

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

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

Refer to Core Protocol Section 7.12.

9.8. Bias control

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. Allocation concealment will be maintained by using centralized randomization that is remote from study sites. At this time, all interventions are provided on an open-label basis. However, the design does not preclude the blinding of treatment status. The primary outcome of all-cause mortality at 90 days is not subject to ascertainment bias. Wherever possible, trial management personnel, who are blinded to

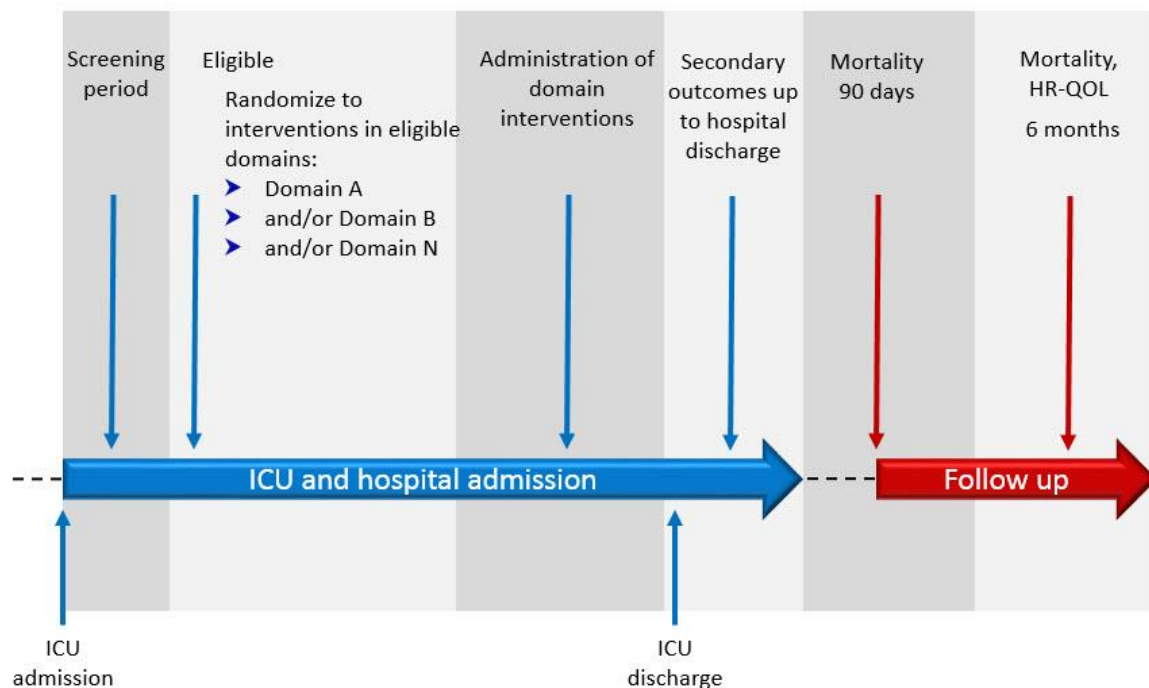
allocation status, will conduct any follow up after discharge. Strategies will be implemented to minimize missing data. Refer to Core Protocol Section 7.7.

10. TRIAL CONDUCT

At initiation, the REMAP will have three domains (Antibiotic Domain, Macrolide Duration Domain, and Corticosteroid Domain), refer to [Section 12](#) below for information on these domains. It is anticipated that the Ventilation Domain, an Antiviral Domain, and a Registry will commence in the near future.

The flow of a single patient through their enrollment and admission to ICU and hospital is displayed in Figure 3.

Figure 3: Study Procedures (Figure 6 in Core Protocol)



Refer to Core Protocol Section 8.

10.1. Criteria for discontinuation of a participant in the trial

Criteria for discontinuation from all REMAP interventions 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

Refer to Core Protocol Section 8.7.

11.DATA MANAGEMENT, QUALITY ASSURANCE AND MONITORING

The case report form (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. All data will be collected by trained staff who will have access to a comprehensive data dictionary. 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. The trial will be conducted in accordance with the current approved protocol, Good Clinical Practice (GCP), relevant regulations and standard operating procedures (SOPs). The study will be monitored by a representative of the Regional Coordinating Center (RCC). Routine monitoring visits will be conducted the frequency of which will be determined by each sites rate of recruitment. A single DSMB will take responsibility for the trial in all regions in which it is conducted.

12.GOVERNANCE AND ETHICAL CONSIDERATIONS

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. The principles of confidentiality that will apply to this trial, are that all trial staff will ensure that the confidentiality of all participant 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.

13.DOMAIN SUMMARIES

13.1. Antibiotic Domain Summary

REMAP-CAP: Antibiotic Domain Summary	
Interventions	• Ceftriaxone + Macrolide • Moxifloxacin or Levofloxacin • Piperacillin-tazobactam + Macrolide • Ceftaroline + Macrolide • Amoxicillin-clavulanate + Macrolide
Unit-of-Analysis and Strata	There is one unit-of-analysis in this domain. Analysis and Response Adaptive Randomization are applied to all randomized patients with no strata utilized.
Evaluable treatment-by-treatment Interactions	No interactions will be evaluated with any other domain.
Nesting	There is one nest, comprising Ceftriaxone + Macrolide, Piperacillin-tazobactam + Macrolide, Ceftaroline + Macrolide, and Amoxicillin-clavunate + Macrolide
Timing of Reveal	Randomization with Immediate Reveal and Initiation
Inclusions	Inclusion criteria are the same as the REMAP see Core Protocol Section 7.4.1
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • Received more than 48 hours of intravenous antibiotic treatment for this index illness • More than 24 hours has elapsed since ICU admission • Known hypersensitivity to all of the study drugs in the site randomization schedule • A specific antibiotic choice is indicated, for example: ○ Suspected or proven concomitant infection such as meningitis ○ Suspected or proven infection with resistant bacteria where agents being trialed would not be expected to be active. This includes cystic fibrosis, bronchiectasis or other chronic suppurative lung disease where infection with <i>Pseudomonas</i> may be suspected but does not include patients with suspected methicillin-resistant staphylococcus aureus (MRSA) infection (see MRSA below). ○ Febrile neutropenia or significant immunosuppression (including organ or bone marrow transplantation, human immunodeficiency virus (HIV) Infection with CD4 cell count <200 cells/μL, systemic immunosuppressive, systemic corticosteroids comprising prednisolone, or equivalent, ≥20mg/day for > 4 preceding weeks). ○ Suspected melioidosis (tropical sites during melioidosis season – see melioidosis below) ○ There is specific microbiological information to guide specific antibacterial therapy • The treating clinician believes that participation in the domain would not be in the best interests of the patient

Intervention-Specific Exclusions	• Known non-serious hypersensitivity to penicillins will result in exclusion from receiving interventions that include piperacillin and amoxicillin • Known non-serious hypersensitivity to cephalosporins will result in exclusion from receiving interventions that include ceftriaxone and ceftaroline • Known serious hypersensitivity to beta-lactams, including penicillins or cephalosporins, will result in exclusion from interventions that include piperacillin, amoxicillin, ceftriaxone, and ceftaroline. • Known hypersensitivity to moxifloxacin or levofloxacin will result in exclusion from moxifloxacin or levofloxacin intervention • Known serious hypersensitivity to the macrolide will result in exclusion from interventions that include piperacillin, amoxicillin, ceftriaxone, and ceftaroline. • Known or suspected pregnancy will result in exclusion from moxifloxacin or levofloxacin and ceftaroline interventions. It is normal clinical practice that women admitted who are in an age group in which pregnancy is possible will have a pregnancy test conducted. The results of such tests will be used to determine interpretation of this exclusion criteria.
Outcome measures	Primary REMAP endpoint: all-cause mortality at 90 days. Secondary REMAP endpoints refer to Core Protocol Section 7.6.2 Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrollment): • Multi-resistant organisms (MRO) colonization/infection: Isolation of multi-drug resistant (MDR) bacteria from clinical or screening specimens including vancomycin resistant enterococci (VRE), methicillin-resistant <i>Staphylococcus aureus</i> (MRSA), extended spectrum beta-lactamase (ESBL)-producing enterobacteriaceae, carbapenem resistant enterobacteriaceae (CRE). • <i>C. difficile</i> illness based on detection from feces using current standard of care diagnostics used at site • Serious Adverse Events (SAE) as defined in CORE protocol

13.2. Macrolide Duration Domain Summary

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

13.3. Corticosteroid Domain Summary

REMAP-CAP: Corticosteroid Domain Summary	
Interventions	• No corticosteroid including hydrocortisone (no placebo) • Fixed duration hydrocortisone for 7 days • Shock-dependent hydrocortisone while the patient is in septic shock
Unit-of-analysis and Strata	There are four units-of-analysis for this domain, specified by the combination of shock and influenza strata status. Analysis and Response Adaptive Randomization are applied by shock and influenza status, with borrowing permitted.
Evaluable treatment-by-treatment Interactions	Treatment-treatment interactions will be evaluated between interventions in this domain and interventions in the Antiviral Domain. No other interactions will be evaluated with any other domain.
Nesting	None
Timing of Reveal	Randomization with Immediate Reveal and Initiation
Inclusions	Inclusion criteria are the same as the Platform see Core Protocol Section 7.4.1
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • Known hypersensitivity to hydrocortisone • An indication to prescribe systemic corticosteroids for a reason that is unrelated to the current episode of CAP (or direct complications of CAP), such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven <i>Pneumocystis jiroveci</i> pneumonia • More than 24 hours have elapsed since ICU admission • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	Nil, not applicable
Outcome measures	Primary REMAP endpoint: all-cause mortality at 90 days. Secondary REMAP endpoints refer to Core Protocol Section 7.6.2 Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrollment): • Serious Adverse Events (SAE) as defined in CORE protocol

13.4. Antiviral Domain Summary

REMAP-CAP: Antiviral Domain Summary	
Interventions	• No antiviral agents (no placebo) • 5 days of oseltamivir • 10 days of oseltamivir
Unit of Analysis and Strata	The unit-of-analysis for this domain is the influenza present stratum. Analysis and Response Adaptive Randomization are applied by influenza strata. Some patients will be randomized who are in the influenza absent stratum and will be analysed separately, but borrowing will be permitted. The shock strata does not contribute to the unit-of-analysis for this domain.
Evaluable treatment-by-treatment Interactions	Treatment-treatment interactions will be evaluated between interventions in this domain and interventions in the Corticosteroid Domain. No other interactions will be evaluated with any other domain.
Nesting	There is one nest, comprising the 5- and 10-day duration of oseltamivir.
Timing of Reveal	Randomization with Immediate Reveal and Initiation.
Inclusions	Inclusion criteria are the same as the REMAP see Core Protocol Section 7.4.1, and • Influenza infection is suspected by the treating clinician or has been confirmed by microbiological testing
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • More than 24 hours has elapsed since Intensive Care Unit (ICU) admission • Known hypersensitivity to oseltamivir • Patient has already received two or more doses of oseltamivir or other neuraminidase inhibitors • Intention to commence or continue, if already commenced, an antiviral active against influenza other than oseltamivir • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	Nil, not applicable.
Outcome measures	Primary REMAP endpoint: all-cause mortality at 90 days. Secondary REMAP endpoints refer to Core Protocol Section 7.6.2 Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrolment): • Virologic endpoints (at selected sites): ○ Change from baseline in influenza virus levels measured at D3 and D7 or ICU discharge in upper and lower respiratory tract specimens. ○ Incidence of emergence of amino acid changes associated with reduced susceptibility to oseltamivir at D3 and D7 or ICU discharge. • Serious adverse event (SAE) as defined in Core Protocol