Protocol Amendment Summary

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

REMAP-CAP Protocol Amendment Summary Version 3 dated 02 September 2019

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1. CURRENT VERSIONS OF PROTOCOL DOCUMENTS

The current versions of protocol documents:

- 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 July 2019
    - Canadian Region-Specific Appendix Version 2, dated 05 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 3, dated 10 July 2019
- Statistical Analysis Appendix Version 3, dated 24 August 2019
- Registry Appendix Version 1, dated 11 September 2019
- Protocol Summary Version 3, dated 11 September 2019

2. ORIGINAL PROTOCOL

The original modular Protocol was established and published in November 2016.

Protocol Version 1 documents:

- REMAP-CAP Core Protocol Version 1, dated 20 November 2016
- Region-Specific Appendices
    - European Region-Specific Appendix Version 1, dated 20 November 2016
    - Australia and New Zealand Region-Specific Appendix Version 1, dated 20 November 2016
- Domain-Specific Appendices
    - Antibiotic Domain-Specific Appendix Version 1, dated 18 November 2016
    - Corticosteroid Domain-Specific Appendix Version 1, dated 19 November 2016
    - Macrolide Duration Domain-Specific Appendix Version 1, dated 20 November 2016
- Statistical Analysis Appendix Version 1, dated 7 November 2016

3. AMENDMENT 1

The Core protocol, European RSA, Australia and New Zealand RSA, Antibiotic DSA, Macrolide Duration DSA and Corticosteroid protocol documents underwent a minor amendment in March, April 2017.

The changes are summarized in REMAP-CAP Protocol Amendment Summary Version 1 dated 20 April 2017.

4. AMENDMENT 2

The Core protocol, European RSA, Australia and New Zealand RSA, Antibiotic DSA, Macrolide Duration DSA and Corticosteroid DSA protocol documents underwent a major amendment in December 2017.

The changes are summarized in REMAP-CAP Protocol Amendment Summary Version 2 dated 13 December 2017

4.1. Core protocol version 2.1

Due to the international nature of the REMAP-CAP trial, a nomenclature was developed to address changes to protocol documents that were required only in specific countries or regions, in order to avoid unnecessary protocol amendments in countries or regions that were unaffected by these changes. In such instances, the Protocol document is identified using the version number of the master version of the document, as well as a minor designation (e.g. Version 2.1).

Core Protocol Version 2 was amended to reflect ethical requirements in parts of Europe. The resulting version was identified as Version 2.1, and was only submitted for ethical approval in Europe. Version 3 of the core protocol incorporates all changes made from Version 2 to Version 2.1.

5. AMENDMENT 3

The Core protocol, European RSA, Canadian RSA, Australia and New Zealand RSA, Antibiotic DSA, Macrolide Duration DSA, Corticosteroid DSA, Statistical Analysis Appendix and Protocol Summary documents underwent a major amendment in July and August 2019. This Protocol Amendment Summary details the changes to each document.

5.1. Core protocol

5.1.1. REMAP-CAP Core Protocol Version 3, dated 10 July 2019

Section	Original text	New Text	Reason
Front page and whole document header	Version 2 dated 12 December 2017	Version 3 dated 10 July 2019	Administrative change to version and date
SECTION 1 ABBREVIATIONS AND GLOSSARY	**Original text**	**New Text**	**Reason**
1.1 Abbreviations Page 7	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	ANZ Australia and New Zealand APACHE Acute Physiology and Chronic Health Evaluation ARDS Acute Respiratory Distress Syndrome BHM Bayesian Hierarchical Model CAP Community-Acquired Pneumonia CIHR Canadian Institutes of Health Research CIHR-SPOR Canadian Institutes of Health Research Strategy for Patient-Oriented Research CRF Case Report Form DSA Domain-Specific Appendix DSMB Data Safety and Monitoring Board DSWG Domain-Specific Working Group eCIS Electronic Clinical Information System eCRF Electronic Case Report Form EMA European Medicines Agency	Updated with all abbreviations used in this version of the document

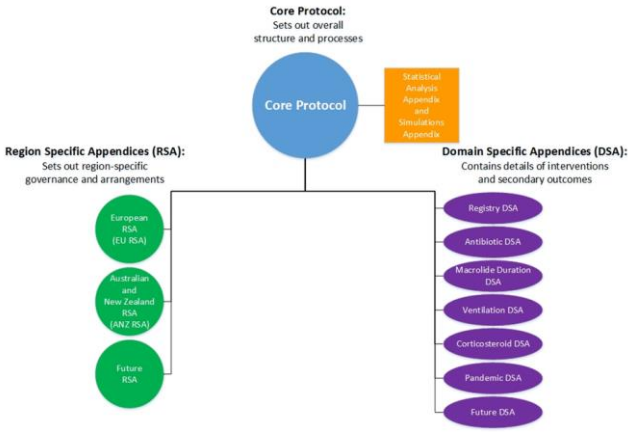
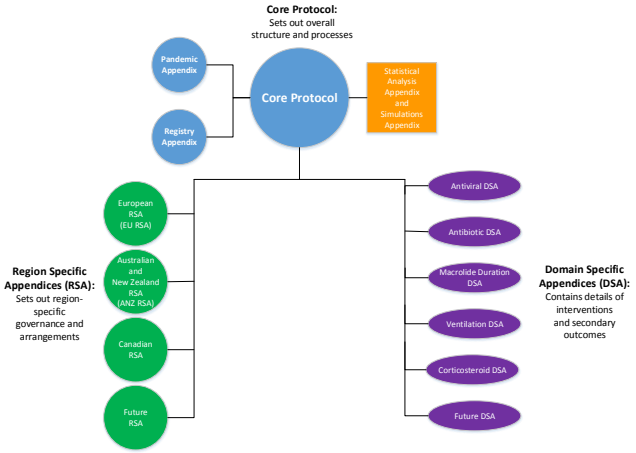
	ICMJE International Committee of Medical Journal Editors ICU Intensive Care Unit IEIG International Embedding Interest Group IIG International Interest Group ILTOHEIG International Long-term Outcomes and Health Economics Interest Group ISIG International Statistics Interest Group ITSC International Trial 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	EU European FDA Food and Drug Administration (United States) GCP Good Clinical Practice HDU High Dependency Unit HRC Health Research Council HRQoL Health Related Quality of Life ICMJE International Committee of Medical Journal Editors ICU Intensive Care Unit IEIG International Embedding Interest Group IIG International Interest Group ILTOHEIG International Long-term Outcomes and Health Economics Interest Group IPWG International Pandemic Working Group ISIG International Statistics Interest Group ITSC International Trial Steering Committee ITT Intention-To-Treat LOS Length of Stay ~~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 PEEP Positive End-Expiratory Pressure	

	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	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 WG Working Group WHODAS World Health Organization Disability Assessment Schedule	
1.2 Glossary Page 9	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	These appendices are modules of the protocol that contain all information about the interventions, which are nested within a domain that will be a subject of this	Correction of grammar error – *contains* changed to *contain*

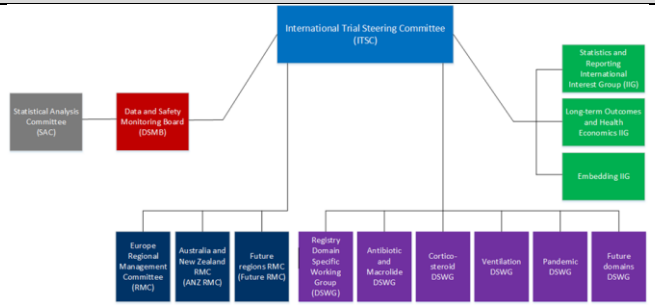
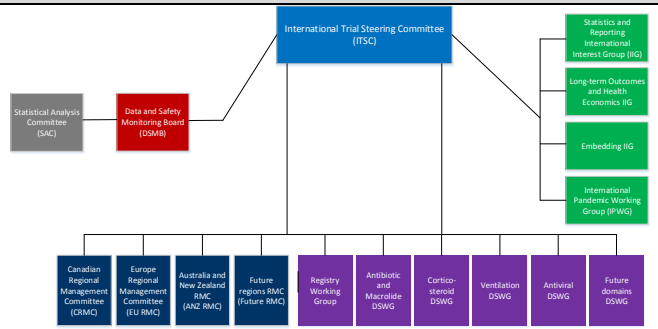
	REMAP.	REMAP.	
1.2 Glossary Page 10	Monte Carlo methods are also used to provide updated posterior probability distributions for the ongoing analyzes of the trial.	Monte Carlo methods are also used to provide updated posterior probability distributions for the ongoing analyses of the trial.	Correction of spelling error. The protocol uses US spelling
1.2 Glossary Page 10	Blank	Pandemic Appendix describes an appendix to the Core Protocol that includes the modifications to the Core Protocol that will occur during a pandemic of respiratory infection that results in severe CAP.	Definition of Pandemic Appendix added, noting that a Pandemic Appendix has not yet been submitted for approval
1.2 Glossary Page 10	Platform Trial is a type of clinical trial that studies multiple interventions being studied simultaneously. Common features of a platform trial include frequent adaptive analyzes 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.	Platform Trial is a type of clinical trial that studies multiple interventions simultaneously. Common features of a platform trial include frequent adaptive analyses using Bayesian statistical analysis, Response Adaptive Randomization (RAR), evaluation of treatment effect in pre-specified strata, and evaluation of multiple research questions simultaneously that can be perpetual with substitution of answered research questions with new questions as the trial evolves.	Correction of spelling error. The protocol uses US spelling. Correction of error in grammar – *being studied* removed
1.2 Glossary Page 11	Each region will have its own regional-specific appendix (RSA). The role, responsibilities, and composition of each RMC are specified in each region's Region-Specific Appendix	Each region will have its own Regional-Specific Appendix (RSA). The role, responsibilities, and composition of each RMC are specified in each region's (RSA).	Administrative change to use study nomenclature

	(RSA).		
1.2 Glossary Page 11	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.	Statistical Analysis Committee takes responsibility for the conduct of the preplanned adaptations in the trial. This task generally consists of running predetermined statistical models at each adaptive analysis and providing this output to the DSMB.	Correction of error in grammar – *provides* changed to *providing*
1.2 Glossary Page 11	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.	A Statistical Trigger applies to a stratum but may be reached in more than one stratum for the same intervention at the same adaptive analysis.	Changed to correct word. Strata is plural, stratum is singular
1.2 Glossary Page 11	Blank	Unit-of-analysis is the group of patients who are analyzed together within the model for a particular domain. The unit-of-analysis can be all patients who have received an allocation status in that domain or a sub-group of patients who received an allocation status determined by their status with respect to one or more strata. Within a domain, the RAR is applied to the unit-of-analysis.	Addition of a new definition that is relevant to a modification to the principles of statistical analysis
SECTION 2 INTRODUCTION	**Original text**	**New text**	**Reason**
2.1 Synopsis Page 13	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. Current conventional clinical trials methods to assess the	Of all the treatments that clinicians use for patients with severe CAP, only a small minority have been tested in randomized controlled trials to determine their comparative effectiveness. Current conventional clinical trials methods to assess the efficacy of treatments for pneumonia generally compare	Administrative change to use study nomenclature - *severe community-acquired pneumonia* deleted Administrative change to use words rather than

	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).	two treatment options (either two options for the same treatment modality, where both are in common use; or a new treatment against no treatment or placebo where the effectiveness of the new treatment is not known).	numbers - *2* changed to *two*
2.1 Synopsis Page 14	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).	The possible results are that a difference is detected or no that no difference is detected. However, when the conclusion of the statistical test is "no difference", this could be that there truly is no meaningful difference, or that the result is indeterminate (i.e. it is possible that if more patients had been enrolled a clinically relevant difference may have been detected).	Updated to improve clarity of definition
2.1 Synopsis Page 14	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); 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.	In comparison to a conventional trial, this REMAP uses an adaptive design, relying on pre-specified criteria for adaptation, that: avoids indeterminate results; concludes an answer to a question when sufficient data have accrued (not when a pre-specified sample is reached); Furthermore, in the event of a future epidemic of a novel or re-emerging respiratory pathogen (which typically present as severe CAP), this REMAP would be adapted to evaluate the most relevant treatment options.	Correction of error in grammar – *pre-specific* changed to *pre-specified* and *presently* changed to *present*
2.2 Protocol Structure Page 14	While, all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over	While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over	Updated to allow for future Pandemic

	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.	time, for example by the introduction of new domains or interventions or both (see glossary for definitions of these terms), by changing aspects of the trial during a pandemic, and commencement of the trial in new regions.	Appendix
2.2 Protocol Structure Page 15	 The protocol has multiple modules, comprising a Core Protocol, multiple DSAs, multiple RSAs, a Statistical Analysis Appendix and a Simulations Appendix.	 The protocol has multiple modules, comprising a Core Protocol, Pandemic Appendix to the Core Protocol, multiple DSAs, multiple RSAs, and a Statistical Analysis Appendix. A Pandemic Appendix to the Core Protocol is intended to be added subsequently. A Simulations Appendix is updated periodically as an operational document.	Updated figure and text to include new and updated appendices to the protocol
2.2.2 Domain-Specific Appendices Page 17	Each modification to a DSA will be subject of a separate ethics application for approval.	Each new DSA or addition of one or more interventions to an existing DSA will be submitted for ethical approval prior	Addition of more detail for clarity.

		to commencement.	
2.2.5 Pandemic Appendix Page 19	Blank	2.2.5. Pandemic Appendix The Pandemic Appendix (to the Core Protocol) contains information about how the core elements of the REMAP will be modified during a pandemic of severe acute respiratory infection that results in CAP. The Pandemic Appendix has the following structure: • The background and rationale for studying severe CAP caused by a pandemic • The procedure that will determine activation of the Pandemic Appendix • How the trial design adapts during a pandemic, including changes to one or more of study setting, treatment allocation, strata, trial endpoints, and principles of statistical analysis that will operate during a pandemic, as well as how the platform resets following a resolution of a pandemic	Addition of Pandemic Appendix information
2.2.6 Version History Page 19	Version 1: Approved by the ITSC on 20 November 2016 Version 1.1: Approved by the ITSC on 10 April 2017 Version 2: Approved by the ITSC on 12 December 2017	Version 1: Approved by the ITSC on 20 November 2016 Version 1.1: Approved by the ITSC on 10 April 2017 Version 2: Approved by the ITSC on 12 December 2017 Version 2.1: Approved by the ITSC on 26 March 2019 Version 3: Approved by the ITSC on 10 July 2019	Protocol version chronology updated
2.3 Lay Description Page 20	This trial differs from conventional clinical trials by being randomized, embedded, multifactorial adaptive and a	This trial differs from conventional clinical trials by being randomized, embedded, multifactorial, adaptive, and a	Correction of punctuation and an

	platform (“REMAP”).	platform (a “REMAP”).	error in grammar – addition of the word *a*
2.3 Lay Description Page 20	Blank	The REMAP is also designed to adapt to test relevant interventions during a pandemic caused by lung infection that results in severe pneumonia.	Updated to allow for Pandemic Appendix
2.4 Trial registration Page 20	This is a single trial, conducted in multiple regions, but will, as a minimum, be registered in ClinicalTrials.gov.	This is a single trial conducted in multiple regions, but will, as a minimum, be registered with ClinicalTrials.gov.	Correction of grammar error – *in* changed to *with*
2.5 Funding of the trial Page 21	Blank	In Canada, the trial has been funded by the Canadian Institute of Health Research, Strategy for Patient-Oriented Research (CIHR-SPOR) Innovative Clinical Trials Program Grant (no. 158584) for CAD $1,497,200, for the recruitment of 300 patients.	Updated to include addition of new region (Canada)
SECTION 3 & 4 STUDY ADMINISTRATION STRUCTURE	**Original text**	**New text**	**Reason**
Page 22			Updated figure to include new administrative groups (Antiviral DSWG, IPWG and CRMC)
3.1.2 Members	Professor Derek Angus, Chair Corticosteroid DSWG and	Professor Derek Angus, Chair Corticosteroid DSWG and	Updated to all current

Page 23	Foundation member Ms. Wilma van Bentum-Puijk, European (EU) Project Manager Dr. Scott Berry, President and Senior Statistical Scientist of Berry Consultants, Foundation member and Executive Director of International Statistics Interest Group (ISIG) Professor Marc Bonten, European Executive Director and Chair European RMC Professor Frank Brunkhorst, member EU RMC Professor Allen Cheng, Chair Antibiotic Domain and Macrolide Duration DSWG Dr. Lennie Derde, European Coordinating Investigator Professor Herman Goossens, Principle Investigator for PREPARE Professor Anthony Gordon, member EU RMC Professor Roger Lewis, Foundation member Dr. Ed Litton, member Australian and New Zealand (ANZ) RMC Dr. Colin McArthur, ANZ Deputy Executive Director and Chair Registry DSWG Dr. Shay McGuinness, Chair ANZ RMC Professor Alistair Nichol, Chair Ventilation DSWG Ms. Genevieve O'Neill, Australian Project Manager Dr. Rachael Parke, member ANZ RMC	Foundation member Ms. Wilma van Bentum-Puijk, European (EU) Project Manager Dr. Scott Berry, President and Senior Statistical Scientist of Berry Consultants, and Foundation member Ms. Zahra Bhimani, Canadian Project Manager Professor Marc Bonten, European Executive Director, Chair European RMC, and PREPARE Work Package 5 co-lead (specific issues) Professor Frank Brunkhorst, member EU RMC Professor Allen Cheng, Chair Antibiotic Domain and Macrolide Duration DSWG Professor Menno De Jong, member Antiviral DSWG Dr. Lennie Derde, European Coordinating Investigator, PREPARE Work Package 5 co-lead (specific issues) Professor Herman Goossens, Principal Investigator for PREPARE Professor Anthony Gordon, member EU RMC Mr. Cameron Green, Global Project Manager Professor Roger Lewis, Foundation member (will step down when SAC is convened) Dr. Ed Litton, member Australian and New Zealand (ANZ) RMC Professor John Marshall, Canadian Executive Director	members. Notes that Roger Lewis will step off this committee, prior to the first adaptive analysis, to take on role of Chair of the Statistical Advisory Committee. Correction of spelling error – *Principle* changed to *Principal*

	Professor Steve Webb, ANZ Executive Director and Foundation member	Dr. Colin McArthur, ANZ Deputy Executive Director and Chair Registry WG Dr. Shay McGuinness, Chair ANZ RMC Associate Professor Srinivas Murthy, Canadian Deputy Executive Director and Chair Antiviral DSWG Professor Alistair Nichol, Chair Ventilation DSWG ~~Ms. Genevieve O'Neill, Australian Project Manager~~ Associate Professor Rachael Parke, member ANZ RMC Ms. Jane Parker, Australian Project Manager Professor Kathy Rowan, member EU RMC Ms. Anne Turner, New Zealand Project Manager Professor Steve Webb, ANZ Executive Director and Foundation member	
3.4 International Interest Groups Page 25	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)	The following International Interest Groups (IIG) contribute to the trial: • REMAP-CAP International Statistics Interest Group (ISIG) • REMAP-CAP International Embedding Interest Group (IEIG) • REMAP-CAP International Long-term Outcomes and Health Economics Interest Group (ILTOHEIG) • REMAP-CAP International Pandemic Working Group (IPWG)	Updated to include new Working Group (IPWG)
3.5 Sponsors Page 26	In relation to recruitment that occurs in: • countries in Europe the sponsor is University Medical	In relation to recruitment that occurs in: • countries in Europe the sponsor is University Medical	Addition of new region's sponsor (Canada)

	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.	Center Utrecht. • Australia the sponsor is Monash University. • New Zealand the sponsor is the Medical Research Institute of New Zealand. • Canada the sponsor is Unity Health Toronto.	
4. International Trial Steering Committee Authorization Page 26	**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** Frank Brunkhorst **ITSC Member** Allen Cheng **ITSC Member** Lennie Derde **ITSC Member**	**EU Executive Director** Marc Bonten **ANZ Executive Director** Steve Webb **ANZ Deputy Director** Colin McArthur **ITSC Member** Derek Angus **ITSC Member** Wilma van Bentum-Puijk **ITSC Member** Scott Berry **ITSC Member** Zahra Bhimani **ITSC Member** Frank Brunkhorst **ITSC Member** Allen Cheng **ITSC Member** Menno De Jong	Signatures of new ITSC members authorizing the protocol update added and Genevieve O'Neill's signature deleted

	Herman Goossens **ITSC Member** Anthony Gordon **ITSC Member** Roger Lewis **ITSC Member** Ed Litton **ITSC Member** Shay McGuinness **ITSC Member** Alistair Nichol **ITSC Member** Genevieve O'Neill **ITSC Member** Rachael Parke	**ITSC Member** Lennie Derde **ITSC Member** Herman Goossens **ITSC Member** Anthony Gordon **ITSC Member** Cameron Green **ITSC Member** Roger Lewis **ITSC Member** Ed Litton **ITSC Member** John Marshall **ITSC Member** Shay McGuinness **ITSC Member** Srinivas Murthy **ITSC Member** Alistair Nichol **ITSC Member** Rachael Parke **ITSC Member** Jane Parker	

		ITSC Member Kathy Rowan **ITSC Member** Anne Turner	
SECTION 5 BACKGROUND & RATIONALE	**Original text**	**New text**	**Reason**
5.1.2 Epidemiology Page 28	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. 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.	Throughout the remainder of this protocol, we will use the term ICU for units that provide specialized care for critically ill patients, including HDU, Critical Care Units, and Intensive Treatment Units. 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.	Correction of spelling errors. The protocol uses US spelling. Added a hyphen to *middle-income*
5.1.3 Standard care for patients with severe CAP Page 30	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	Examples of commonly used therapies that support failed organ systems or prevent the complications of critical illness and its treatment include oxygen therapy, invasive and non-invasive mechanical ventilation, intravenous fluid resuscitation, vasoactive drugs, dialysis, provision of nutrition, sedation, physiotherapy including mobilization, diuretic medications, suppression of gastric acid production, and mechanical or pharmacological	Correction of spelling error. The protocol uses US spelling

	interventions to prevent venous thromboembolism.	interventions to prevent venous thromboembolism.	
5.1.5 Variation in care and compliance with guidelines Page 31	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.	There is also widely reported variation in compliance with many supportive therapies for patients with severe CAP, such as use of low tidal volume ventilation, type of resuscitation fluid, and thresholds for the administration of transfusion for anemia.	Correction of spelling error. The protocol uses US spelling
5.2 Influenza pandemics and emerging pathogens Page 32	Blank	More detailed background information about pandemics of respiratory infection, together with challenges associated with the clinical research response are outlined in the Pandemic Appendix.	Addition to include new Pandemic Domain
5.3.1 Generating clinical evidence Page 33	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 use of RAR, which allows the allocation ratios to change over time based on accruing outcomes data, maximizes the chance of good outcomes for trial participants.	Correction of spelling error. The protocol uses US spelling
5.3.2 Underlying Principles of the Study Design Page 33	The design maximises the efficiency with which available sample size is applied to evaluate treatment options as rapidly as possible. 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. • frequent adaptive analyzes using Bayesian statistical	The design maximizes the efficiency with which available sample size is applied to evaluate treatment options as rapidly as possible. A REMAP uses five approaches to minimize the impact of assumptions on trial efficiency and also maximizes the benefit of participation for individuals who are enrolled in the trial. • frequent adaptive analyses using Bayesian statistical	Correction of spelling errors. The protocol uses US spelling

	methods	methods	
5.3.5 Embedding Page 36	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. 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.	Wherever possible trial treatment allocations will be integrated with electronic customized order sets, produced at the point of delivery of care that also includes each site's local care standards for concomitant therapies. 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.	Correction of spelling errors. The protocol uses US spelling. Added a hyphen to *high-fidelity*
5.3.7.1 Page 37	5.3.7.1. Frequent adaptive analyzes Frequent adaptive analyzes using Bayesian statistical methods will be undertaken using Markov Chain Monte Carlo (MCMC) estimates of the Bayesian posterior probability distributions.	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.	Correction of spelling errors. The protocol uses US spelling
5.3.7.2 Page 38	This document, the Core Protocol, sets out the pre-specified rules for interpreting the results of analyzes. Figure 3: Adaptive Analyzes	This document, the Core Protocol, sets out the pre-specified rules for interpreting the results of analyses. Figure 3: Adaptive Analyses	Correction of spelling errors. The protocol uses US spelling
5.3.7.4 Analysis within and between strata	The frequent adaptive analyzes will evaluate the primary endpoint, within each stratum. The statistical models for	The frequent adaptive analyses will evaluate the primary endpoint, within one or more stratum. Where specified,	Correction of spelling errors. The protocol uses

Page 40	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 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.	US spelling
5.3.7.5 Frequency of adaptive analyses Page 41	5.3.7.5. Frequency of adaptive analyzes Adaptive analyzes will occur frequently, with the frequency being approximately proportional to the rate of recruitment, and will be a largely automatic process; 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	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 DSMB, in conjunction with the ITSC, having reached a Platform Conclusion, and in deciding to terminate an intervention or domain (in conjunction with a Public Disclosure), may take into account one or more issues such as the value of continuing randomization so as to evaluate additional clinically relevant endpoints or to evaluate potential interactions	Correction of spelling errors. The protocol uses US spelling Correction of grammar error – the word *of* deleted
SECTION 7 SUMMARY OF TRIAL DESIGN	**Original text**	**New text**	**Reason**
7.1 Introduction Page 45	Frequent adaptive analyzes 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. The intention-to-treat (ITT) principle will be used for all	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. The intention-to-treat (ITT) principle will be used for all	Correction of spelling errors. The protocol uses US spelling

	primary analyzes.	primary analyses.	
7.3 Study setting and participating regions Page 47	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 enrollment 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 enrollment 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 enrollment 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	The current regions are: • Europe, with funding from a European Union FP7 grant (FP7-HEALTH-2013-INNOVATION-1, grant number 602525), to support the enrollment of 4000 participants. This funding terminates in 2021. • Australia and New Zealand. In Australia the project has received funding from a NHMRC Project Grant (APP1101719), to support the enrollment of 2000 participants. This funding terminates in December 2021, although some extension may be feasible. In New Zealand the project has received funding from a HRC Programme Grant (16/631), to support the enrollment of 800 participants. This funding terminates in November 2021. • Canada. In Canada the project has received funding for a CIHR grant (158584), to support the enrollment of 300 participants. This funding terminates in 2022. It is intended that additional regions will be added if funding can be secured in other locations. It is desirable that the REMAP is active in as many locations as possible. There is no upper limit to the number of regions and the number of participating sites.	Updated information to termination dates of funding in Europe and Australia. Canadian grant details added. Wording changed from *the trial will be launched in the following regions* to *the current regions* and previous current regions deleted from the end of the paragraph.
7.4 Eligibility criteria Page 48	Criteria for inclusion in the Registry Domain, in which patients do not receive any randomized intervention, may	Criteria for inclusion in the registry, in which patients do not receive any randomized intervention, may be broader	Administrative change to use study nomenclature

	be broader than the entry criteria for the REMAP	than the entry criteria for the REMAP	– *Registry Domain* changed to *registry.* The registry is now not considered a domain and the term domain is reserved for when interventions are allocated using randomization
7.4.1 REMAP Inclusion Criteria Page 48	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	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	Definition of inclusion criteria changed to operationalize exclusion of patients with chronic pneumonia, which had occurred previously at domain level, to provide better clarification of nature of radiological changes, provide a time-window during which organ support is necessary for inclusion. Replaced *requirement* (which involves

			interpretation) with *receiving* which can be observed.
7.4.2 REMAP Exclusion criteria Page 48	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.	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.	Definition of exclusion criteria changed to provide better operational characteristics, based on feedback from recruiting sites. A hyphen has been added to *long-term*.
7.4.3 Domain-Specific Entry criteria Page 49	The additional eligibility criteria that are specific to a domain are provided in the DSA.	The additional eligibility criteria that are specific to a domain are provided in each DSA.	Correction of error in grammar – *each* added
7.5.2 Treatment allocation and Response Adapative Randomization Page 50	The RAR proportions are then updated at the first adaptive analysis and at all subsequent adaptive analyzes.	The RAR proportions are then updated at the first adaptive analysis and at all subsequent adaptive analyses.	Correction of spelling error. The protocol uses US spelling
7.6 Endpoints Page 52	Blank	The Primary Endpoint (or the end-point that is used for RAR) may be modified during a pandemic and will be outlined in the Pandemic Appendix.	Addition to endpoints to include future Pandemic Appendix.
7.6.2 Secondary Endpoints Page 53	Hospital outcomes: • Hospital LOS censored 90 days after enrollment;	Hospital outcomes: • Hospital LOS censored 90 days after enrollment;	Addition of wording to definition of hospital

	• Destination at time of hospital discharge	• Destination at time of hospital discharge (characterized as home, rehabilitation hospital, nursing home or long-term care facility, or another acute hospital);	destination for improved clarity
7.7.5 Follow up and missing data Page 54	No imputation will be made for missing data in the statistical analysis with regard to the determination of RAR, Statistical Triggers and Platform Conclusions.	If values necessary for the Bayesian modelling of the primary endpoint and the RAR are missing they may be imputed, using available data. For example, if strata or state is missing, it will be multiply imputed based on the available variables and a prior distribution on the relative prevalence of each strata or state. Values for the primary endpoint will not be imputed. Additional details are provided in the Statistical Analysis Appendix.	Changes to the Statistical Analysis Appendix have been incorporated into the Core Protocol for consistency across all protocol documents.
7.8.2 Introduction Page 55	Within the REMAP, two or more interventions within a domain are evaluated and sequential Bayesian statistical analyzes 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. Participants will be classified by membership in different populations defined by strata and the eligibility criteria for each domain.	Within the REMAP, two or more interventions within a domain are evaluated and sequential Bayesian statistical analyses are used over time to incorporate new trial outcome information to determine if an intervention is superior, if one or more interventions are inferior in comparison to all other interventions, or if one or more pairs of interventions are equivalent, with respect to the primary endpoint. Participants will be classified by membership in different populations defined by one or more strata. The unit-of-analysis for a domain is the most granular level, defined by one or more stratum, or a state, within which the	Correction of spelling errors. The protocol uses US spelling. Clarification that inferiority of an intervention requires it to be inferior to all other interventions within a domain and that evaluation of equivalence involves comparison of all possible pairs of

	Inference in this REMAP is determined by analyzes 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 different stratum in the REMAP. 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.	treatment effect of interventions within that domain may vary in the statistical model. Participants are also classified by the criteria that determine eligibility for each domain. Inference in this REMAP is determined by analyses using pre-specified statistical models that incorporate region, country, time periods, age, and disease severity to adjust for heterogeneity of enrolled participants that might influence risk of death. These models incorporate variables that represent each intervention assigned to participants and possible interactions between interventions in different domains. The efficacy of each intervention within a domain may be modeled as not varying in any of the strata, or possibly varying in the one or more of the different strata in the REMAP. Where the efficacy of each intervention within a domain is modeled as possibly varying, borrowing between strata is permitted. The unit-of-analysis that will be modeled may comprise the entire population (i.e. no categorization by strata is applied) or may be defined by one or more stratum. The unit-of-analysis and whether borrowing can occur between strata is pre-specified for each domain. At each analysis the current active statistical model (or models) is (are) used, and may include patients who were	interventions, which was not clarified previously. The concept of unit-of-analysis is introduced so that the strata structure can be applied selectively, as appropriate, in different domains. The role of borrowing between strata is clarified, as it applies to the application of the strata structure.

		enrolled when previous versions of the model were being used. The current model is described in an operational document, maintained by the SAC. Unless otherwise specified (see Section 8.12) modifications and implementation of modifications to the model require the approval of the ITSC and do not require a protocol amendment. At any given adaptive analysis, a Statistical Trigger may be reached for all participants or for one or more stratum and will be reviewed immediately by the DSMB. When a Statistical Trigger is confirmed by the DSMB, based on a thorough review of the data including an evaluation of the proportion of patients for whom monitoring of variables that contribute to the model has been completed, and totality of evidence, and where no compelling reason exists not to reach a conclusion (see Section 7.8.9) regarding that question the result that has led to a Statistical Trigger will be specified to be a Platform Conclusion.	Clarifies the relationship between the statistical model and the protocol. Correct use of term stratum. Recognition that, in an adaptive platform trial, consideration of declaration of a Platform Conclusion by the DSMB should include information regarding extent of monitoring.
7.8.3 Heading Page 56	7.8.3. Target populations (strata and states) and implications for evaluation of treatment-treatment interactions	7.8.3. Target populations (strata and states) and implications for evaluation of treatment-by-treatment and treatment-by-strata interactions	Modification of title updated to reflect modifications to principles of statistical

			analysis
7.8.3.1 Introduction Page 56	First, covariates determined at the time of enrollment that are identified in the design as possibly having differential treatment effect (i.e. interventions may have differential efficacy for the different levels of the covariate) are referred to as strata. 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 enrollment or may develop after the time of enrollment.	First, covariates determined at the time of enrollment that are identified in the design as possibly having differential treatment effect (i.e. interventions may have differential efficacy for the different levels of the covariate) are referred to as strata. Strata are used to define the unit-of-analysis for a domain within a model. In this regard, the concept of 'state' is used to define participants with characteristics that define a target population that will be evaluated by a domain, analyzed within the REMAP, and for which the characteristics can be present at the time of enrollment or may develop after the time of enrollment. State can also be used to define the unit-of-analysis for a domain within the model.	Addition of sentences to improve the clarity of definitions of strata and state and relationship between strata and states and unit-of-analysis. Correction of error in grammar – *defines* changed to *define*
7.8.3.2 Stratum Page 57	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 enrollment.	A covariate in the REMAP that can be used as a unit- of-analysis within a Bayesian statistical model that allows for the possibility of differential treatment effects for different levels of the variable is referred to as a strata. The covariate is classified into mutually exclusive and exhaustive sets for analysis of treatment effect, as well as for defining separate RAR. The criteria that define a stratum are based on a characteristic that is present at or before the time of enrollment.	Changes to correct word. Strata is plural, stratum is singular. Clarification of definitions of how strata allows evaluation of potential differential treatment effect and clarification that criteria

	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 2N 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.	The simplest structure for strata is a single dichotomous stratum variable, which divides participants in the REMAP into two stratum. More complex arrangements are possible, such as a single strata variable that is ordinal or two (or more) dichotomous or ordinal strata variables the combination of which defines a single stratum (i.e. there are 2N stratum when there are N dichotomous stratum variables). The number of strata variables and the number of strata within the REMAP may be varied, depending on the impact of such decisions on statistical power, as determined by simulations. The modeling of strata may assume no differential effect for some domains. This may occur in two ways. Firstly, when the strata structure defines the entry criteria for a domain. Secondly, when two or more stratum are combined within a single unit-of-analysis (i.e. the unit-of-analysis comprises two or more stratum). If the unit-of-analysis comprises less than all available strata the analysis that is performed assumes that treatment effect does not vary between stratum combined within a common unit-of-analysis. The RAR is applied according to the model. So, the RAR applies to the patients that comprise the unit-of-analysis, irrespective of whether the unit-of-analysis comprises a single stratum or	that define a strata are based on characteristics present at time of enrolment. Detailed explanation of the options for pre-specification in relation to how strata variables can be applied differently to different domains. For some domains it is specified that it is possible that there is no application of strata, i.e. analysis applies to all randomized patients as a

		two or more stratum. A strata variable can be set that is maintained as a silent or 'sleeping' strata which becomes active under pre-defined circumstances, such as the occurrence of a pandemic. In this situation, during the inter-pandemic period, all participants are categorized as non-pandemic but, during a pandemic, a distinction is made between patient with proven or suspected pandemic infection and patients in whom pandemic infection is neither proven nor suspected. The *a priori* defined strata that are used for determination of results and for RAR may be changed during the life of the REMAP as knowledge is accumulated and, if this occurs, will result in amendment of one or both of the Core Protocol and DSAs. Data from patients enrolled before the change in the strata can be used to determine priors that are incorporated into the model at the outset of the incorporation of the new strata into the model.	single group. Introduction of the concept of a strata that is not applied at all times, but can be 'switched-on', such as during a pandemic to allow for evaluation of differential treatment effect of current or future interventions in patients with pandemic infection. Rewriting of a previous section that permitted modification of the strata variables during the life of the platform but with clarification that data from previously enrolled patients can be used when applied to the new strata structure.
7.8.3.3 Treatment-by-	Blank	Where specified in the statistical model, the treatment	An improved explanation

strata interactions; borrowing between strata Page 58		effect of an intervention is allowed to vary between different strata. A Bayesian Hierarchical Model (BHM) is used for all treatment-by-strata interactions. In the BHM a hyperprior is used for the differing treatment effects across strata. The standard deviation of the hyperprior, gamma, is a modeling starting estimate for the variation in the magnitude of the difference in treatment effects between strata. By default, the starting estimate of the difference is zero. The gamma parameter influences the extent to which the treatment effect of different interventions is permitted to vary between strata. At the commencement of a model, the gamma parameter must be set, for each domain-strata pair. In this REMAP, only three options are permitted with respect to specifying the gamma parameter for each domain-strata pair. Firstly, gamma may be set to zero. The effect of this is that treatment effect of an intervention is not permitted to differ between specified strata. The unit-of-analysis is not sub-divided according to the stratum variable. If gamma is set to zero for all strata for a domain, the unit of analysis is all patients randomized in that domain. Secondly, and at the opposite extreme, gamma can be set to infinity. In this situation treatment effect is evaluated separately and independently in each stratum	of methods that are unchanged from previous protocol in relation to how treatment-strata interactions are evaluated as well as some modifications. Explanation of how unit-of-analysis is applied within the statistical structure for evaluation, or not, of treatment-strata interactions. Clarification that, when specified, borrowing is permitted but with relevant priors (related to potential variability of interaction) being pre-specified and the same for all domain.

		(with no borrowing between stratum). Thirdly, gamma may be set to a defined number between zero and infinity. This parameter value cannot be varied for different domain-strata pairs, a global REMAP value has been selected. This specified value for gamma places a constraint on the variance of the difference in treatment effect in different stratum but permits the model to estimate treatment effect in one stratum by borrowing from other stratum. Borrowing occurs to the extent that it is supported by the accumulated data, but the setting of gamma influences the amount of borrowing and how quickly borrowing is able to occur. The value of gamma that has been chosen has been determined by simulations to achieve a compromise between type I and type II error in baseline scenarios that assume either equivalence or superiority. Where a value for gamma is specified in the model, in this REMAP the value of gamma will be 0.15. The specification of gamma determines the unit of analysis in the model and the extent of borrowing. For each domain-strata pair, the unit of analysis can be all patients (gamma = zero), each stratum with borrowing (gamma = 0.15), or each stratum separately (gamma = infinity). The gamma that will be set, and hence the unit-of-analysis, for each domain-strata pair is specified in each	Explanation of how unit-of-analysis and whether borrowing is permitted is

		DSA.	specified in each DSA as it relates to that domain.
7.8.3.4 Analysis set for strata, timing of enrollment and timing of information regarding strata membership Page 59	Blank	It has already been specified that the criteria that define a stratum must be present at or before the time of enrollment. In some situations, the information necessary to determine membership of a stratum may become available after the time of enrollment or may be acquired from information derived after enrollment where the understanding of biology of a disease makes it reasonable to assume that the criteria was met at the time of enrollment. This situation might apply to status with respect to a particular pathogen where results of microbiological testing are not available until after enrollment or when the sample that is tested is not collected until after enrollment. In this situation randomization is permitted within patients where the criteria is suspected or proven at the time of randomization. With regards to possible infection with a specified pathogen, suspected or proven infection at the time of randomization is sufficient to allow an allocation status to be made. For a patient with suspected infection, membership within the strata is defined by the final test results, but a patient who is suspected but is never tested is analyzed as a positive. If a Platform Conclusion is	Modification to how strata are determined to allow information that relates to the time of assessment of eligibility but may not become available until after the time of assessment of eligibility can still be used to define a stratum validly. Modification has been necessary to evaluate differential treatment effect according to the pathogen responsible for infection. Sometimes this information is known at time of eligibility but often the information

		reached for one or more stratum, analyses will also be done on patients with suspected infection who receive the intervention but who turn out to be negative. Whether borrowing between strata is permitted will be specified in the DSA.	only becomes available at a later time point.
7.8.3.5 State Page 60	Blank	Data from patients enrolled before the change in the state can be used to determine priors that are incorporated into the model at the outset of the incorporation of the new state into the model.	Modification to state that corresponds to previous modification of strata to allow changes in state with utilization of data from patients enrolled previously.
7.8.3.6 Timing of randomization and revealing of allocation status Page 60	In circumstances where the participant is eligible for inclusion in the REMAP but is not eligible for a domain at the time of enrollment but might become eligible, if the participant's state changes, 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 enrollment but the intervention is only administered if and when eligibility occurs. This is referred	In circumstances where the participant is eligible for inclusion in the REMAP but is not eligible for a domain at the time of enrollment but might become eligible, if the participant's state changes, the participant's allocation status is revealed only if and when the patient enters the state that confers eligibility. This is referred to as **Randomization with Delayed Reveal.** Another situation applies when eligibility is determined by information that relates to the condition of the patient at the time of initial assessment of eligibility and is relevant to determination of eligibility but is not known until later.	Clarification of definition of delayed reveal of allocation status. Substitution of a previous category of reveal with a new category, referred to as *Deferred Reveal*. This

	to as Randomization with Immediate Reveal and Delayed Initiation. If prospective consent or other form of agreement is deemed necessary for such a domain, Randomization with Immediate Reveal and Delayed Initiation is interpreted as being randomization with reveal occurring as soon as consent or other form of agreement is obtained with initiation of the intervention occurring only after consent is obtained (but without knowledge of allocation status being available until consent is obtained). Randomization with Immediate Reveal and Immediate Initiation allows for the analysis to enact an intent-to-treat approach to the invention 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 enrollment. 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	In this circumstance, the participant's allocation status can be revealed when the additional information becomes available. Examples of this type of information include the results of microbiological tests and the outcome of a request for consent. Information related to the safety of an intervention in individuals that may change between the time of initial assessment of eligibility and initiation of an intervention may also be reassessed and be used to determine if an allocation status will be revealed. Where initiation of the intervention is deferred pending availability of this additional information, this is referred to as **Randomization with Deferred Reveal.** It is noted that submission of information regarding microbiological results, consent, or safety information occurs without knowledge of allocation status. Variation in relation to the timing of revealing and initiation of an intervention has implications to the treatment-by-treatment interactions that are potentially evaluable. Analysis of participants who are enrolled in one or more domains on the basis of Randomization with Immediate Reveal can be conducted within a state, for which membership occurs for at least some participants at the time of enrollment.	describes situation in which additional information is necessary for reveal that may not be available at time of assessment of eligibility but where it is known that the information would have applied at the time of eligibility. Creation of this category of reveal allows the statistical model to validly evaluation interactions between interventions specified in domains with Deferred Reveal and domains with Immediate Reveal.

	Initiation within a stratum. For such participants, their allocation status is revealed at the time of enrollment but the intervention is only initiated after the time of enrollment 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.	The final scenario to consider involves participants who are enrolled in one or more domains on the basis of Randomization with Deferred Reveal within a stratum. For such participants, their allocation status is revealed at, or close to, the time of deferred initiation of the intervention, when additional information necessary to establish eligibility has become available but relates to information that applies at baseline. Participants in this category are analyzed within baseline stratum in an ITT fashion.	Explanation of how Deferred Reveal will be operationalized.
7.8.3.7 Treatment-by-treatment interactions Page 62	Blank	Where specified in the statistical model, the treatment effect of an intervention is allowed to vary depending on treatment allocation in another domain (i.e. allow evaluation of treatment-by-treatment interaction). A BHM is used for all treatment-by-treatment interactions. In the BHM, a hyperprior is used for the differing treatment-by-treatment interaction effects. The standard deviation of the hyperprior, lambda, is a modeling starting estimate for the variation in the magnitude of the difference in treatment effect dependent on an intervention assignment in another domain. By default, the starting estimate of the difference is zero (i.e. no interaction). The lambda parameter influences the extent to which the treatment effect of different interventions is permitted to	An improved explanation of methods that are unchanged from previous protocol in relation to how treatment-treatment interactions are evaluated and specified in each DSA.

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

		0.075. The third choice is to allow no borrowing of the treatment-by-treatment interactions. This is equivalent to selecting a lambda of infinity. This choice would be the most aggressive choice in estimating treatment-by-treatment interactions. The lambda that will be set for each domain-domain pair is specified in each DSA.	
7.8.3.8 Nested analysis of interventions within a domain Page 63	Blank	Within domains in which there are three or more interventions, some interventions may be more likely to have a similar treatment effect. There are several examples of such similarity. For example, the interventions within a domain may comprise a no intervention option and two doses or strategy of administration of the same intervention, or two or more interventions within a domain may belong to the same class of drug than one or more other interventions in that domain. In situations in which interventions may be more similar than others, the model may nest the more similar interventions within a higher-level intervention category that comprises all the interventions deemed similar. In this situation, and to evaluate the occurrence of a Statistical Trigger, there are two models for analysis. Firstly, all patients receiving the nested interventions, treated as a single combined intervention, are compared with all other	Explanation of an additional statistical principle. This allows evaluation of the treatment effect of interventions within the same domain that are more similar (i.e. antibiotics from the same class) to be evaluated both at the level of the individual intervention (as occurred previously) as well as evaluated using analysis that takes into account class effects (which is new). It is now

		interventions in the domain. Secondly, all interventions are modeled individually. In this analysis, the interventions within a nest are modeled using a BHM incorporating the nesting structure. The BHM has a hyperprior specified for the shrinkage across interventions within the nest. This analysis will compare all interventions within a domain to all other interventions. This BHM analysis is used for the RAR assignments. Whether nested analysis will be performed and, if so, the membership of category of more similar interventions will be specified in the DSA.	permitted to reach a statistical trigger and a platform conclusion for a group of interventions that are pre-specified (for example as a group, antibiotic interventions that are beta-lactams could be deemed superior or inferior to the fluroquinolone intervention).
7.8.3.9 Current strata and states Page 63	At the launch of this REMAP, the default strata are defined, at the time of enrollment, by: • Shock, defined in 2 categories, present or absent, with present defined as the patient is receiving continuous infusion of intravenous vasoactive medications at the time of enrollment 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	The default strata are defined, at the time of enrollment, by: • Shock, defined in 2 categories, present or absent, with present defined as the patient is receiving continuous infusion of intravenous vasopressor or inotrope medications at the time of enrollment • Influenza defined in two categories, present or absent, based on the results of microbiological tests for influenza. Any patient with suspected influenza who is not tested will be deemed positive. The availability and interpretation of microbiological tests are likely to change during the REMAP and an operational document will be used to	Clarification of nomenclature for vasoactive medications Addition of new strata for influenza status. This has been added to facilitate addition of a new domain, which tests antiviral agents active

	ventilation;, participants who are receiving invasive mechanical ventilation and have a ratio of arterial partial pressure of oxygen to fractional inspired concentration of oxygen (P:F ratio) of ≥ 200 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, what treatment- treatment interactions will be evaluated are specified in each DSA.	specify how different tests are interpreted. Eligibility for a domain that tests antiviral medications active against influenza will be based on status with respect to influenza being proven or suspected at time of enrollment but it is noted that strata status is defined by the final results of influenza testing which may not be known at time of enrollment and may include analysis of samples collected after enrollment where it is reasonable to presume that the sample reflected influenza status at time of enrollment. • Pandemic infection defined in two categories, proven or suspected pandemic infection or neither proven nor suspected pandemic infection. This is a 'sleeping strata' and will not be active before or after a pandemic but may be activated during a pandemic. The decision to activate a pandemic infection strata is specified in the Pandemic Appendix to the Core Protocol. The default states are defined by the occurrence of: • Hypoxemia, defined in 3 categories, comprising participants who are not receiving invasive mechanical ventilation;, participants who are receiving invasive mechanical ventilation and have a ratio of arterial partial pressure of oxygen to fractional inspired concentration of	against influenza and also allows for the possibility of differential treatment effect of interventions in other domains (corticosteroid) for patients with or without influenza Addition of 'sleeping strata' for proven or suspected pandemic infection. This is necessary to accommodate plans for how the platform will adapt during a pandemic which will be specified in a Pandemic Appendix which has not yet been submitted for approval. Modification of definition

		oxygen (P:F ratio) of ≥ 200 mmHg or are receiving invasive mechanical ventilation with the Positive End-Expiratory Pressure (PEEP) set to less than 5 cm of water (irrespective of the P:F ratio); and participants who are receiving invasive mechanical ventilation with a PEEP of 5 cm of water or more and have a P:F ratio of <200 mmHg. The domains to which each strata or state applies, the unit-of-analysis (which determines which if any treatment-by-strata interactions are evaluated in the model), the relationship between the timing of domain eligibility and the revealing of allocation status, whether nested analysis will occur, and what treatment-by-treatment interactions will be evaluated are specified in each DSA.	of states to take into account role of PEEP in interpretation of the P:F ratio. Clarification of how unit-of-analysis for treatment-strata interactions, nesting, and treatment-treatment interactions are specified in each DSA.
7.8.3.10 Pre-specified subgroup analysis after achievement of a Platform Conclusion Page 64	Following the achievement of a Platform Conclusion it is permissible for additional sub-group analyzes 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 analyses will only be conducted following the determination of a Platform Conclusion.	Following the achievement of a Platform Conclusion it is permissible for additional sub-group analyses to be conducted. The variables that specify such sub-groups are outlined a priori in each DSA. These variables are different to those that define strata or states in the model and are not used in determination of a Statistical Trigger or RAR for that domain. In a domain in which the unit-of-analysis comprises two or more stratum, additional sub-group analyses can be conducted for variables that do specify stratum that have been combined to determine the unit-of-analysis.	Correction of spelling error. The protocol uses US spelling. With removal of application of some strata in some domain (via application of unit-of-analysis) pre-

		All such analysis will only be conducted following the determination of a Platform Conclusion and, although reported, such analyses are always regarded as preliminary. Following a Platform Conclusion, the results of a pre-specified subgroup analysis may be used to make changes to the model and, where appropriate and to an appropriate degree, data derived from the REMAP can be used to set the prior distribution at the commencement of the new model.	specification of unanalyzed stratum as sub-groups that will be evaluated after a Platform Conclusion. Pre-specification of potential to use data derived from previous patients to set prior distributions at commencement of a new model, following modification after a Platform Conclusion.
7.8.4 Bayesian Statistical modeling Page 65	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). It is not precluded that, under certain circumstances, such as during a pandemic and where there was strong prior	Inferences in this trial are based on a Bayesian statistical model, that will calculate the probability of superiority, inferiority, and equivalence of the interventions (known as a posterior probability distribution) within a unit-of-analysis that is defined by one or more stratum, taking into account the evidence accumulated during the trial (based on data on the outcomes of participants) and on assumed prior knowledge (known as a prior distribution). It is not precluded that, under certain circumstances, such	Correction of spelling errors. The protocol uses US spelling. Introductory section to Bayesian statistical modeling which is updated to reflect earlier described change to strata structure and unit-

	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. In this trial, frequent adaptive analyzes will be performed, creating a very complicated sample space, and hence the Bayesian approach is a very natural one for these adaptive designs. In contrast to frequentist confidence intervals which have awkward direct interpretation, Bayesian analyzes return probability estimates that are directly interpretable as probabilities that statements are true (like the probability that one intervention is superior to another). 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,	as during a pandemic and where there was strong prior evidence along with an ethical imperative to evaluate a particular choice of therapy, that the design could allow an informative prior to be used for the analysis of results from the trial. It may also be permitted to use an informative prior when data that is incorporated in the informative prior is derived from patients already randomized within this REMAP. If informative priors are used this will be specified in the relevant DSA. The study design can use informed priors to guide some elements of the design, such as for the evaluation of interaction terms, and will be described in the Statistical Analysis Appendix. As outlined above, gamma will be set to allow and influence the evaluation of treatment-by-strata interactions and lambda will be set to allow and influence the evaluation of treatment-by-treatment interactions. 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. In contrast to frequentist confidence intervals which have	of-analysis. Clarification, as outlined in previously described amendments, which permits use of data from patients enrolled in platform previously to be used to set informative priors. Addition of clarification of how treatment-strata and treatment-treatment interactions are evaluated.

	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. 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 analyzes 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). The adaptive analyzes 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	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). Each stratum, combination of stratum, or state (where eligibility is defined by a state) is analyzed separately but the model captures the commonalities across such sub-groups. Additionally, and where specified, the statistical model allows evidence relating to the effectiveness of an intervention in one stratum to contribute (via 'borrowing') to the estimation of the posterior probability in other strata, but this only occurs to the extent that treatment effect is similar in different strata. It is acknowledged that the estimate of treatment effect for a stratum may be contributed to by borrowing from adjacent strata but the results from the strata that have contributed to borrowing will not be reported. The results of these analyses are used to achieve the primary objective of the trial which is to determine the effectiveness of interventions and, where specified, the extent to which that effectiveness varies between strata (intervention-stratum interaction). Additionally, but only	Combination of stratum added to allow for addition of unit-of-analysis. Addition of where specified, as previously borrowing applied in all circumstances. *Be reported* was missing from previous version.

	analyzes. The frequency of adaptive analyzes 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 analyzes.	where specified a priori, the model is able to estimate the effectiveness of an intervention in one domain contingent on the presence of an intervention in another domain treatment-by-treatment interaction). 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.	Replacement of term *intervention-intervention* thoughout by term *treatment-by-treatment* interaction.
7.8.6 Intervention Superiority Statistical Trigger Page 68	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.	At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being a member of the optimal regimen, for that unit-of-analysis, then that intervention will be deemed as being superior to all other interventions in that domain in that target population.	Correction of errors in grammar and terminology – stratum changed to *unit-of-analysis, stratum* changed to *target population* to provide better clarity.
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	At any adaptive analysis, if a single intervention has less than a 0.01 posterior probability of being a member of the	Correction of errors in grammar and

Page 69	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.	optimal regimen, for a unit-of-analysis, then that intervention will be deemed as being inferior for that target population. If superiority and inferiority were to be discovered simultaneously (for example when there are two interventions), the result will be interpreted as demonstrating superiority.	terminology – stratum changed to *unit-of-analysis, stratum* changed to *target population* and the number *2* changed to the word *two*
7.8.8 Intervention Equivalence Statistical Trigger Page 69	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.	If two interventions within a domain, for a unit-of-analysis, have at least a 0.90 probability of being within a pre-specified delta for the primary endpoint then these interventions will be deemed as being equivalent. The size of the pre-specified odds ratio delta is 0.20, meaning equivalence is reached with at least a 90% probability of neither intervention increasing the odds ratio of mortality by more than 0.20. An odds ratio delta of 0.2 has been chosen on the basis that it is consistent with guidance from the Food and Drug Administration (FDA) (U.S. Department of Health and Human Services, 2016) and the European Medicines Agency (EMA) (European Medicines Agency, 2005), as well as discussed in academic literature, and the magnitude of treatment effect that has been specified in published superiority trials that enroll patients who are critically ill (Aberegg et al., 2010, Ware and Antman, 1997, European Medicines Agency, 2005, U.S.	The section on evaluation of equivalence has been redesigned after identification of ambiguity in previous version (equivalence of all interventions compared with equivalence of a pair of interventions) and the conduct of simulations revealed limitations with use of an absolute delta, when it was likely that baseline incidence of primary outcome would

		Department of Health and Human Services, 2016). A measure of relative treatment effect (odds ratio) is specified, rather than an absolute difference in treatment effect. This choice is made because it is reasonable to expect the mortality rates to vary between strata, and the relative effect is a more robust analysis method across these differences. In a domain with two interventions equivalence is evaluated between the single pair of interventions. In a domain with more than two interventions, equivalence is evaluated for every possible pairwise comparison. A DSA may define levels of delta for equivalence that are different from the default delta. This includes the possibilities of specifying a delta that may be asymmetrical for some or all pair-wise comparisons or both. The DSA will set out the rationale for any variation in delta and may include, but are not limited to, cost or burden. This Statistical Trigger for equivalence may also be applied for a state that defines the target population for a domain.	vary between stratum. The changes are to specify a relative, rather than absolute, difference for declaration of equivalence and to clarify that equivalence is evaluated between all pairs of interventions (no different to previously for a domain with two interventions but different from previously in domains with three or more interventions).
7.8.9.1 Introduction Page 70	Blank	Introduction	Text of section 7.8.9 divided into separate paragraphs
7.8.9.2 Actions following Statistical Trigger	Blank (no heading) At that point randomization to all remaining interventions	Actions following Statistical Trigger for superiority At that point randomization to all other remaining	Changes made to terminology. The word

for superiority Page 70	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).	interventions in the domain in that unit-of-analysis will be halted at sites at which the superior intervention is available (randomization to the non-superior interventions may continue at sites at which the superior intervention is not available pending its availability).	*other* added to improve clarity and the word stratum changed to *unit-of-analysis*
7.8.9.3 Actions following Statistical Trigger for inferiority Page 70	Blank (no heading) At that point the intervention will not be randomized to any more participants in that stratum.	Actions following Statistical Trigger for inferiority At that point the intervention will not be randomized to any more participants in that unit-of-analysis.	Changes made to terminology. The word stratum changed to *unit-of-analysis*
7.8.9.4 Actions following Statistical Trigger for equivalence Page 71	Blank (no heading) 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 analyzes, for example, of clinically relevant secondary endpoints. A combination of the primary analysis and any secondary analyzes 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	Actions following Statistical Trigger for equivalence If a Statistical Trigger arises because one or more pairs of interventions are deemed as being equivalent within a unit-of-analysis, this will be communicated to the ITSC by the DSMB. The ITSC in conjunction with the DSMB may undertake additional analyses, for example, of clinically relevant secondary endpoints. The approach to a Statistical Trigger for equivalence is different depending on the number of interventions within a domain. For domains with only two interventions a valid Statistical Trigger for equivalence will be reported as a Platform Conclusion. With respect to the adaptation of the domain, the following actions are possible: • Removal of the domain from the Platform	Extensive review of actions and adaptations following a finding of equivalence in domains with different numbers of interventions. This follows from modification to clarify that equivalence is evaluated between all possible pairs of interventions in a domain including clear description of role of DSMB and role of ITSC, in

	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.	• Switching the allocation status to deterministically assign one of the Interventions, for example the less burdensome or less expensive intervention • No change to the interventions within the domain with continuation of RAR. This could be to further evaluate secondary endpoints, a smaller delta of equivalence, or interest in interactions with other Interventions. Such changes would require amendment to the DSA. Factors that should be taken into account by the DSMB and the ITSC include the results of the primary analysis, analysis of clinically relevant secondary end-points, the possibility of treatment-by-treatment interactions, the relative burden and cost of the two interventions, the clinical interpretation of the adequacy of the delta, and the possibility that ongoing randomization with a smaller delta might also allow a Statistical Trigger for superiority (with a small effect size). The options following a Statistical Trigger for a pair of Interventions in a Domain with three or more Interventions are more complex. Within a domain with three or more interventions the information provided by the DSMB to the ITSC may include specification of the ordinal rank of the equivalent interventions within the domain. With respect to reporting of Platform Conclusions	different circumstances.

		and adaptations of the domain the following actions are possible: • A pair of equivalent interventions may be compressed into a single group for the purposes of ongoing analysis. Both interventions continue to be interventions that are available within the domain for allocation, but the primary analysis considers the effect of the two interventions as a single group, where a balanced randomization will be assigned to each of the intervention pair within this compressed group. Secondary analyses can continue to be conducted to determine if equivalence is maintained with the possibility of the intervention being restored as individual interventions if results no longer support equivalence. It is acknowledged that re-analysis of the domain immediately following compression of one (or more) pairs of equivalent interventions may result in the occurrence of other Statistical Triggers (e.g. a compressed pair may be superior or inferior to all remaining interventions). Any statistical Trigger that results from compression of one or more pairs will be responded to as outlined in this section with reporting of the cascade of Statistical Triggers. Compression of a pair of interventions can occur with or without reporting of a Platform Conclusion.	

		• Removal of one of the pair of equivalent interventions from the domain, for example the more burdensome or more expensive intervention, which will result in a reporting of a Platform Conclusion. • No change to the interventions within the domain with continuation of RAR. This could be to further evaluate secondary endpoints, a smaller delta of equivalence, or interest in interactions with other interventions. Such changes would require amendment to the DSA. This could occur with or without reporting a Platform Conclusion. Factors that should be taken into account by the DSMB and the ITSC include the results of the primary analysis, analysis of clinically relevant secondary end-points, the possibility of treatment-by-treatment interactions, the relative burden and cost of the two interventions, the clinical interpretation of the adequacy of the delta, the possibility that ongoing randomization with a smaller delta might also allow a Statistical Trigger for superiority (with a small effect size) and the ordinal position of the equivalent pair within the domain. In a domain that comprises three or more interventions, but in which two or more interventions are analyzed in a nested manner, the nested group may be combined for analyses of equivalence. Where compression converts a	

		domain with three or more interventions into a domain with two interventions (and data continues to support equivalence of the compressed interventions) such a domain will be regarded as a two-intervention domain for the purposes of evaluation of Statistical Triggers for superiority, inferiority, and equivalence. If a Platform Conclusion is reached, the ITSC will take responsibility to undertake Public Disclosure as soon as practicable with the dissemination of the research result via presentation or publication or both. There is no automated adaptation when equivalence is deemed to have occurred. Where appropriate each DSWG will produce an operational document, that is publicly accessible, that considers a range of plausible scenarios and provides guidance as to the actions that should occur in the event of a Statistical Trigger for equivalence for different pairs of interventions. If any of these documents are updated, previous versions will be archived but continue to be publicly accessible.	
7.8.10 Analysis set for reporting Page 73	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.	The primary analysis set that will be used for reporting a Public Disclosure will comprise all participants who are analyzed at the time the adaptive analysis that results in the occurrence of a Statistical Trigger.	Changes made to terminology. *In conjunction* changed to *at the time*
7.8.12. Updating model after	Blank	If any variable that contributes to the model is identified	Clarification that

monitoring Page 74		to be inaccurate at a monitoring visit, the data will be corrected and utilized for the next interim analysis. Any change to a previous statistical trigger will be reviewed by the DSMB to determine the implications. The DSMB will advise the ITSC if there is any material change in a Platform Conclusion which, if published, will be reported to the journal as an erratum.	identification of any inaccurate data identified at a monitoring visit will be corrected and incorporated at the next adaptive analysis with correction of any published results, if required.
7.11 Registry of non-randomized patients Page 75	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.	Where this occurs the operation of the registry, including eligibility criteria, ethical issues, and variables that will be collected, will be described in a separate Registry Appendix.	Administrative change to use study nomenclature. The Registry is now an appendix to the Core protocol and not a Domain of the study
7.12 Criteria for termination of the trial Page 75	Frequent adaptive analyzes 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	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	Correction of spelling error. The protocol uses US spelling. The bullet point relating to funding was removed as it was considered self-evident by an EU Competent Authority.

	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	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	
SECTION 8 TRIAL CONDUCT	**Original text**	**New text**	**Reason**
8.6 Unblinding of allocation status Page 79	A system for emergency unblinding will be provided in the DSA of any domain that includes interventions that are administered in a blinded fashion.	A system for emergency unblinding will be provided in the DSA of any domain that includes interventions that are administered in a blinded fashion. Any unblinding process will ensure that the investigator can directly and rapidly unblind in an emergency situation.	Addition of further detail to improve clarity
8.9.2 Variables to be collected Page 81	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.	The generic variables to be collected for all domains in this REMAP are as detailed, indicatively, in the Core Protocol, below. Additional domain-specific variables are outlined in the relevant DSAs. Baseline variables are defined as at or before the time of randomization.	Addition of further detail to improve clarity
8.9.2.1 Baseline and required for randomization Page 81	• Overall REMAP Inclusion / exclusion check list • Date and time of hospital admission • Date and time of first ICU admission • Domain-specific exclusion checklist • Shock • Hypoxemia	• Overall REMAP Inclusion / exclusion check list • Date and time of hospital admission • Date and time of first ICU admission • Domain-specific exclusion checklist • Shock status • Hypoxemia status	Addition of variables to include new Antiviral Domain data and allow for addition of Pandemic Appendix

		• Influenza status • Pandemic status	
8.9.2.2 Baseline but not required for randomization Page 81	• Demographic data (date of birth, age, sex, estimated body weight and height) • Co-existing illnesses and risk factors for pneumonia • Source of ICU admission • Acute Physiology and Chronic Health Evaluation (APACHE) II score • Intervention allocation status within domains and randomization number	• Demographic data (date of birth, age, sex, estimated body weight and height) • Co-existing illnesses and risk factors for pneumonia • Source of ICU admission • Acute Physiology and Chronic Health Evaluation (APACHE) II variables • Sequential Organ Failure Assessment (SOFA) variables • Intervention allocation status within domains and randomization number • Results of microbiological testing	Modification necessary to report against updated sepsis definitions Clarification that results of microbiological testing are platform-level data
8.9.2.3 Daily from randomization until discharge from ICU or day 28 whichever comes first Page 81	• Occurrence of administration of vasopressors/inotropes • Administration of dialysis • Administration of invasive or non-invasive ventilation • P:F ratio components	• Hypotension and administration of vasopressors/inotropes • Administration of dialysis • Administration of invasive or non-invasive ventilation • P:F ratio components	Removal of requirement for *hypotension* which is often not present because of administration of vasopressors and / or inotropes
8.2.9.5 Hospital outcome data Page 82	• Date and time of hospital discharge • Survival status at hospital discharge • Discharge destination	• Date and time of hospital discharge • Survival status at hospital discharge • Discharge destination	Clarification that results of microbiological testing are platform-level data

		• Results of microbiological testing	
8.9.2.6 Antimicrobial Administration Page 82	Blank	8.9.2.6 Antimicrobial Administration • Administration of antibiotic medications • Administration of antiviral medications	Addition for operational reasons and to accommodate antiviral domain, combined antimicrobial administration data collection
8.9.2.7 Outcome data Page 82	• Survival status at 90 days • Survival status at 6 months • HRQoL measured by EQ-5D at 6 months • Disability status measured by WHODAS at 6 months	• Survival status at 90 days • Survival status at 6 months • HRQoL measured by EQ-5D at 6 months • Disability status measured by WHODAS at 6 months and baseline information to interpret disability • Opinions and beliefs regarding participation in research (reported at 6 months)	Addition of *baseline information.* Collection of information about participation in platform from participants following recovery from critical illness
8.9.3 Data required to inform Response Adaptive Randomization Page 82	This REMAP will use frequent adaptive analyzes and incorporate RAR. All variables used to inform RAR will be pre-specified. The key variables include: 1. Baseline a. Unique trial-specific number	This REMAP will use frequent adaptive analyses and incorporate RAR. All variables used to inform RAR will be pre-specified. The key variables include: 1. Baseline and allocation status a. Unique trial-specific number	Correction of spelling error. The protocol uses US spelling. Addition of variables that

	b. Intervention for each revealed domain c. Strata i. Shock or no shock d. State i. Hypoxemia 2. Outcome a. All-cause mortality at 90 days b. For each enrolled domain, whether the allocated status of the intervention(s) to which they were randomized were revealed.	b. Location (Country and Site code) c. Date and time of randomization d. Eligibility for each domain e. Intervention allocation for each domain f. Reveal status for each intervention allocation for each domain g. Age category h. Strata i. Shock or no shock ii. Influenza status iii. Pandemic strata i. State i. Hypoxemia 2. Outcome a. All-cause mortality at 90 days b. Date of hospital discharge	had always been in statistical model but omitted from this list. Corresponds to addition of influenza strata Corresponds to addition of pandemic strata *Date of hospital discharge* added
8.10.1 Source Data Page 83	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.	These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarized into the eCRF), clinical and office charts, laboratory and pharmacy records, radiographs, and correspondence.	Correction of spelling error. The protocol uses US spelling.

8.11.2 Data Monitoring Page 84	Routine monitoring visits will be conducted the frequency of which will be determined by each sites rate of recruitment.	Routine monitoring visits will be conducted the frequency of which will be determined by each site's rate of recruitment.	Spelling correction
8.12 Data safety and monitoring board Page 85	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.	The DSMB will not make design decisions. If the DSMB believes the trial's algorithms are no longer acceptable from an ethical, safety, or scientific point of view it will make recommendations to the ITSC which has ultimate decision-making authority regarding the trial design. Where the DSMB and the SAC agree on a temporary deviation from the study protocol for safety reasons, they are not required to inform the ITSC of this decision. If the DSMB and SAC agree that a permanent change is necessary, the chairs of the DSMB, SAC and ITSC will meet to discuss the best way to proceed to ensure patient safety and the scientific integrity of the trial. Where the SAC and DSMB disagree on the need to deviate from the pre-specified trial design, the DSMB must inform the ITSC of their recommendations and the rationale for these.	Updated definition to clarify the process of communication between the DSMB, SAC & ITSC Addition recommended by statistical consultants based on recent experience with conduct of Bayesian adaptive trials to allow for situation in which specified statistical model does not perform satisfactorily, particularly with respect to participant safety.
8.13.3 Reporting procedures for Serios Adverse Events Page 86	Where an SAE is not a trial end point it should 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	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	Correction of error in grammar - the word *be* added

8.13.5 Attribution of a death to study interventions or study participation Page 87	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.	Where the trial evaluates interactions that are novel and not part of usual standard care the threshold for considering attribution to the novel experimental intervention should be lower than if an intervention is already in widespread use and its safety profile has already been established.	Correction of error in grammar - *evaluations* changed to *evaluates*. The final sentence has been deleted

5.2. Region-specific appendices

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

Section	Original text	New Text	Reason
Front page and whole document header	REMAP-CAP European Region-Specific Appendix Version 2 dated 12 December 2017		
SECTION 1 ABBREVIATIONS	**Original text**	**New Text**	**Reason**
Section 1 abbreviations	blank	AE Adverse event	Abbreviation added (updated in version 2.2)
Section 1 abbreviations	blank	AMG Arzneimittelgesetz (German drug law)	Abbreviation added (updated in version 2.2)
Section 1 abbreviations	blank	CA Competent Authority	Abbreviation added (updated in version 2.2)
Section 1 abbreviations	DIIGN	DGIIN	Correction of error in abbreviation (updated in version 2.1)
Section 1 abbreviations	blank	EC Ethics Committee	Abbreviation added (updated in version 2.2)
Section 1	blank	GDPR General Data Protection Regulation	Abbreviation added

abbreviations			(updated in version 2.2)
Section 1 abbreviations	blank	ICH-GCP International Conference on Harmonization-Good Clinical Practice	Abbreviation added (updated in version 2.2)
Section 1 abbreviations	blank	NET-GER Network Germany	Abbreviation added (updated in version 2.2)
SECTION 2			
General text section 2	blank	Additionally, any of the adjustments made in the protocol as described in Section 5.3.7.7 of the Core Protocol or a change in the statistical evaluation concept will be considered as a substantial amendment of the protocol and will be provided as such to the Ethics Committee (EC) and Competent Authority (CA) for approval and will only be implemented when approval is obtained from EC and CA.	Extra clarification added (updated in version 2.2)
General text section 2	The current version of the Core Protocol, DSAs, RSAs and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org) and the PREPARE Workpackage 5 website (https://www.prepare-europe.eu/About-us/Workpackages/Workpackage-5)	The current version of the Core Protocol, DSAs, RSAs and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org) and the PREPARE Workpackage 5 website (https://www.prepare-europe.eu/About-us/Workpackages/Workpackage-5)	Removed reference to (http://prepare.ersnet.org/workpackages/workpackage-5.aspx). Since protocol is not available here. (updated in version 2.2)

	(http://prepare.ersnet.org/workpackages/workpackage-5.aspx).	~~(http://prepare.ersnet.org/workpackages/workpackage-5.aspx).~~	
2.2. Version History	Version 1: Approved by the Europe Regional Management Committee (Eu RMC) on 20 November 2016 Version 1.1: Approved by the Eu RMC on 09 May 2017 Version 2: Approved by the Eu RMC on 12 December 2017	Version 1: Approved by the Europe Regional Management Committee (Eu RMC) on 20 November 2016 Version 1.1: Approved by the Eu RMC on 09 May 2017 Version 2: Approved by the Eu RMC on 12 December 2017 Version 2.1: Approved by the Eu RMC on 24 May 2018 Version 2.2: Approved by the Eu RMC on 26 October 2018 Version 2.3: Approved by the Eu RMC on 26 March 2019 Version 2.4: Approved by the Eu RMC on 25 April 2019	Protocol version chronology updated (updated in version 2.1 to version 2.4)
SECTION 3. EUROPEAN REGION			
Section 3. European region	• Netherlands (commenced 2016)	• Netherlands ~~(commenced 2016)~~	Commenced 2016 removed (updated in version 2.2)

SECTION 4. EUROPEAN STUDY ADMINISTRATION STRUCTURE			
4.1.1. Responsibilities	Bulletpoint 11 old text: • Data management (in cooperation with Work Package 8 (WP8) of Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE).	Bulletpoint 11 new text: • Data management (in cooperation with Work Package 8 (WP8) of Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE) and SPIRAL Web Solutions Ltd.)	Addition of SPIRAL Web Solutions as additional database. (updated in version 2.2)
4.1.1. Responsibilities	Bullet point 16 old text: • Monitoring and close-out site visits	Bullet point 16 new text: • Initiation, monitoring and close-out site visits	Initiation visit added (updated in version 2.2)
4.2.2.Members	Chair Professor Marc Bonten	~~Chair~~ Co-chairs Professor Marc Bonten Dr. Lennie Derde	Co-chairs are available in the EU for the REMAP-CAP study as of this point. Subsequently Dr. Lennie Derde removed from list of members. (updated in version 2.2)
4.2.2.Members	blank	Professor Mathias Pletz	Mathias Pletzz added to list of members

			(updated in version 3)
4.2.2.Members	Associate Professor Gernot Rohde	~~Associate~~ Professor Gernot Rohde	Title updated (updated in version 2.1)
4.3.2. Project Management	E-mail W.W.Puijk-2@umcutrecht.nl	Email W.W.Puijk-2@umcutrecht.nl	Spelling error corrected (updated in version 2.2)
SECTION 5. Eu REGIONAL MANAGEMENT COMMITTEE AUTHORISATION			
5.	25 April 2019	23 August, 2019	Date signature updated to date according version 3. Intermediate signature dates: • Version 2.1: 24 May 2018 • Version 2.2: 26 October 2018 • Version 2.3 26 March 2019 • Version 2.4: 25 April 2019
SECTION 9. TRIAL DESIGN			

9.2.4. Antiviral Domain	blank	9.2.4. Antiviral Domain This antiviral domain will be offered to any site in this region.	New section added to reflect addition new domain to the REMAP-CAP study. (updated in version 3)
9.2.5. Ventilation Domain	9.2.4. Ventilation Domain	9.2.5. Ventilation Domain	Section number updated (updated in version 3)
9.2.6. Registry	blank	9.2.6. Registry Site(s) participation in the Registry is optional within the EU. Participation is possible by countries, or by regions within countries, where there is an existing healthcare-related registry or database, which routinely captures data on the entire study population specified for the Registry. The study population specified for the Registry comprises adult patients admitted to an ICU for CAP. This population is divided into two mutually exclusive cohorts: those eligible for the platform and assigned treatment within one or more REMAP-CAP domains (“Platform-randomized”) and those who are either platform ineligible or platform eligible but not assigned treatment within one or more REMAP-CAP domains	Information regarding registry added. (updated in version 3)

		("Registry-only"). The purpose of the Registry is to provide limited information on all patients admitted to an ICU with CAP so that the characteristics of patients who are randomized within the Platform ("Platform-randomized") can be compared with the patients with CAP admitted to an ICU at participating sites ("Registry-only"). Registry data will overlap with, but will not be more extensive than, the minimum dataset collected for patients who are randomized within the Platform. The Registry does not specify any interventions and only utilizes the routine data captured for administration and clinical care.	
9.5.Criteria for termination of the trial	• Funding or other necessary support is no longer available	• ~~Funding or other necessary support is no longer available~~	text deleted (updated in version 2.3)
9.5.Criteria for termination of the trial	blank	Current funding within Europe would allow recruitment until 31st January 2021. The last patient last visit in Europe would be 6 months later and would be the end	Clarification regarding criteria for termination of the trial in the EU

		date of the trial in Europe.	(updated in version 2.3)
SECTION 10. TRIAL CONDUCT			
10.2 Pregnancy testing and breastfeeding	blank	For specifically identified countries in the EU, according to local requirements, pregnancy testing is mandatory for female patients of childbearing age. This is necessary because in such countries pregnancy will be a platform-level exclusion criteria, i.e. excludes a patient from receiving a randomization allocation in all domains, but does not exclude the patient from the registry. For specifically identified countries in the EU, according to local requirements, breastfeeding is also a platform-level exclusion criteria, i.e. excludes a patient from receiving a randomization allocation in all domains, but does not exclude the patient from the registry. Countries to which this requirement applies will be listed in operational documents.	Regional requirements regarding pregnancy testing and breastfeeding inserted. (updated in version 2.2)
10.3 Treatment allocation	Central randomization will occur online and be managed and operated by WP8 of PREPARE through the	Central randomization will occur online and be managed and operated ~~by WP8 of PREPARE through the ResearchOnline 2 website (www.researchonline.org)~~ by	Revised information regarding centralized randomization

	ResearchOnline 2 website (www.researchonline.org).	SPIRAL Web Solutions Ltd.. Data management and transfer will comply with GDPR requirements in the country in which a site is located.	implemented. (updated in version 2.2)
10.4. Distribution of study drug	The processes and management of distribution of any possible drug provided by the study, will be outlined in operational documents and, as required, specified in the contract.	The processes and management of distribution of any possible drug provided by the study, will be outlined in operational documents and, as required, specified in the contract. Although the default is the provision of open-label treatments the blinding of treatment status is not precluded within the REMAP. Whether interventions are open-label or blinded will be specified in DSAs.	Clarification regarding distribution of study drugs. (updated in version 2.1)
10.5. Unblinding of allocation status	blank	Unblinding of any blinded treatment by site research staff or the treating clinician should only occur only when it is deemed that knowledge of the actual treatment is essential for further management of the participant. A system for emergency unblinding will be provided in a future DSA of any domain that includes interventions that are administered in a blinded fashion. Any unblinding process will ensure that the investigator can directly and rapidly unblind in an emergency situation. All unblindings and reasons as they occur will be documented in the CRF. Unblinding should not	New section. Description of unblinding procedure inserted. (updated in version 2.1)

		necessarily be a reason for study drug discontinuation.	
10.6. Data collection	10.5. Data collection	10.6. Data collection	Section number updated (updated in version 3)
10.6. Data collection	90will	90 will	Space added between 90 and will. (updated in version 2.2)
10.7. Data management	10. 6.Data management Data will be entered into a secure, password protected web based CRF designed by WP8 of PREPARE, ResearchOnline 2. The Project Managers and the coordinating center will coordinate data entry and data management.	10. 7. Data management ~~Data will be entered into a secure, password protected web based CRF designed by WP8 of PREPARE, ResearchOnline 2. The Project Managers and the coordinating center will coordinate data entry and data management.~~ Data used to establish eligibility will be entered into a secure, password protected web based CRF designed by SPIRAL Web Solutions Ltd., in New Zealand, using a server located in Australia. All allocations and all other data collected in the trial will be entered into a secure, password protected web based CRF designed by WP8 of PREPARE, ResearchOnline 2,	Section number updated Text adapted to reflect centralized randomization (updated in version 2.2)

		Located in the Netherlands. Each subject will be allocated a unique trial number that is used as the common identifier in both databases. Data management and transfer will comply with GDPR requirements in the country in which a site is located. The Project Managers and the coordinating center will coordinate data entry and data management.	
10.8..Trial group linkage / participation	10.7..Trial group linkage / participation	10.8..Trial group linkage / participation	Section number updated (updated in version 3)
10.9. Site start up and initiation	10.8. Site start up and initiation	10.9. Site start up and initiation	Section number updated (updated in version 3)
10.10.. Quality assurance and monitoring	10.9.. Quality assurance and monitoring	10.10.. Quality assurance and monitoring	Section number updated and subsequently all

			subsection numbers. (updated in version 3)
10.10.2. Monitoring	A representative of the UMC Utrecht will monitor the study. Monitoring will be conducted by quality control reviews of protocol compliance, data queries and safety reporting.	A representative of the UMC Utrecht or a local representative at request of the UMC Utrecht will monitor the study. Monitoring will be conducted by quality control reviews of protocol compliance, data queries and safety reporting.	Added local representative for UMCU to better reflect local situation (updated in version 2.2)
10.11. Safety reporting	10.10.. Safety reporting	10.10.. Safety reporting	Section number updated (updated in version 3)
10.10. Safety reporting	Safety reporting will occur as outlined in the Core Protocol Section 8.13. All Serious Adverse Events (SAE) will be recorded in the electronic Case Report Form (eCRF). For sites in Europe, all SAEs must be reported to the coordinating center (UMC Utrecht) via email (prepare_icu@umcutrecht.nl) within 24-hours of the investigators becoming aware of the event. The investigator should notify the Institutional / Ethics	Safety reporting will occur as outlined in the Core Protocol Section 8.13. ~~All Serious Adverse Events (SAE) will be recorded in the electronic Case Report Form (eCRF). For sites in Europe, all SAEs must be reported to the coordinating center (UMC Utrecht) via email (prepare_icu@umcutrecht.nl) within 24-hours of the investigators becoming aware of the event.~~ ~~The investigator should notify the Institutional / Ethics~~	Clarification on requirements on Safety reporting inserted. (updated in version 2.1 and refined in version 3)

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

		relevant Domain Specific Appendix and the relevant Summary of Patient Characteristics referred to.	contraceptive use inserted. (updated in version 2.1)
SECTION 11. ETHICAL CONSIDERATIONS			
11.1. Ethical and regulatory issues	The trial will be conducted in accordance with EU and national legislation relevant in each European country. Research ethics and regulatory authorities approvals will be obtained prior to the start of the study at each institution from the responsible local or national IRB and relevant competent authority. It is the principal investigator's responsibility to ensure that all conditions for approval of the study are met and that amendments to the protocol, or trial design, including new domain specific appendices or serious adverse events are also reported to the IRB as required by that committee and all relevant regulatory authorities.	The trial will be conducted in accordance with EU and national legislation relevant in each European country. Research ethics and regulatory authorities' approvals will be obtained prior to the start of the study at each institution from the responsible local or national IRB and relevant ~~competent authority~~ CA. It is the principal investigator's responsibility to ensure that all conditions for approval of the study are met and that amendments to the protocol, or trial design, including new domain specific appendices or serious adverse events are also reported to the IRB as required by that committee and all relevant regulatory authorities..	Clarification that regulatory approvals also should be obtained when applicable. (updated in version 2.1)
Section 12 MODIFICATIONS			

SPECIFIC TO A NETWORK IN EUROPE			
12.1. Introduction	Blank	This section identifies any issue that is different within a specific network in Europe to vary the protocol in that network from what is specified elsewhere in this RSA or the Core Protocol or both.	Section added to describe local requirements for Germany. (updated in V2.3 and refined in section 2.4)
12.2. Network Germany (NET-GER)	Blank	12.2.1. Recruitment numbers The initial planned enrollment in NET-GER will be 600 participants. 12.2.2. Repeat enrollment A patient who has been enrolled previously in REMAP-CAP is not eligible for re-enrolment in any second or subsequent episode of CAP. 12.2.3. Process for obtaining consent As outlined in Core Protocol and in the Antibiotic and Corticosteroid DSAs, some interventions specified in this	Section added to describe local requirements for Germany. (updated in V2.3 and refined in section 2.4)

		REMAP meet the requirement for emergency indication (§ 41 para. 2 Arzneimittelgesetz (AMG)) that apply to patients who are unable to consent for themselves and, if necessary, without a declaration of consent from the legal representative. The process for establishing participation in Germany for a patient who is not competent to consent is outlined below. Wherever possible, a presumed will of the patient has to be asked for (contact close relatives or existing legal representative). The legal representative is asked for consent. The legal representative is a person with participant's power of attorney or a person appointed by the court. If consent cannot be obtained directly from a legal representative or the legal representative is unavailable, a patient's inability to consent and the urgency of participating in the study must be confirmed by an independent consultant physician. Once this is established by the independent consultant physician, a patient may then be enrolled. To be eligible as an independent consultant physician, the physician must not have any involvement with the trial, must not hold an appointment at the institution that is conducting the	

		trial and must not be a member of the team that is providing care to the patient. The consultant independent physician must document the relevant findings and conclusions in writing. If a patient is enrolled by a determination by an independent consultant physician, the patient's legal representative must be approached to ask for a subsequent declaration of consent or a legal representative has to be appointed by the court. It is the responsibility of the site investigator to identify promptly a suitable person to act as the legal representative and if required submit an application to the appropriate court as soon as possible after randomization. The legal representative can withdraw the participant from the trial at any time. However, data collected before this time will continue to be available and utilized in the analysis of the trial. When an enrolled participant regains competency, their participation should be explained and an opportunity provided to the participant to provide their ongoing consent. The patient can withdraw from participation from the trial at any time. However, data collected before this time will continue to be available and utilized in the analysis of the trial.	

		Patients or their legal representatives can withdraw their consent at any time and without giving reasons and can cancel participation in the study. In such a case, the patient is asked to state the reason for termination, but is advised that this is not necessary to do so. Information as to when and in which study arm a patient was randomized as well as the withdrawal of their consent and time of withdrawal must be documented. In this situation, the patient must also be informed that stored data may be further used, if necessary, to: • determine the effects of the medicinal product to be tested; and • ensure that the legitimate interests of the participant are not prejudiced. 12.2.4. (Serious) Adverse Events Contrary to the Core Protocol 8.13, the following applies to Germany without exception: 12.2.4.1. Definitions According to GCP-V § 3 (31), an Adverse Event (AE) is any adverse event that occurs to a subject who has	

		been administered an investigational product and is not necessarily causally related to that treatment. According to ICH-GCP, these may be signs of disease (including e.g. abnormal laboratory values), diseases or symptoms associated with the use of an investigational product. This is independent of whether the event is causally related to the investigational product or not. According to GCP-V § 3 (31), a Serious Adverse Event (SAE) or a Serious Adverse Reaction (SAR) is any adverse event or adverse reaction that is fatal, life-threatening, requires hospitalization or prolongation of treatment, results in permanent or serious disability or disability, or results in congenital anomaly or birth defect. 12.2.4.2. Documentation and Reporting The documentation and notification obligations according to GCP-V §12 (4) - (6) shall be strictly observed. All adverse non-serious and serious events must be recorded completely with the study data, regardless of whether a causal relationship with the investigational drug or the study procedures can be assumed. All	

		events that are not documented as part of the endpoint capture must be documented using the AE form of the eCRF. Medical or surgical procedures are not documented as AEs, but rather the disease that led to the necessary intervention. Daily variations in the clinical picture as well as the usual progression of severe CAP are not listed as AEs. Diseases that already exist before inclusion in the study are not considered an AE, but an accompanying disease (documented in medical history). The clinically relevant worsening of a pre-existing condition that is not associated with severe CAP is considered an adverse event. A measure to treat a pre-existing condition that was planned prior to inclusion in the study is not considered an adverse event. For AEs, a description (medical term), start, end, causality, measures for handling the investigational drug and the event as well as the outcome are documented. Each AE must be checked for the criteria of an SAE and, if necessary, the SAE reporting procedure must be followed (see Section 10.11.).	

5.3. Domain-specific appendices

5.3.1. REMAP-CAP Antibiotic Domain-Specific Appendix Version 3 dated 10 July 2019

Section	Original text	New Text	Reason
Front page and whole document header	REMAP-CAP Antibiotic Domain-Specific Appendix Version 2 dated 12 December 2017	REMAP-CAP Antibiotic Domain-Specific Appendix Version 3 dated 10 July 2019	Administrative change to version and date
SUMMARY	**Original text**	**New Text**	**Reason**
Page 2	In this domain of the REMAP-CAP trial, participants with community-acquired pneumonia admitted to participating intensive care units will be randomized to receive one of up to 5 antibiotic interventions depending on availability and acceptability:	In this domain of the REMAP-CAP trial, participants with community-acquired pneumonia admitted to participating intensive care units requiring empiric antibiotic therapy will be randomized to receive one of up to 5 antibiotic interventions depending on availability and acceptability:	Addition of text to improve clarity of Domain cohort definition
Unit of analysis and strata Page 3	Analysis and Response Adaptive Randomization are by strata (shock) to allow for strata-by-intervention interaction	There is one unit-of-analysis in this domain. Analysis and Response Adaptive Randomization are applied to all randomized patients with no by strata utilized.	Modification so that strata are applied in the antibiotic domain, i.e. there is a single group (all randomized patients) and the model does not incorporate evaluation of differential treatment effect in any strata. This better preserves statistical power and content experts prior

			belief was that differential treatment effect by current strata was unlikely.
Evaluable treatment-by-treatment Interactions Page 3	Intervention-intervention interactions will be evaluated between beta-lactam antibiotic interventions in this domain and interventions in the Macrolide Duration Domain; and between all interventions in this domain and the Corticosteroid Domain.	No interactions will be evaluated with any other domain.	No interactions are evaluated with any other domain. This better preserves statistical power and content experts prior belief was that interaction with treatments in other current domains was unlikely.
Nesting Page 3	Blank	There is one nest, comprising Ceftriaxone + Macrolide, Piperacillin-tazobactam + Macrolide, Ceftaroline + Macrolide, and Amoxicillin-clavunate + Macrolide.	Specifies that all beta-lactam antibiotics will be evaluated within a single nest
Timing of reveal Page 3	Randomization with Immediate Reveal of allocation and Initiation	Randomization with Immediate Reveal and Initiation	Administrative change - *of allocation* removed for consistency of nomenclature
Domain-Specific exclusions Page3	• 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	• 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	Final bullet point removed *Chronic pneumonia* has been moved from a domain-level to platform-level exclusion.

	suppurative lung disease where infection with Pseudomonas may be suspected but does not include patients with suspected methicillin-resistant staphylococcus aureus (MRSA) infection (see MRSA below). - Febrile neutropenia or significant immunosuppression (including organ or bone marrow transplantation, human immunodeficiency virus (HIV) Infection with CD4 cell count <200 cells/µL, systemic immunosuppressive, systemic corticosteroids comprising prednisolone, or equivalent, ≥20mg/day for > 4 preceding weeks). - Suspected melioidosis (tropical sites during melioidosis season – see melioidosis below) - Chronic pneumonia (more than 2-weeks of symptoms) or where non-bacterial pneumonia is suspected (including fungal pneumonia, tuberculosis).	suppurative lung disease where infection with Pseudomonas may be suspected but does not include patients with suspected methicillin-resistant staphylococcus aureus (MRSA) infection (see MRSA below). - Febrile neutropenia or significant immunosuppression (including organ or bone marrow transplantation, human immunodeficiency virus (HIV) Infection with CD4 cell count <200 cells/µL, systemic immunosuppressive, systemic corticosteroids comprising prednisolone, or equivalent, ≥20mg/day for > 4 preceding weeks). - Suspected melioidosis (tropical sites during melioidosis season – see melioidosis below) - There is specific microbiological information to guide specific antibacterial therapy	
Outcome measures Page 4	Serious adverse event (SAE) as defined in CORE protocol	Serious Adverse Events (SAE) as defined in CORE protocol	Administrative change to use study nomenclature
SECTION 1 ABBREVIATIONS	**Original text**	**New Text**	**Reason**
Page 8	ATS American Thoracic Society CAP Community Acquired Pneumonia	ATS American Thoracic Society CAP Community Acquired Pneumonia	Updated with all abbreviations used in this

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

	RAR Response Adaptive Randomization RSA Region-Specific Appendix RSV Respiratory Syncytial Virus SAE Serious Adverse Event Severe CAP Severe Community Acquired Pneumonia VRE Vancomycin Resistant Enterococci	Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia RAR Response Adaptive Randomization RSA Region-Specific Appendix RSV Respiratory Syncytial Virus SAE Serious Adverse Event ~~Severe CAP Severe Community Acquired Pneumonia~~ VRE Vancomycin Resistant Enterococci	
SECTION 3 ANTIBIOTIC DOMAIN-SPECIFIC APPENDIX VERSION	**Original text**	**New Text**	**Reason**
3.1 Version History Page 11	Version 1: Approved by the Antibiotic Domain-Specific Working Group (DSWG) on 18 November 2016 Version 1.1: Approved by the Antibiotic DSWG on 30 March 2017 Version 2: Approved by the Antibiotic DSWG on 12 December 2017	Version 1: Approved by the Antibiotic Domain-Specific Working Group (DSWG) on 18 November 2016 Version 1.1: Approved by the Antibiotic DSWG on 30 March 2017 Version 2: Approved by the Antibiotic DSWG on 12 December 2017 Version 3: Approved by the Antibiotic DSWG on 10 July 2019	Updated with new version details
SECTION 4 ANTIBIOTIC DOMAIN GOVERNANCE	**Original text**	**New Text**	**Reason**
4.1 Domain members Page 11	Professor Richard Beasley Professor Marc Bonten	Professor Richard Beasley Professor Marc Bonten	Updated to all current members

	Dr. Lennie Derde Dr. Robert Fowler Associate Professor David Gattas Associate Professor Peter Kruger Dr. Colin McArthur Dr. Steve McGloughlin Dr. Susan Morpeth Professor Alistair Nichol Ms. Genevieve O'Neill Professor David Paterson Associate Professor Gernot Rohde Professor Steve Webb	Dr. Nick Daneman Dr. Lennie Derde Dr. Robert Fowler Associate Professor David Gattas Professor Anthony Gordon Mr. Cameron Green Associate Professor Peter Kruger Dr. Colin McArthur Dr. Steve McGloughlin Dr. Susan Morpeth Dr. Srinivas Murthy Professor Alistair Nichol ~~Ms. Genevieve O'Neill~~ Professor David Paterson Professor Mathias Pletz Associate Professor Gernot Rohde Professor Steve Webb	
4.2 Contact details Page 12	Fax +61 3 9903 0247	Blank	Fax number deleted
SECTION 6 BACKGROUND AND RATIONALE	**Original text**	**New Text**	**Reason**
6.1 Domain definition Page 13	This is a domain within REMAP-CAP to test the effectiveness of different empiric antibiotic treatments in patients with severe community-acquired pneumonia (severe CAP) who are admitted	This is a domain within REMAP-CAP to test the effectiveness of different empiric antibiotic treatments in patients with severe community-acquired pneumonia (CAP) who are admitted to an	The word *severe* deleted

	to an Intensive Care Unit (ICU).	Intensive Care Unit (ICU).	
6.2 Domain-specific background Page 13	Antibiotics are an essential component of therapy for all patients with suspected or proven community-acquired pneumonia (CAP).	Antibiotics are an essential component of therapy for all patients with suspected or proven CAP.	The words *community-acquired pneumonia* deleted
6.2.1 Microbiology of CAP Page 13	Pathogens associated with outbreaks include Legionella spp, viral pathogens (particularly in closed environments such as cruise ships and institutions) and emerging infectious diseases such as Middle East Respiratory Syndrome coronavirus.	Pathogens associated with outbreaks include Legionella spp, viral pathogens (particularly in closed environments such as cruise ships and institutions) and emerging infectious diseases such as Middle East Respiratory Syndrome (MERS) coronavirus.	Addition of acronym *MERS*
6.2.2 Table 2 Page 15	Respiratory fluoroquinolone AND aztre onam	Respiratory fluoroquinolone AND aztreonam	Correction of spelling error.
SECTION 7 DOMAIN OBJECTIVES	**Original text**	**New Text**	**Reason**
Page 19	The objective of this domain is to determine the comparative effectiveness of different antibiotics or antibiotic combinations in the empiric treatment of severe CAP. We hypothesize that the probability of all-cause mortality at 90 days will differ based on the empiric antibiotic treatment received. The current antibiotic and antibiotic combinations that will be available to be tested are: • Ceftriaxone + Macrolide • Moxifloxacin or Levofloxacin • Piperacillin-tazobactam + Macrolide	The objective of this domain is to determine the comparative effectiveness of different antibiotics or antibiotic combinations for patients with severe CAP requiring empiric antibiotic therapy. We hypothesize that the probability of all-cause mortality at 90 days after enrollment will differ based on the allocated empiric antibiotic treatment. The following interventions will be available: • Ceftriaxone + Macrolide • Moxifloxacin or Levofloxacin • Piperacillin-tazobactam + Macrolide • Ceftaroline + Macrolide	Changes in language to improve clarity of Antibiotic Domain objective definition

	• Ceftaroline + Macrolide • Amoxicillin-clavulanate + Macrolide We hypothesize that the treatment effect of different empiric antibiotic and antibiotic combinations is different depending on the presence or absence of shock at the time of enrollment (strata-by-intervention interaction). We hypothesize that the treatment effect of different empiric beta-lactam agents is different depending on the duration of concomitant treatment with a macrolide. This is an intervention by intervention interaction between the beta-lactam antibiotic options in this domain and the Macrolide Duration Domain (i.e. the Macrolide Duration Domain is nested within the beta-lactam antibiotic interventions in this domain). We hypothesize that the treatment effect of different antibiotic choices is different depending on whether corticosteroids are administered. This is an intervention by intervention interaction between the Antibiotic Domain and the Corticosteroid Domain.	• Amoxicillin-clavulanate + Macrolide	Three previous hypotheses deleted as these related to treatment-strata and treatment-treatment interactions that are no longer being evaluated in the statistical model. This decision was based on simulations and continuing to have these hypotheses had an adverse impact on statistical power to evaluate primary hypothesis.
SECTION 8 TRIAL DESIGN	**Original text**	**New Text**	**Reason**
Page 20	This domain will be conducted as part of a REMAP-CAP trial of CAP (see Core Protocol Section 7). Treatment	This domain will be conducted as part of the REMAP-CAP trial (see Core Protocol Section 7). Treatment	Correction of errors in grammar – *a* changed to *the*

	allocation will be adaptive, as described in the Core Protocol Section 7.5.2.	allocation will be adaptive, as described in the Core Protocol Section 7.5.2.	and unnecessary words, *of CAP,* deleted
8.2 Eligibility criteria Page 20	Patients are eligible for this domain if they meet all of the REMAP-level inclusion and none of the REMAP-level exclusion criteria (see Core Protocol Section 7.4). Patients who may be eligible for the REMAP may have conditions that may exclude them from the Antibiotic Domain, or from one or more of the individual interventions available within this domain.	Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria (see Core Protocol Section 7.4). Patients eligible for the REMAP may have conditions that exclude them from the Antibiotic Domain, or from one or more of the individual interventions available within this domain.	Correction of errors in grammar – *REMAP* changed to *platform* and words *who may be* and *may* deleted
8.2.1 Domain inclusion criteria Page 20	Blank	Nil	Added to clarify that there are no inclusion criteria
8.2.2 and 8.2.3 Domain exclusion criteria Page 20 and 21	8.2.2 Exclusion criteria from this domain 8.2.3 Exclusion criteria from this domain	8.2.2 Domain exclusion criteria 8.2.3 Domain exclusion criteria	Changed for consistency in protocol nomenclature
8.2.2 Domain exclusion criteria Page 20	• A specific antibiotic choice is indicated, for example: - Suspected or proven concomitant infection such as meningitis - Suspected or proven infection with resistant bacteria where agents being trialed would not be expected to be active. This includes cystic fibrosis, bronchiectasis or other chronic suppurative lung disease where infection with Pseudomonas may be suspected but does not include patients with suspected	• A specific antibiotic choice is indicated, for example: - Suspected or proven concomitant infection such as meningitis - Suspected or proven infection with resistant bacteria where agents being trialed would not be expected to be active. This includes cystic fibrosis, bronchiectasis or other chronic suppurative lung disease where infection with Pseudomonas may be suspected but does not include patients with suspected	*Chronic pneumonia* example deleted (as no longer a domain-level exclusion) and one new example added based on operational experience Correction of error in grammar – *below"interventions"* changed

	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) - Chronic pneumonia (more than 2-weeks of symptoms) or where non-bacterial pneumonia is suspected (including fungal pneumonia, tuberculosis) • The treating clinician believes that participation in the domain would not be in the best interests of the patient MRSA: Patients in whom MRSA might be suspected should be included (below "interventions" Section 8.3).	methicillin-resistant staphylococcus aureus (MRSA) infection (see MRSA below). - Febrile neutropenia or significant immunosuppression (including organ or bone marrow transplantation, human immunodeficiency virus (HIV) Infection with CD4 cell count <200 cells/µL, systemic immunosuppressive, systemic corticosteroids comprising prednisolone, or equivalent, ≥20mg/day for > 4 preceding weeks). - Suspected melioidosis (tropical sites during melioidosis season – see melioidosis below) - There is sufficient microbiological information to guide specific antibacterial therapy • The treating clinician believes that participation in the domain would not be in the best interests of the patient MRSA: Patients in whom MRSA might be suspected should be included (see Section 8.3).	to *see*
8.3.1 Interventions Page 22	Patients will be randomly assigned to receive one of the following study interventions.	Patients will be randomly assigned to receive one of the following open-label study interventions.	The words *open-label* added to improve clarity of study

			interventions definition
8.3.4 Duration of administration of antibiotics Page 24	• Change to oral antibiotics once patient is clinically stable • Change to a targeted antibiotic therapy if a microbiological diagnosis has been made • Cease antibiotics if an alternative diagnosis is made • Cease antibiotics when there is evidence of sufficient clinical improvement, no microbiological diagnosis has been made and no clinical evidence of deep infection (e.g. empyema or lung abscess). The duration of antibiotic therapy will be decided by the treating clinician and local guidelines.	• Change to enteral antibiotics once patient is clinically stable • Change to a targeted antibiotic therapy if a microbiological diagnosis has been made • Cease antibiotics if an alternative diagnosis is made • Cease antibiotics when there is evidence of sufficient clinical improvement, no microbiological diagnosis has been made and no clinical evidence of deep infection (e.g. empyema or lung abscess). The duration of antibiotic therapy will be decided by the treating clinician and local guidelines. • Discontinuation if the patient experiences a serious adverse event (SAE) that is thought to be related to a study drug	The word *oral* changed to *enteral* for consistency in terminology and additional criterion added to definition
8.5.2 Secondary endpoints Page 25	Multi-resistant organisms (MRO) colonization/infection: Isolation of multi-drug resistant (MDR) bacteria from clinical or screening specimens including vancomycin resistant enterococci (VRE), methicillin-resistant Staphylococcus aureus (MRSA),	Multi-resistant organisms (MRO) colonization/infection: Isolation of multi-drug resistant (MDR) bacteria from clinical or screening specimens including vancomycin resistant enterococci (VRE), MRSA,	The words *methicillin-resistant Staphylococcus aureus* deleted; abbreviation only used
SECTION 9 TRIAL CONDUCT	**Original text**	**New Text**	**Reason**
9.2.1 Clinical data collection Page 26	Additional domain-specific data will be collected. • Risk factors for aspiration – neuromuscular weakness, hazardous alcohol intake	Additional domain-specific data will be collected. • Isolation or detection of MROs • C. difficile isolation from feces	Three criteria deleted as now included as platform-level data and *isolation or*

	• Selected microbiological results • Antimicrobial susceptibility results • C. difficile isolation from feces		*detection of MROs,* which is a sub-set of selected microbiological results that is not collected at platform-level.
9.3 Criteria for discontinuation Page 26	Refer to Core Protocol Section 8.7 for discontinuation criteria for participation in REMAP-CAP. Once a bacterial pathogen has been isolated, then it is expected that antimicrobial therapy will be modified but patients will continue in the trial.	Refer to Core Protocol Section 8.7 for criteria for discontinuation of participation in the trial.	Correction of errors in grammar – first sentence reworded. Second sentence deleted to avoid confusion between continuation in trial on study treatment compared with continuation on trial for data collection
SECTION 10 STATISTICAL CONSIDERATIONS	**Original text**	**New Text**	**Reason**
10.2 Unit-of-analysis and strata Page 27	10.2. Strata Both analysis of treatment effect and the Response Adaptive Randomization (RAR) will utilize the stratum of shock in this domain.	10.2. Unit-of-analysis and strata The unit-of-analysis for this domain is all patients who receive an allocation status in this domain. No strata are applied in the model that is used for analysis and specification of Response Adaptive Randomization (RAR).	Specification that the unit-of-analysis is all randomized patients with no application of strata in this domain.
10.3 Timing of revealing of randomization	(see section 7.8.3.4 in Core Protocol)	(see section 7.8.3.6 in Core Protocol)	Administrative change to correct paragraph

status Page 27			
10.4. Interactions with interventions in other domains Page 27	An a priori interaction with the beta-lactam antibiotics and the Macrolide Duration Domain is considered possible and will be incorporated into the statistical models used to analyze this domain. An a priori interaction with the Corticosteroid Domain is considered possible and will be incorporated into the statistical models used to analyze this domain. No interaction is evaluable between the Ventilation Domain and this domain.	An a priori interaction with the beta-lactam antibiotics and the Macrolide Duration Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain. An a priori interaction with the Corticosteroid Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain. An a priori interaction with the Antiviral Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain. No interaction is evaluable between the Ventilation Domain and this domain.	Specification that no treatment-treatment interactions are evaluated in the operative statistical model.
10.5 Nesting of interventions Page 28	Blank	There is one nest within this domain, comprising ceftriaxone + macrolide, piperacillin-tazobactam + macrolide, amoxicillin-clavulanate + macrolide, and ceftaroline + macrolide (see Section 7.8.3.8 in Core Protocol). The rationale for this is that each of these interventions comprises a beta-lactam antibiotic combined with a macrolide. The Macrolide component contributes to all interventions and the beta-lactam agents are all members of the same class of antibiotic.	Specification that beta-lactam antibiotics, from the same class of antibiotics, will be evaluated as a nest.
10.6. Threshold	Blank	The threshold odds ratio for equivalence in this	Specification of the default

odds ratio delta for equivalence Page 28		domain is that specified in the Core Protocol (Section 7.8.8).	odds ratio for equivalence
10.7 Post-trial sub-groups Page 28	Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The a priori sub-groups of interest include: • The causative organism, in patients from whom a microbiological diagnosis for the qualifying pneumonia has been made on the basis of culture or other investigations (nucleic acid testing, urinary antigen testing). • Patients with risk factors for aspiration pneumonia (neuromuscular weakness, hazardous alcohol use) • Elderly (≥65 years) and non-elderly (<65 years) patients • Chronic Obstructive Pulmonary Disease (COPD)	Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The a priori patient sub-groups of interest are: • The causative organism, in patients from whom a microbiological diagnosis for the qualifying pneumonia has been made on the basis of culture or other investigations (nucleic acid testing, urinary antigen testing). • Risk factors for aspiration pneumonia (neuromuscular weakness, hazardous alcohol use) • Elderly (≥65 years) and non-elderly (<65 years) • Chronic Obstructive Pulmonary Disease (COPD) • Shock strata • Influenza strata • All potentially evaluable treatment-by-treatment interactions with other domains	Correction of errors in grammar and three sub-groups added which correspond to the strata variables which are no longer applied in this domain and treatment-treatment interactions which are also no longer applied in this domain
SECTION 11 ETHICAL CONSIDERATIONS	**Original text**	**New Text**	**Reason**
11.2 Potential domain-specific adverse events Page 29	Other SAEs should reported only where, in the opinion of the site-investigator, the event might reasonably have occurred as a consequence of a study	Other SAEs should be reported only where, in the opinion of the site-investigator, the event might reasonably have occurred as a consequence of a study	Correction of error in grammar – the word *be* added

	intervention or study participation	intervention or study participation	
SECTION 12 GOVERNANCE ISSUES	**Original text**	**New Text**	**Reason**
12.1 Funding of domain Page 30	The REMAP trial is funded by an Australian National Health and Medical Research Council project grant (APP1101719), a European Union 7th Framework Programme for Research and Technological Development grant (602525) and a Health Research Council New Zealand Programme grant (16/631).	Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. This domain has not received any additional domain-specific funding.	Updated with Domain-specific funding information only. Overall trial funding information deleted because this is in the Core protocol
12.2 Funding of domain interventions and outcome measures Page 30	12.2. Funding of domain interventions	12.2. Funding of domain interventions and outcome measures	Clarification of heading

5.3.2. REMAP-CAP Macrolide Duration Domain-Specific Appendix Version 3, dated 10 July 2019

Section	Original text	New Text	Reason
Front page and whole document header	REMAP-CAP Macrolide Duration Domain-Specific Appendix Version 2 dated 12 December 2017	REMAP-CAP Macrolide Duration Domain-Specific Appendix Version 3 dated 10 July 2019	Administrative change to version and date
SUMMARY	**Original text**	**New Text**	**Reason**
Page 2	In this domain of the REMAP-CAP trial, participants with community-acquired pneumonia admitted to intensive care units will be randomized to receive: • Short course macrolide (for 3 days) • Extended course macrolide (for 14 days)	In this domain of the REMAP-CAP trial, participants with community-acquired pneumonia admitted to intensive care units and allocated to receive a beta-lactam antibiotic intervention in the Antibiotic Domain will be randomized to receive: • Standard course macrolide (for 3 to 5 days) • Extended course macrolide (for 14 days)	*Short* course changed to *standard* course throughout to reflect variation in practice at participating sites and duration of standard course extended to maximum of 5 days to reflect variation in how quickly results of microbiological tests become available at different participating sites.
Interventions Page 3	Short course macrolide discontinued after 3 days unless there is confirmed or strongly suspected microbiological cause for prolonged administration	Standard course macrolide discontinued after 3 to 5 days unless there is confirmed or strongly suspected microbiological cause for prolonged administration	Updated nomenclature and duration of standard course
Unit-of-analysis and Strata Page 3	Analysis and Response Adaptive Randomization are by strata (shock) to allow for strata-by-intervention interaction	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.	Modification so that strata are applied in the antibiotic domain, i.e. there is a single group (all randomized

			patients) and the model does not incorporate evaluation of differential treatment effect in any strata. This better preserves statistical power and content experts prior belief was that differential treatment effect by current strata was unlikely.
Evaluable treatment-by-treatment Interactions Page 3	Intervention-intervention interactions will be evaluated between interventions in this domain and the beta-lactam antibiotic interventions in the Antibiotic Domain and between interventions in this domain and the Corticosteroid Domain.	No interactions will be evaluated with any other domain.	No interactions are evaluated with any other domain. This better preserves statistical power and content experts prior belief was that interaction with treatments in other current domains was unlikely.
Nesting Page 3	Blank	None	Nesting is not possible in a domain with two interventions
Timing of Reveal Page 3	Randomization with Immediate Reveal and Delayed Initiation (with reveal and initiation only occurring after consent or agreement for participation is obtained)	Randomization with Deferred Reveal	Change, outlined in Core Protocol, that describes modification of method of reveal of allocation status

Domain-Specific Exclusions Page 3	Domain exclusions: • The treating clinician believes that participation in the domain would not be in the best interests of the patient	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	Operationalization of the macrolide domain has been reorganized on the basis of feedback from sites to make it easier and safer to implement. It is no longer 'intention' to provide short course (contingent on yet to be available microbiological results), rather it waits for microbiological results to be available. At that point, these modified exclusion criteria are applied. The requirement for consent is unchanged. The requirement to already have excluded a microbiological reason for exclusion from domain is unchanged in principle, but applied at a better time-point. Exclusion for already having ceased macrolide is now

			necessary, because of delayed assessment of other exclusion criteria. The best interests statement is unchanged, but now applied, more appropriately at time of reveal of allocation status.
SECTION 1 ABBREVIATIONS	**Original text**	**New Text**	**Reason**
Page 6	CAP Community Acquired Pneumonia CCU Coronary Care Unit COPD Chronic Obstructive Pulmonary Disease DC Direct Current DSA Domain-Specific Appendix DSWG Domain-Specific Working Group DSMB Data Safety and Monitoring Board ICU Intensive Care Unit IDSA Infectious Diseases Society of America ITSC International Trial Steering Committee IV Intravenous O2 Oxygen PCR Polymerase Chain Reaction RAR Response Adaptive Randomization RCT Randomized Controlled Trial	ATS American Thoracic Society CAP Community Acquired Pneumonia ~~CCU Coronary Care Unit~~ COPD Chronic Obstructive Pulmonary Disease ~~DC Direct Current~~ DSA Domain-Specific Appendix DSWG Domain-Specific Working Group DSMB Data Safety and Monitoring Board ICU Intensive Care Unit IDSA Infectious Diseases Society of America ISIG International Statistics Interest Group ITSC International Trial Steering Committee IV Intravenous ~~O2 Oxygen~~ ~~PCR Polymerase Chain Reaction~~	Updated with all abbreviations used in this version of the document

	REMAP Randomized, Embedded, Multifactorial Adaptive Platform trial REMAP-CAP Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia RSA Region-Specific Appendix SAE Serious Adverse Event Severe CAP Severe Community Acquired Pneumonia	RAR Response Adaptive Randomization RCT Randomized Controlled Trial REMAP Randomized, Embedded, Multifactorial Adaptive Platform trial REMAP-CAP Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia RSA Region-Specific Appendix SAE Serious Adverse Event ~~Severe CAP Severe Community Acquired Pneumonia~~	
SECTION 3 MACROLIDE DURATION DOMAIN-SPECIFIC APPENDIX VERSION	**Original text**	**New Text**	**Reason**
3.1 Version history Page 8	Version 1: Approved by the Macrolide Duration Domain-Specific Working Group (DSWG) on 20 November 2016 Version 1.1: Approved by the Macrolide Duration DSWG on 30 March 2017 Version 2: Approved by the Macrolide Duration DSWG on 12 December 2017	Version 1: Approved by the Macrolide Duration Domain-Specific Working Group (DSWG) on 20 November 2016 Version 1.1: Approved by the Macrolide Duration DSWG on 30 March 2017 Version 2: Approved by the Macrolide Duration DSWG on 12 December 2017 Version 3: Approved by the Macrolide Duration DSWG on 10 July 2019	Updated with new version details
SECTION 4	**Original text**	**New Text**	**Reason**

MACROLIDE DURATION DOMAIN GOVERNANCE			
4.1 Domain Members Page 8	Professor Richard Beasley Professor Marc Bonten Dr. Lennie Derde Dr. Robert Fowler Associate Professor David Gattas Associate Professor Peter Kruger Dr. Colin McArthur Dr. Steve McGloughlin Dr. Susan Morpeth Professor Alistair Nichol Ms. Genevieve O'Neill Professor David Paterson Associate Professor Gernot Rohde Professor Steve Webb	Professor Richard Beasley Professor Marc Bonten Dr. Nick Daneman Dr. Lennie Derde Dr. Robert Fowler Associate Professor David Gattas Professor Anthony Gordon Mr. Cameron Green Associate Professor Peter Kruger Dr. Colin McArthur Dr. Steve McGloughlin Dr. Susan Morpeth Dr. Srinivas Murthy Professor Alistair Nichol Professor David Paterson Professor Mathias Pletz Associate Professor Gernot Rohde Professor Steve Webb	Updated to all current members
4.2 Contact details Page 9	Fax +61 3 9903 0247	Blank	Fax number deleted
SECTION 6 BACKGROUND AND RATIONALE	**Original text**	**New Text**	**Reason**

6.1 Domain definition Page 10	This is a domain within the REMAP-CAP to test the effectiveness of different durations of macrolide administration in patients with severe community-acquired pneumonia (severe CAP) who are admitted to an Intensive Care Unit (ICU).	This is a domain within the REMAP-CAP to test the effectiveness of different durations of macrolide administration in patients with severe community-acquired pneumonia (CAP) who are admitted to an Intensive Care Unit (ICU).	The word *severe* deleted
6.2 Domain-specific background Page 10	Antibiotics are an essential component of therapy for all patients with suspected or proven community-acquired pneumonia (CAP). In patients with sepsis (including pneumonia) requiring admission to intensive care with organ dysfunction, guidelines recommend initiation of antibiotics within 60 minutes of presentation.	Antibiotics are an essential component of therapy for all patients with suspected or proven CAP. In patients with sepsis (including pneumonia) requiring admission to intensive care with organ dysfunction, guidelines recommend initiation of antibiotics within 60 minutes of presentation.	The words *community-acquired pneumonia* deleted for consistency with study nomenclature
6.2.1. Guidelines recommend either macrolides or quinolones to treat "atypical" respiratory pathogens Page 10	Macrolide antibiotics include azithromycin (available for intravenous (IV) or enteral administration), clarithromycin (available for IV or oral administration), roxithromycin (available only for enteral administration), and erythromycin (available for IV or oral administration). Erythromycin is an older macrolide, the use of which has declined substantially.	Macrolide antibiotics include azithromycin (available for intravenous (IV) or enteral administration), clarithromycin (available for IV or enteral administration), roxithromycin (available only for enteral administration), and erythromycin (available for IV or enteral administration). Erythromycin is an older macrolide, the use of which has declined substantially.	The word *oral* changed to *enteral* for accuracy. *Oral* is a subset of enteral administration, with enteral also including administration by a gastric tube.
6.2.1. Guidelines recommend either macrolides or quinolones to treat "atypical" respiratory	Studies suggest a wide diversity of antibiotic regimens are used for pneumonia in Europe; the most common antibiotics used included penicillin/beta-lactamase inhibitors, macrolides, quinolones and third	Studies suggest a wide diversity of antibiotic regimens are used for pneumonia in Europe; the most common antibiotics used include penicillin/beta-lactamase inhibitors, macrolides, quinolones and third	Correction of error in grammar – *included* changed to *include* and rewording to improve grammar

pathogens Page 12	generation cephalosporins, broad spectrum penicillins and second generation cephalosporins but there is little information available about the duration of macrolide therapy when macrolides are used. If a macrolide is included in the choice of empiric antibiotics it is typically continued if an 'atypical' cause of pneumonia is identified. It usually requires several days for the results of microbiological tests to be available and so usual practice is to continue a macrolide antibiotic, for several days, until the results of such tests are available and to then cease the macrolide unless 'atypical' pneumonia is confirmed or strongly suspected.	generation cephalosporins, broad spectrum penicillins and second generation cephalosporins but there is little information available about the duration of macrolide therapy when macrolides are used. If a macrolide is included in the choice of empiric antibiotics it is typically continued if an 'atypical' cause of pneumonia is identified. The time interval for the results of microbiological tests to become available varies between sites, but at the vast majority of sites results for tests of Legionella and other atypical organisms are available before day 3 to 5. It is usual practice is to continue a macrolide antibiotic until the results of such tests are available and to then cease the macrolide unless 'atypical' pneumonia is confirmed or strongly suspected.	Explanation for modification to allow reveal up to study day 5 because of feedback from some participating sites that it may take up until day 5 for the results of relevant microbiological tests to become available.
SECTION 7 DOMAIN OBJECTIVES	**Original text**	**New Text**	**Reason**
Page 15	The objective of this domain is to determine the effectiveness of short course versus extended course macrolide treatment, in patients co-treated with a beta-lactam antibiotic in the treatment of severe CAP. The interventions that will be compared are: • Short course macrolide discontinued after 3 days	The objective of this domain is to determine the effectiveness of standard course versus extended course macrolide treatment, in patients co-treated with a beta-lactam antibiotic who do not have a known microbiological indication for administration of extended course of macrolide, in the treatment of	Changed definition from *short* to *standard* course (reason outline previously in summary section, above) Objective reframed to take into account change in

	unless there is confirmed or strongly suspected microbiological cause for prolonged administration • Extended course macrolide for 14 days or hospital discharge, whichever occurs first Azithromycin is the preferred macrolide but at sites where azithromycin is not available, the use of other macrolides will be permitted (see Section 8.3). We hypothesize that the probability of all-cause mortality at 90 days will differ depending on the duration of administration of a macrolide. We hypothesize that the treatment effect of extended macrolide duration is different depending on the presence or absence of shock at the time of enrollment (strata-by-intervention interaction). We hypothesize that the treatment effect extended macrolide duration is different depending on the different empiric beta-lactam antibiotic that is administered. This is an intervention by intervention interaction between this domain and the beta-lactam antibiotic options in the Antibiotic Domain (i.e. the macrolide duration domain is nested within the beta-lactam antibiotic interventions in the Antibiotic Domain). We hypothesize that the treatment effect of extended	severe CAP. We hypothesize that the probability of all-cause mortality at 90 days after enrollment will differ based on the duration of administration of a macrolide. The following interventions will be available: • Standard course macrolide discontinued between day 3 and day 5 • Extended course macrolide for 14 days or hospital discharge, whichever occurs first Azithromycin is the preferred macrolide but at sites where azithromycin is not available, the use of other macrolides will be permitted (see Section 8.3).	population due to changed exclusion criteria. Three hypotheses deleted as these related to treatment-strata and treatment-treatment interactions that are no longer being evaluated in the statistical model. This decision was based on simulations and continuing to have these hypotheses had an adverse impact on statistical power to evaluate primary hypothesis. Both treatment-strata and treatment-by-treatment interactions were thought unlikely by content experts. The original primary hypothesis is retained (main effect of allocation status to standard or extended duration treatment).

	macrolide duration is different depending on whether corticosteroids are administered. This is an intervention by intervention interaction between the Macrolide Duration Domain and the Corticosteroid Domain.		
SECTION 8 TRIAL DESIGN	**Original text**	**New Text**	**Reason**
Page 16	This domain will be conducted as part of a REMAP trial for severe CAP (see Core Protocol Section 7).	This domain will be conducted as part of the REMAP-CAP trial (see Core Protocol Section 7).	Administrative change for consistency of nomenclature
8.2 Eligibility criteria Page 16	Participants are included in the platform if they have all the REMAP-level inclusions and none of the REMAP-level exclusion criteria	Participants are included in the platform if they have all the platform-level inclusions and none of the platform-level exclusion criteria	Administrative change for consistency of nomenclature
8.2.1 Domain inclusion criteria Page 16	8.2.1. Inclusion criteria for this domain Patients are eligible for this domain only if they have been allocated a beta-lactam plus macrolide intervention within the Antibiotic Domain. In this regard, the Macrolide Duration Domain is nested solely within the beta-lactam plus macrolide interventions within the Antibiotic Domain. It should be noted that to be eligible for this domain it is not necessary to be randomized to a beta-lactam plus macrolide intervention, just allocated to receive a beta-lactam plus macrolide intervention (i.e. a patient allocated to receive a beta-lactam plus macrolide intervention within the Antibiotic Domain because	8.2.1. Domain inclusion criteria Patients are eligible for this domain only if they have been allocated a beta-lactam plus macrolide intervention within the Antibiotic Domain. In this regard, the Macrolide Duration Domain sits solely within the beta-lactam plus macrolide interventions of the Antibiotic Domain. Patients allocated to receive moxifloxacin or levofloxacin in the Antibiotic Domain are not eligible for this domain.	Title changed for consistency in protocol nomenclature to avoid confusion due to the term 'nesting' now having specific meaning in the Core Protocol. Rewording to improve grammar and wording deleted Deletion of previous possibility of randomization when participant had not received a treatment allocation within the

	that is the only intervention for which the patient is eligible, because of intervention-level exclusions, is still eligible for randomization in this domain). Patients allocated to receive moxifloxacin or levofloxacin in the Antibiotic Domain are not eligible for this domain.		antibiotic domain as this proved too difficult to operationalize using software that evaluates eligibility.
8.2.2 Domain exclusion criteria Page 16	8.2.2. Exclusion criteria from this domain Patients will be excluded from this domain, at the time of randomization, if: • The treating clinician believes that participation in the domain would not be in the best interests of the patient Patients with suspected legionella or other atypical organisms are eligible for inclusion but if the diagnosis is confirmed after enrollment this influences the implementation of the intervention. It should be noted that patients with known Legionella, at the time of first enrollment in the Platform, are not eligible for the Antibiotic Domain (because specific antimicrobial therapy is indicated) and patients with known intolerance to macrolides have an intervention-level exclusion to receive beta-lactam plus macrolide interventions within the Antibiotic Domain.	8.2.2. Domain exclusion criteria Reveal of allocation status will not be permitted, resulting in exclusion from this domain: • Study day 6 has commenced • Agreement to participate in this domain has not been obtained • There is microbiological confirmation or the clinician strongly suspects Legionella or any other form of atypical pneumonia • Macrolide antibiotics have already been discontinued for more than 36 hours • The treating clinician believes that participation in the domain would not be in the best interests of the patient It should be noted that patients with known Legionella, at the time of first enrollment in the Platform, are not eligible for the Antibiotic Domain (because specific antimicrobial therapy is indicated) and patients with known intolerance to macrolides	See Summary section, above, for explanation.

		have an intervention-level exclusion to receive beta-lactam plus macrolide interventions within the Antibiotic Domain.	
8.2.3 Intervention exclusion criteria Page 17	Blank	8.2.3 Intervention exclusion criteria Nil	Added to clarify that there are no intervention exclusion criteria and to standardize structure of all DSAs.
8.3.1 Macrolide intervention Page 17	8.3.1. Macrolide Intervention Patients will be randomly assigned to intention to receive one of the following study interventions. • Short course macrolide discontinued after 3 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	8.3.1. Macrolide intervention Patients will be randomly assigned to receive one of the following open-label study interventions. • Standard course macrolide discontinued between day 3 and day 5 • Extended course macrolide for 14 days or hospital discharge, whichever occurs first	The word *intention* has been deleted and the words *open-label* added to improve clarity of the definition of the intervention. The rationale for extension of standard course to be up to 5 days is outlined in summary section, above.
8.3.2 Recommended Macrolide Dosing Page 17	Heading blank A switch from IV to enteral macrolide is permitted once the patient is clinically improving as determined by the treating clinician. If, within the first 3 days, there is confirmed diagnosis (or a strong clinical suspicion) of legionellosis or other	8.3.2. Recommended macrolide dosing A switch from IV to enteral macrolide is permitted as directed by the treating clinician. If, at any time after reveal, there is confirmed diagnosis (or a strong clinical suspicion) of legionellosis	New paragraph created that describes macrolide dosing to improve clarity. Modification of wording to achieve same outcome

	microbiological diagnosis of an 'atypical' organism, then effective treatment for 'atypical' organisms must be continued. This can be either prolonged macrolide treatment or substitution with a fluoroquinolone or other active agent. Patients in whom legionellosis or another 'atypical' organism is diagnosed after day 3, can re-start or continue macrolide, or commence treatment with a fluoroquinolone or other active agent. The Macrolide should be discontinued if the patient experiences a serious adverse event (SAE) that is thought to be related to the study drug and may be discontinued at the discretion of the treating clinician if continued treatment is not in the best interests of the patient. In this regard, consideration should be given to evaluation of the QT interval, particularly at the time of discharge from the ICU.	or other microbiological diagnosis of an 'atypical' organism, then effective treatment for 'atypical' organisms must be provided. This can be either prolonged macrolide treatment or substitution with a fluoroquinolone or other active agent. Any patient randomized to standard course macrolide, in whom legionellosis or another 'atypical' organism is diagnosed after cessation of macrolide, must commence treatment that is effective against the organisms such as a macrolide or fluoroquinolone.	(appropriate treatment for patients with Legionella or other cause of atypical pneumonia) that is necessary because of change in time of reveal of allocation status and application of exclusion criteria immediately prior to reveal of allocation status.
8.3.3 Timing of initiation of intervention Page 18	The intervention is identical administration of macrolide, for the first 3 days after enrollment. Microbiological tests are usually available before the fourth day to determine if, in patients randomized to short duration of macrolide, whether there is a microbiological reason for why the macrolide (or suitable alternative antibiotic) should be continued for	Reveal of allocation status can occur at any time before the end of study day 5 when sufficient information is available to evaluate the exclusion criteria necessary for reveal. If reveal occurs before study day 3, and the patient is allocated to standard course macrolide, the intervention should be ceased on study day 3. If reveal occurs after study day 3, and	Clarification of process for evaluation of exclusion criteria prior to deferred reveal of allocation status and corresponding information that describes how intervention is delivered once

	a prolonged course.	the patient is allocated to standard course macrolide, discontinue immediately. Irrespective of the timing of reveal, if the patient is allocated to extended course macrolide, continuation to study day 14 should be prescribed.	exclusion criteria have been evaluated.
8.3.4 Duration of administration of macrolide Page 19	The duration of macrolide therapy is the primary research question in this domain. In the short course intervention, patients will receive 3 days of macrolide therapy unless there is confirmed or strongly suspected cause to continue.	The duration of macrolide therapy is the primary research question in this domain. In the standard course intervention, patients will receive 3 to 5 days of macrolide therapy. The Macrolide should be discontinued if the patient experiences a serious adverse event (SAE) that is thought to be related to the study drug and may be discontinued at the discretion of the treating clinician if continued treatment is not in the best interests of the patient. In this regard, consideration should be given to the development of ventricular dysrhythmias and evaluation of the QT interval, particularly at the time of discharge from the ICU.	Reinforcement of appropriate clinical practice in relation to patient safety and patient best interests.
8.4 Concomitant care Page 19	The use of low dose erythromycin (up to 250mg q6h) to promote gastric emptying is permitted.	The use of low dose erythromycin (up to 250mg q6h) to promote gastric emptying is discouraged, but is not considered a protocol deviation.	The word– *permitted* changed to *discouraged, but is not considered a protocol deviation* to improve clarity.
SECTION 9 TRIAL CONDUCT	**Original text**	**New Text**	**Reason**

9.3. Criteria for discontinuation Page 21	Refer to Core Protocol Section 8.7 for discontinuation criteria for participation in REMAP-CAP.	Refer to Core Protocol Section 8.7 for criteria for the discontinuation of participation in the REMAP-CAP trial.	Administrative change to improve grammar
9.4.1 Blinding Page 21	All antibiotics will be administered on an open-label basis.	Macrolides will be administered on an open-label basis.	The words *all antibiotics* changed to *Macrolides*
SECTION 10 STATISTICAL CONSIDERATIONS	**Original text**	**New Text**	**Reason**
10.2 Unit-of-analysis and strata Page 21	Strata Both analysis of the treatment effect and the Response Adaptive Randomization (RAR) will utilize the stratum of shock in this domain.	Unit-of-analysis and strata The unit-of-analysis for this domain is all patients who receive an allocation status in this domain. No strata are applied in the model that is used for analysis and specification of Response Adaptive Randomization (RAR).	Specification that the unit-of-analysis is all randomized patients with no application of strata in this domain.
10.3. Timing of revealing of randomization status Page 21	The timing of the revealing of allocation status and administration of interventions is as specified to be Randomization with Immediate Reveal and Delayed Initiation with reveal not occurring until after consent or some other form of agreement has been obtained (see section 7.8.3.64 in Core Protocol).	The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Deferred Reveal after domain-specific exclusion criteria have been evaluated (see section 7.8.3.64 in Core Protocol).	The word *immediate* changed to *deferred* and wording of definition changed to reflect modified process by which exclusion criteria are evaluated after initial assessment of eligibility to allow reveal of allocation status, in absence of any of the new exclusion criteria.
10.4 Interactions with interventions	An a priori interaction with the Corticosteroid Domain	An a priori interaction with the Corticosteroid Domain	Specification that no

in other domains Page 22	is considered possible and will be incorporated into the statistical models used to analyze this domain. An a priori interaction with the beta-lactam specified in the Antibiotic Domain is considered possible and will be incorporated into the statistical models used to analyze this domain. No interaction is evaluable between this domain and administration of moxifloxacin or levofloxacin in the Antibiotic Domain. No interaction is evaluable between the Ventilation Domain and this domain	is not considered possible and will not be incorporated into the statistical models used to analyze this domain. An a priori interaction with the beta-lactam specified in the Antibiotic Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain. By design, no interaction is evaluable between this domain and administration of moxifloxacin or levofloxacin in the Antibiotic Domain. An a priori interaction with the Antiviral Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain. No interaction is evaluable between the Ventilation Domain and this domain.	treatment-treatment interactions are evaluated in the operative statistical model (including with the new antiviral domain).
10.5 Nesting Page 22	Blank	Nesting is not applicable to this domain.	Nesting is not possible in a domain with only two interventions.
10.6 Threshold odds ratio delta for equivalence Page 22	Blank	The threshold odds ratio for equivalence in this domain is that specified in the Core Protocol (Section 7.8.8).	Specification of the default odds ratio for equivalence
10.7 Post-trial Sub-groups Page 22	Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The a priori sub-groups of interest include:	Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The a priori patient sub-groups of interest are:	Correction of errors in grammar and three sub-groups added which correspond to the strata

	• Patients in whom a microbiological diagnosis has been made on the basis of culture or other investigations such as antigen detection or polymerase chain reaction (PCR) o Patients with pneumococcal pneumonia o Patients without Legionella spp or other 'atypical' pneumonia • Elderly (≥65 years) and non-elderly (<65 years) patients • Chronic Obstructive Pulmonary Disease (COPD) • Azithromycin versus other macrolides	• A microbiological diagnosis of pneumococcal pneumonia • Elderly (≥65 years) and non-elderly (<65 years) • Chronic Obstructive Pulmonary Disease (COPD) • Azithromycin versus other macrolides • Shock strata • Influenza strata • All potentially evaluable treatment-by-treatment interactions with other domains.	variables which are no longer applied in this domain and treatment-treatment interactions which are also no longer applied in this domain
SECTION 11 ETHICAL CONSIDERATIONS	**Original text**	**New Text**	**Reason**
11.2. Potential domain-specific adverse events Page 22	Please refer to Core Protocol (section 8.12) for information about safety monitoring and reporting	Other SAEs should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see Core Protocol Section 8.13).	Updated with Domain-specific SAE information only. Overarching SAE information is in the Core protocol
11.3. Domain-specific consent issues Page 23	Most international guidelines do not specify the duration of treatment where a specific diagnosis (e.g. legionella) has not been diagnosed.	Most international guidelines do not specify the duration of treatment where a specific diagnosis (e.g. Legionella) has not been diagnosed.	Correction of spelling error – *Legionella* and administrative changes to improve grammar

	As all severe CAP patients receive at least 3 days of macrolide treatment as standard of care, and because extended duration macrolide therapy is not part of the spectrum of standard care, initiation of the intervention, before the fourth day after enrollment, will not occur until consent is obtained from the participant or agreement is obtained from an authorized representative.	Although many CAP patients receive 3 to 5 days of macrolide treatment as standard of care, extended duration macrolide therapy is not part of the spectrum of standard care. On this basis eligibility for this domain requires the agreement of either the participant or an authorized representative.	
SECTION 12 GOVERNANCE ISSUES	**Original text**	**New Text**	**Reason**
21.1 Funding Page 24	The REMAP trial is funded by an Australian National Health and Medical Research Council project grant (APP1101719), a European Union 7th Framework Programme for Research and Technological Development grant (602525) and a Health Research Council New Zealand Programme grant (16/631).	Funding sources for the REMAP-Cap trial are specified in the Core Protocol Section 2.5. This domain has not received any additional domain-specific funding.	Updated with Domain-specific funding information only. Overall trial funding information is in the Core protocol
12.2. Funding of domain interventions and outcome measures Page 24	12.2. Funding of domain interventions In New Zealand funding will be available to reimburse sites for up to two doses per patient of IV azithromycin (see ANZ RSA Section 9.2.1).	12.2. Funding of domain interventions and outcome measures In New Zealand, Health Research Council funding will be available to reimburse sites for up to two doses per patient of IV azithromycin (see ANZ RSA Section 9.2.2).	Administrative changes to improve clarity and correctly align with another protocol referred to

5.3.3. REMAP-CAP Corticosteroid Domain-Specific Appendix Version 3, dated 12 July 2019

Section	Original text	New Text	Reason
Front page and whole document header	REMAP-CAP Corticosteroid Domain-Specific Appendix Version 2 dated 12 December 2017	REMAP-CAP Corticosteroid Duration Domain-Specific Appendix Version 3 dated 12 July 2019	Administrative change to version and date
SUMMARY	**Original text**	**New Text**	**Reason**
Page 2	In this domain of the REMAP-CAP trial, participants with community-acquired pneumonia admitted to intensive care units will be randomized to receive either: • Hydrocortisone intravenous (IV), 50 milligrams every 6 hours for up-to 7 days • No hydrocortisone (i.e. hydrocortisone is not prescribed during the subsequent 7 days and there is no administration of a placebo)	In this domain of the REMAP-CAP trial, participants with community-acquired pneumonia admitted to participating intensive care units will be randomized to receive one of up to three steroid-use strategies depending on availability and acceptability: • No corticosteroid including hydrocortisone (no placebo) • Fixed duration hydrocortisone for 7 days • Shock-dependent hydrocortisone while the patient is in septic shock At this participating site the following interventions have been selected within this domain: ☐ No corticosteroid including hydrocortisone (no placebo) ☐ Fixed duration hydrocortisone for 7 days ☐ Shock-dependent hydrocortisone while the patient is in septic shock	Addition of a new (third) intervention in this domain. This intervention is added for two reasons. Firstly, on the basis of the results of the ADRENAL trial, some but not all clinicians, had changed practice to usually or always administer hydrocortisone to patients with septic shock, which is a complication in a proportion of patients with severe CAP. The

			previous domain structure (either fixed dose of hydrocortisone for 7 days, as used evaluated in ADRENAL) or no hydrocortisone would not have been acceptable at some participating sites (loss of equipoise to withhold hydrocortisone in patients with septic shock). Secondly, many clinicians do administer hydrocortisone to patients with septic shock, but do not follow the fixed 7 day course, rather administer hydrocortisone for the duration of the episode

			of septic shock (either shorter or longer than 7 days). The intervention added to this domain is to administer hydrocortisone for the duration of the episode of septic shock. Sites may choose to participate in any two or all three interventions, depending on their equipoise for each intervention.
Interventions Page 3	• Intravenous Hydrocortisone, 50 milligrams (mg) every 6 hours for up-to 7 days. • No hydrocortisone (i.e. hydrocortisone is not prescribed during the subsequent 7 days and there is no administration of a placebo)	• No corticosteroid including hydrocortisone (no placebo) • Fixed duration hydrocortisone for 7 days • Shock-dependent hydrocortisone while the patient is in septic shock	Listing of the three interventions. Rationale is outlined immediately above.
Unit-of-analysis and Strata Page 3	Strata Analysis and Response Adaptive Randomization are by strata (shock) to allow for strata-by-intervention	Unit-of-analysis and Strata There are four units-of-analysis for this domain, specified by the combination of shock and influenza strata status.	Based on simulations and advice from content experts, and in

	interaction.	Analysis and Response Adaptive Randomization are applied by shock and influenza status, with borrowing permitted.	conjunction with addition of a strata for influenza infection, the strata applied to this domain are both shock status and influenza status. This allows for the statistical model to report any observed differential treatment effect depending on whether the patient meets definition for shock status in combination with influenza status (i.e. 4 cells of the shock x influenza 2 x 2 table). To the extent appropriate, as determined by data, the statistical model permits borrowing between one or more

			stratum cells.
Nesting Page 3	Blank	None	Nesting is not possible in this domain because of the divergent consequences to administration of hydrocortisone in the shock-duration dependent intervention. If the patient does not develop shock, the intervention is more similar to the no hydrocortisone intervention. If the patient develops shock, the intervention is more similar to the fixed duration for 7 days intervention. This divergence, with respect to the other two interventions in

			the domain, precludes nesting.
Domain-specific Exclusions Page 3	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 other than community-acquired pneumonia (CAP) (or severe sepsis) such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven Pneumocystis jiroveci pneumonia • Have received an immunomodulatory dose of systemic corticosteroid therapy in the24 hours prior to the time of enrollment. An immunomodulatory dose is defined as >20mg of hydrocortisone, >5mg prednisone, >4mg methylprednisolone or >0.8mg dexamethasone per 24 hours. • The treating clinician believes that participation in the domain would not be in the best interests of the patient	Patients will be excluded from this domain if they have any of the following: • Known hypersensitivity to hydrocortisone • An indication to prescribe systemic corticosteroids for a reason that is unrelated to the current episode of CAP (or direct complications of CAP), such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven Pneumocystis jiroveci pneumonia • More than 24 hours have elapsed since ICU admission • The treating clinician believes that participation in the domain would not be in the best interests of the patient	Administrative change for consistency of nomenclature cross all protocols Exclusion related to prior administration of systemic corticosteroids removed (as too difficult to operationalize) and replaced with *24-hour* time-window that captures much of the same effect.
	Original text	**New Text**	**Reason**
	ADRENAL ADjunctive coRticosteroid trEatment iN criticAlly ilL Patients With Septic Shock Study ARDS Acute Respiratory Distress Syndrome ARDSNet Acute Respiratory Distress Syndrome Clinical Trial Network	ADRENAL ADjunctive coRticosteroid trEatment iN criticAlly ilL Patients With Septic Shock Study APROCCHSS Activated PROtein C and Corticosteroids for Human Septic Shock ARDS Acute Respiratory Distress Syndrome	Updated with all abbreviations used in this version of the document

	CAP Community Acquired Pneumonia CORTICUS The Corticosteroid Therapy of Septic Shock Study DSA Domain-Specific Appendix DSWG Domain-Specific Working Group DSMB Data Safety and Monitoring Board HPA Hypothalamic–Pituitary–Adrenal ICU Intensive Care Unit ISIG International Statistics Interest Group ITSC International Trial Steering Committee IV Intravenous kg Kilogram LOS Length of Stay LUNG-SAFE Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE MODS Multiple Organ Dysfunction Score mg milligram OFFD Organ Failure Free Days P:F Ratio Ratio of Partial Pressure of Oxygen in Arterial Blood and Fraction of Inspired Oxygen Concentration RAR Response Adaptive Randomization RCT Randomized Controlled Trial REMAP Randomized, Embedded, Multifactorial Adaptive	ARDSNet Acute Respiratory Distress Syndrome Clinical Trial Network CAP Community Acquired Pneumonia CORTICUS The Corticosteroid Therapy of Septic Shock Study DSA Domain-Specific Appendix DSWG Domain-Specific Working Group DSMB Data Safety and Monitoring Board HPA Hypothalamic–Pituitary–Adrenal ICU Intensive Care Unit ISIG International Statistics Interest Group ITSC International Trial Steering Committee IV Intravenous kg Kilogram LOS Length of Stay LUNG-SAFE Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE MODS Multiple Organ Dysfunction Score mg milligram OFFD Organ Failure Free Days P:F Ratio Ratio of Partial Pressure of Oxygen in Arterial Blood and Fraction of Inspired Oxygen Concentration RAR Response Adaptive Randomization RCT Randomized Controlled Trial	

	Platform trial REMAP-CAP Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia RSA Region-Specific Appendix SAE Serious Adverse Event Severe CAP Severe Community Acquired Pneumonia VFD Ventilator Free Days	REMAP Randomized, Embedded, Multifactorial Adaptive Platform trial REMAP-CAP Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia RSA Region-Specific Appendix SAE Serious Adverse Event ~~Severe CAP Severe Community Acquired Pneumonia~~ VFD Ventilator Free Days	
SECTION 2 PROTOCOL APPENDIX STRUCTURE	**Original text**	**New Text**	**Reason**
Page 7	The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models) and Simulations Appendix (details of the current simulations of the REMAP), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), and multiple Regions-Specific Appendices (RSA) (detailing regional management and governance).	The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models) and Simulations Appendix (details of the current simulations of the REMAP), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), and multiple Region-Specific Appendices (RSA) (detailing regional management and governance).	Administrative change to use study nomenclature
SECTION 3 CORTICOSTEROID DOMAIN-SPECIFIC APPENDIX VERSION	**Original text**	**New Text**	**Reason**

	Version 1: Approved by the Corticosteroid Domain-Specific Working Group (DSWG) on 19 November 2016 Version 1.1: Approved by the Corticosteroid DSWG on 30 March 2017 Version 2: Approved by the Corticosteroid DSWG on 12 December 2017	Version 1: Approved by the Corticosteroid Domain-Specific Working Group (DSWG) on 19 November 2016 Version 1.1: Approved by the Corticosteroid DSWG on 30 March 2017 Version 2: Approved by the Corticosteroid DSWG on 12 December 2017 Version 3: Approved by the Corticosteroid DSWG on 12 July 2019	Updated with new version details
SECTION 4 CORTICOSTEROID DOMAIN GOVERNANCE	**Original text**	**New Text**	**Reason**
4.1 Domain members Page 9	Ms. Wilma van Bentum-Puijk Dr. Lennie Derde Professor Anthony Gordon Dr. Sebastiaan Hullegie Associate Professor Peter Kruger Dr. Ed Litton Dr. Colin McArthur Professor Alistair Nichol Professor Steve Webb Professor Bala Venkatesh	Ms. Wilma van Bentum-Puijk Dr. Lennie Derde Professor Anthony Gordon Dr. Sebastiaan Hullegie Associate Professor Peter Kruger Dr. Ed Litton Professor John Marshall Dr. Colin McArthur Dr. Srinivas Murthy Professor Alistair Nichol Professor Bala Venkatesh Professor Steve Webb	Updated to all current members
4.2 Contact details Page 10	Fax +412 647 5258	Blank	Fax number deleted

SECTION 6 BACKGROUND AND RATIONALE	Original text	New Text	Reason
6.1 Domain definition Page 11	This is a domain within the REMAP-CAP to test the effectiveness of immune modulation with corticosteroids in patients with severe community-acquired pneumonia (severe CAP) who are admitted to an Intensive Care Unit (ICU).	This is a domain within the REMAP-CAP to test the effectiveness of systemic corticosteroids in patients with severe community-acquired pneumonia (CAP) who are admitted to an Intensive Care Unit (ICU).	Administrative changes to improve clarity
6.2. Domain-specific background Page 11	There is significant uncertainty regarding the use of corticosteroids in patients with community-acquired pneumonia (CAP) who are treated in an ICU. Several studies and meta-analyses of randomized controlled trials (RCTs) have indicated that benefit may exist. (MacDonald, 2018) However, existing evidence is not sufficient to provide guidance to clinicians that is definitive (Annane et al., 2018, Venkatesh et al., 2018) It is also recognized that corticosteroids have a range of potentially adverse effects. Clinicians remain uncertain about the role of corticosteroid treatment in patients with severe CAP. This uncertainty necessitates the conduct of a large pragmatic study to address this question and provide definitive guidance to clinicians.	There is significant uncertainty regarding the use of corticosteroids in patients with CAP who are treated in an ICU. This uncertainty applies to both patients with and without septic shock secondary to CAP. The existing evidence is derived from trials that enrolled overlapping populations. Some trials enrolled patients with septic shock, many of whom had CAP as the source of sepsis, and other enrolled patients with severe CAP, but only a proportion of these patients had septic shock. These trials have largely utilized hydrocortisone as the corticosteroid but have employed a range of doses and delivery strategies (infusion versus intermittent dosing). Several studies and meta-analyses of randomized controlled trials (RCTs) have indicated that benefit may exist. (MacDonald, 2018) However, existing evidence is not sufficient to provide guidance to clinicians that is definitive. If there is a benefit, there is limited evidence to	Entire section 6.2 reformatted and updated to improve clarity and grammar Background section revised to clarify nature of clinical research questions in CAP to make clearer the distinction between the question in patients with CAP but without septic shock and patients with CAP with septic shock.

		suggest that benefit is more likely in patients who are more severely ill. (Annane et al., 2018, Venkatesh et al., 2018) It is also recognized that corticosteroids have a range of potentially adverse effects. Clinicians remain uncertain about the role of corticosteroid treatment in patients with severe CAP. This uncertainty necessitates the conduct of a large pragmatic study to address this question and provide definitive guidance to clinicians.	
6.2.1 Corticiosteroids in critical illness Page 12	6.2.1. Severe CAP is intertwined with the host systemic inflammatory response The clinical manifestations of pneumonia are a product of the interaction between an infective pathogen and the local and systemic inflammatory responses of the host. Interestingly, a more pronounced and aggressive inflammatory response has been shown in several studies to be associated with treatment failure and increased rates of mortality. (Antunes et al., 2002) In support of this hypothesis that an over-active immune response is deleterious, higher levels of pro-inflammatory cytokines and chemokines (i.e. IL-6 and IL-8) have been detected in patients with severe CAP and associated with increased rates of mortality. (Antunes et al., 2002) It has been postulated that a potential dampening of this 'abnormal'	6.2.1. Corticosteroids in critical illness In health, endogenous corticosteroids production is regulated by the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis is central to maintaining homeostasis in the face of exogenous stress. Infectious disease is a common source of exogenous stress that is encountered by humans. As part of an integrated response to infection the host produces additional (above normal homeostasis) corticosteroids. It is speculated that this occurs to calibrate the innate and acquired host response to infection so as to protect the host organism from an excessive immune response, which can damage host tissues. Corticosteroids are immunomodulatory hormones that can stimulate, as well as suppress, immune function depending on the type of immune response, the immune compartment, and the	Restructure of background to provide greater clarity regarding biological rationale (moved in the background).

	immune response to infection, for example by administration of corticosteroids, could improve outcome	cell type involved. (Silverman et al., 2005, Prina et al., 2016) Exogenously administered corticosteroid drugs (e.g. hydrocortisone) elucidate effects similar to endogenously produced cortisol on the host immune response. Furthermore, critically ill patients may benefit from corticosteroid administration due to the presence of relative adrenal insufficiency or inadequate adrenal function in some cases of severe CAP. (Maxime et al., 2009)	
6.2.2 Clinical questions regarding corticosteroids in patients with CAP Page 13	6.2.4 Corticosteroids complications in critical illness The complications associated with the systemic use of corticosteroids treatment have been well described. The duration of administration of corticosteroids in patients with severe CAP is short (up-to a week) and, as a consequence, long-term complications of corticosteroid administration, such as diabetes mellitus, weight gain, and osteoporosis are not a consideration. However, risks associated with the short term use in patients with severe CAP include in increased risk of nosocomial infection (due to the immunosuppressive effect of corticosteroids), hyperglycemia (which can be treated with insulin), and myopathy which may lead to prolongation of the period of mechanical ventilation and weakness during the recovery	6.2.2 Clinical questions regarding corticosteroids in patients with CAP There are several interrelated and overlapping clinical questions regarding the role of corticosteroids in patients with severe CAP. The first of these is whether patients who have septic shock as a complication of severe CAP benefit from corticosteroids. The second is whether patients with severe CAP who do not have septic shock benefit from corticosteroids. The third is whether patients with severe CAP due to influenza respond differently to corticosteroids. Lastly, there is uncertainty about the role of corticosteroids in patients who develop Acute Respiratory Distress Syndrome (ARDS) secondary to severe CAP.	Paragraph 6.2.4 deleted and replaced with 6.2.2 Clarification of the nature of the research questions, as they apply to sub-populations of patients with CAP, that are relevant to administration of hydrocortisone

	phase after critical illness. It remains uncertain, in critically ill CAP patients, what is the overall effect of these potential complications on patient-centered outcomes, including survival. Given that the implications for patients of these complications is uncertain, it is vitally important to conduct a study with the ability to assess the aggregate effects of steroids (i.e. the sum of the potentially beneficial and deleterious effects) on an outcome such as mortality. This is the only way in which clinicians can be certain that they are making the correct decision regarding corticosteroid therapy in severe CAP.		
6.2.3 Role of corticosteroids in septic shock secondary to CAP Page 13	The evidence regarding the effectiveness of corticosteroids in patients with severe sepsis and severe CAP, in particular, has not been straightforward to interpret clearly. The existing trials can be divided in to those that randomized patients with sepsis and septic shock (including many patients with severe CAP) or those in patients with severe CAP (with or without septic shock) to receive corticosteroid or not (placebo or no placebo). The studies that enrolled patients with sepsis or septic shock included patients with a range of different sites of primary infection but, typically, around half of included patients had CAP. The results of these studies are heterogeneous.	6.2.3. Role of corticosteroids in septic shock secondary to CAP? The studies investigating corticosteroids that enrolled patients with septic shock (or sepsis without shock) included patients with a range of different sites of primary infection. In most trials, around half of enrolled patients had CAP. The results of these studies are varied, and this is reflected in international guidelines. The 2013 iteration of the Surviving Sepsis Campaign Guidelines suggests that the administration of intravenous (IV) hydrocortisone should be avoided if adequate fluid resuscitation and vasopressor therapy are able to restore	Updated to improve clarity of background

	The current iteration of the Surviving Sepsis Campaign Guidelines suggests that the administration of intravenous (IV) hydrocortisone should be avoided if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability, but that hydrocortisone should be administered if hemodynamic stability cannot be achieved. (Dellinger et al., 2013) This recommendation is graded as a weak recommendation based on low quality evidence. There are two major trials that influenced this recommendation. In the study by Annane et al, 2002, hydrocortisone improved the duration of survival (within the first 28 days) and resulted in more rapid reversal of septic shock in the sub-group of patients with relative adrenal insufficiency. (Annane et al., 2002) In the CORTICUS study, septic shock was also reversed more rapidly but there was no difference in mortality however this may have been influenced by inclusion of a higher proportion of patients at lower risk of death. (Sprung et al., 2008) The more recent Cochrane meta-analysis suggests that corticosteroid treatment reduces mortality among patients with sepsis, but that the overall quality of evidence is low. (Annane et al., 2015) As a consequence, there is substantial variation in clinical practice and existing evidence is best regarded as	hemodynamic stability, but that hydrocortisone should be administered if hemodynamic stability cannot be achieved. (Dellinger et al., 2013) This recommendation is graded as a weak recommendation based on low quality evidence. There are two major trials that influenced this recommendation. In a study by Annane et al, hydrocortisone improved the duration of survival (within the first 28 days) but not the number of patients who survived; and resulted in more rapid reversal of septic shock in the (non-stratified) sub-group of patients with relative adrenal insufficiency. (Annane et al., 2002) In the CORTICUS study, septic shock was also reversed more rapidly but there was no difference in mortality although this result may have been influenced by inclusion of patients at lower risk of death. (Sprung et al., 2008) A more recent Cochrane meta-analysis suggests that corticosteroid treatment reduces mortality among patients with sepsis, but the quality of evidence was rated as low because of imprecision and inconsistency of results across trials, as well as the inclusion of trials with different study populations and the use of different doses and duration of treatment. (Annane et al., 2015) The recommendation in the current, 2016 International Surviving Sepsis Campaign Guidelines is not changed from	Updated to take into account publication of

	hypothesis generating. (Annane et al., 2002, Bollaert et al., 1998, Briegel et al., 1999, MacDonald, 2018)	the 2013 recommendation. (Rhodes et al., 2017) Since the publication of the Cochrane meta-analysis and the 2016 Guidelines, two additional trials have been published, but have not provided sufficient clarification. A RCT of hydrocortisone in 3,800 patients with septic shock (ADRENAL) showed no reduction in 90-day mortality. (Venkatesh et al., 2018) In this trial, duration of treatment was 7 days or until ICU discharge, whichever occurred first. For patients who still required vasopressor support on day 7, there was evidence of deterioration after steroids were ceased. The other trial, APROCCHSS, investigating hydrocortisone-plus-fludrocortisone in patients with septic shock, reported lower 90-day mortality in the intervention group (RR 0.88, 95% CI 0.78-0.99). (Annane et al., 2018) These trials (Table 1) have not resulted in changes to international guidelines. As a consequence of this uncertainty, there is substantial variation in clinical practice. (Annane et al., 2002, Bollaert et al., 1998, Briegel et al., 1999, MacDonald, 2018)	more recent international guidelines. Updated to reflect publication of two relevant major trials since previous version of protocol that have been pivotal in need to modify the interventions available within the domain.

6.2.3 Role of corticosteroids in septic shock secondary to CAP
Page 14

Table 1: Studies on corticosteroids in CAP (adapted from Prina et al, 2016)

Reference	Study design, population and intervention	Main results (effect of corticosteroids)
(Confalonieri et al., 2005)	Multicenter RCT (n=46), severe CAP Hydrocortisone (200 mg bolus + infusion (10 mg/hour) for 7 days) versus placebo	↑PaO2/FiO2, ↑chest radiograph score, ↓CRP, delayed septic shock, ↓hospital LOS and ↓mortality
(Garcia-Vidal et al., 2007)	Retrospective observational study patients with severe CAP, systemic steroids	↓mortality
(Snijders et al., 2010)	Single center RCT (n=230), CAP Prednisolone (40mg daily for 7 days) versus placebo	Clinical cure at day 7 unchanged was late failure (>72 hours) ↑with prednisolone
(Meijvis et al., 2011)	Bicenter RCT (n=304), CAP Dexamethasone (5 mg daily for 4 days) versus placebo	↓hospital LOS

Table 2: Selected studies of corticosteroids in sepsis

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

Table 1 replaced with a new table for better presentation of results of new trials.

(Chen et al., 2011)	Meta-analysis (6 RCTs, n=437), CAP	↑resolution of symptoms ↑clinical stability ↓rate of relapse
(Nie et al., 2012)	Meta-analysis (9 RCTs, n= 1001), CAP	No change in mortality overall ↓mortality in severe CAP
(Shafiq et al., 2013)	Meta-analysis (8 RCTs, n=1119), CAP	↓hospital LOS, No change in mortality
(Cheng et al., 2014)	Meta-analysis (4 RCTs, n=264), severe CAP	↓hospital LOS, ↓mortality
(Torres et al., 2015)	Multicenter RCT (n=120), CAP Methylprednisolone (0.5 mg/ kg 12 hourly for 5 days) versus placebo	↓treatment failure, No difference for in-hospital mortality
(Blum et al., 2015)	Multicenter RCT (n=785), CAP Prednisolone (50mg daily for 7 days) versus placebo	↓time to clinical stability

al. (2018)	(n=1241) in patients with definite or probable septic shock of hydrocortisone (50 mg every 6 hours and fludrocortisone 50 µg enterally daily) for 7 days versus placebo	mortality at day 90, with more vasopressor- and organ-failure free days

In both ADRENAL and APROCCHSS hydrocortisone was administered for a maximum of 7 days and ceased even if the patient remained in shock. There is anecdotal evidence that many clinicians, who do choose to administer hydrocortisone to patients with septic shock do not administer for a fixed duration (i.e., 7 days) but will administer hydrocortisone for a shorter or longer duration, corresponding to the duration of shock (as determined by vasopressor administration). This strategy has not been evaluated in randomized clinical trials.

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

Details of the intervention in these two new trials and its relationship to current clinical practice.

	(Siemieniuk et al., 2015)	Meta-analysis (12 RCTs, n= 1974), CAP	↓all-cause mortality, ↓mechanical ventilation and ↓ARDS, ↓time to clinical stability, ↓duration of hospitalization	Overall, there is legitimate uncertainty regarding whether corticosteroids are beneficial in patients with septic shock secondary to CAP and, if so whether there are differences in benefit from administration of a fixed-course compared with a duration that is variable corresponding to the duration of septic shock.	Summary of a major question that remain unanswered that is needed to guide practice, following completion of these two new trials.
	(Wan et al., 2016)	Meta-analysis (9 RCTs, n=1667)	No effect on mortality in CAP and Severe CAP, ↓ARDS		
	A large RCT of hydrocortisone in patients with septic shock (ADRENAL) is recruiting currently and is expected to report results during 2017 or 2018. (Venkatesh et al., 2013) The role of corticosteroids in patients with severe sepsis but not septic shock is also uncertain, with a recent study reporting that corticosteroids were not effective in preventing the development of shock. (Keh et al., 2016) This raises the possibility that the effect of corticosteroids in patients with severe sepsis may be different depending on the presence of absence of shock at the time of enrollment.				

	Overall, there is legitimate uncertainty regarding whether corticosteroids are beneficial in patients with septic shock secondary to CAP and, if so whether there are differences in benefit from administration of a fixed-course compared with a duration that is variable corresponding to the duration of septic shock.		
6.2.4 Role of corticosteroids in CAP irrespective of septic shock Page 15	A number of trials have evaluated the effect of administration of corticosteroids in patients with severe CAP. These studies have been reviewed by Prina et al, 2016, and are summarized in Table 1 (modified from Prina et al, 2016). (Chen et al., 2011, Cheng et al., 2014, Confalonieri et al., 2005, Garcia-Vidal et al., 2007, Meijvis et al., 2011, Nie et al., 2012, Shafiq et al., 2013, Siemieniuk et al., 2015, Snijders et al., 2010, Torres et al., 2015, Wan et al., 2016, Prina et al., 2016) A 2011 Cochrane meta-analysis by Chen et al, 2011 (6 RCTs, n=437) suggested that corticosteroid therapy increased the speed of resolution of symptoms and shortened the time-interval to achieve clinical stability but did not demonstrate any effect to reduce mortality. (Chen et al., 2011) A more	The clinical manifestations of pneumonia are a product of the interaction between an infective pathogen and the local and systemic inflammatory responses of the host. A more pronounced and aggressive inflammatory response has been shown in several studies to be associated with treatment failure and increased rates of mortality. (Antunes et al., 2002) In support of this hypothesis that an over-active immune response is deleterious, higher levels of pro-inflammatory cytokines and chemokines (i.e. IL-6 and IL-8) have been detected in patients with severe CAP and associated with increased rates of mortality. (Antunes et al., 2002) This raises the possibility of a beneficial effect of dampening of this 'abnormal' immune response with corticosteroids, irrespective of the presence of septic	Section moved from previous location. Clarifications for grammar.

	recent meta-analysis by Nie et al, 2012 (9 RCTs, n=1001) showed that administration of corticosteroids did not result in a demonstrable decrease in mortality, across all studies, but a beneficial effect on mortality may be present among the sub-group of patients with severe CAP when patients received more than 5 days corticosteroid treatment. (Nie et al., 2012) A 2016 meta-analysis by Wan et al, 2016 (9 RCTs, n=1,667 and six cohort studies, n=4,095 of adult CAP were analyzed and the authors reported that treatment with corticosteroids is safe and may reduce the risk of Acute Respiratory Distress Syndrome (ARDS), and shorten the duration of disease. (Wan et al., 2016) These meta-analyses included heterogeneous populations of CAP (mild, moderate and severe CAP) and heterogeneous interventions (low to very high dose of steroids). Another meta-analysis by Cheng et al, 2014 (4 RCTs, n=264), which includes only patients with severe CAP concluded that, although corticosteroid therapy may reduce mortality for adult patients with severe CAP, the results should be interpreted with caution due to the instability of pooled estimates. (Cheng et al., 2014) The authors concluded that reliable treatment recommendations could only be raised if additional multicenter studies with sufficient statistical power are	shock. A number of trials have evaluated the effect of administration of corticosteroids in patients with severe CAP. These studies have been reviewed by Prina and colleagues (2016) and are summarized in Table 2 (modified from Prina et al, 2016). A 2011 Cochrane meta-analysis by Chen et al (6 RCTs, n=437) suggested that corticosteroid therapy increased the speed of resolution of symptoms and shortened the time-interval to achieve clinical stability but did not demonstrate any effect to reduce mortality. (Chen et al., 2011) A more recent meta-analysis by Nie et al., (9 RCTs, n=1001) showed that administration of corticosteroids did not result in a demonstrable decrease in mortality, across all studies, but a beneficial effect on mortality may be present among the sub-group of patients with severe CAP when patients received more than 5 days of corticosteroid treatment. (Nie et al., 2012) A 2016 meta-analysis by Wan et al., (9 RCTs, n=1,667 and six cohort studies (n=4,095) of adult CAP were analyzed and the authors reported that treatment with corticosteroids is safe and may reduce the risk of ARDS, and shorten the duration of disease. (Wan et al., 2016) These meta-analyses included heterogeneous populations of CAP (mild, moderate and severe CAP) and heterogeneous	

	conducted. (Cheng et al., 2014) Recent Randomized controlled trials Two recent relatively large high quality multicenter RCTs have been published regarding the use of corticosteroids in CAP that are not included in the meta-analyses of patients with CAP. Blum et al, 2015 conducted a multicenter, double-blind, randomized, placebo-controlled trial (n=785) of patients with CAP who were randomized to receive either prednisone (50 milligrams (mg), oral) or placebo for 7 days. The trial reported that corticosteroids reduced the time to reach clinical stability and that hyperglycemia was more common in the corticosteroid group but that the mortality rate was not different between the two groups. (Blum et al., 2015) In the second study, by Torres et al, 2015, a multicenter severe CAP RCT (n=120), participants were randomized to receive either corticosteroids (methylprednisolone at a dose of 0.5mg/kilogram (kg) every 12 hours for 5 days) or not. Treatment with corticosteroids reduced treatment failure in comparison with the placebo group. (Torres et al., 2015) As highlighted in Table 1, the aggregate conclusion from these studies is that there is reasonable evidence to	interventions (low to very high dose of steroids). Another meta-analysis by Cheng et al., (4 RCTs, n=264), which included only patients with severe CAP concluded that, although corticosteroid therapy may reduce mortality for adult patients with severe CAP, the results should be interpreted with caution due to the instability of the pooled estimates. (Cheng et al., 2014) The authors concluded that reliable treatment recommendations could only be produced if additional multicenter studies with sufficient statistical power were conducted. (Cheng et al., 2014) Two recent relatively large high quality multicenter RCTs have been published regarding the use of corticosteroids in CAP that were not included in the meta-analyses of patients with CAP. Blum et al., conducted a multicenter, double-blind, randomized, placebo controlled trial (n=785) of patients with CAP who were randomized to receive either prednisone (50mg, oral) or placebo for 7 days. The trial reported that corticosteroids reduced the time to reach clinical stability and that hyperglycemia was more common in the corticosteroid group but that the mortality rate was not different between the two groups. (Blum et al., 2015) In the second study, by Torres et al, 2015, a	

indicate that use of corticosteroids in CAP results in the following benefits: reduced hospital length of stay (LOS), reduced time to clinical stability, and prevention of ARDS. However, none of these are patient-centered end-points and, as yet, there is no definitive answer regarding the effect of corticosteroids on mortality. This, with the huge heterogeneity in current clinical practice indicating clinical equipoise exists, makes now the time to conduct such a large adequately powered and patient centered outcome orientated study.

Table 3: Studies on corticosteroids in CAP (adapted from Prina et al, 2016)

Reference	Study design, population and intervention	Main results (effect of corticosteroids)
(Confalonieri et al., 2005)	Multicenter RCT (n=46), severe CAP Hydrocortisone (200 mg bolus + infusion (10 mg/hour) for 7 days) versus placebo	↑PaO2/FiO2, ↑chest radiograph score, ↓CRP, delayed septic shock, ↓hospital LOS and ↓mortality

multicenter severe CAP RCT (n=120), participants were randomized to receive either corticosteroids (methylprednisolone at a dose of 0.5mg/kilogram (kg) every 12 hours for 5 days) or not. Treatment with corticosteroids reduced treatment failure in comparison with the placebo group, but not hospital mortality. (Torres et al., 2015)

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

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

Reference	Study design, population and intervention	Main results (effect of corticosteroids)

Previously Table 1.

(Garcia-Vidal et al., 2007)	Retrospective observational study patients with severe CAP, systemic steroids	↓mortality
(Snijders et al., 2010)	Single center RCT (n=230), CAP Prednisolone (40mg daily for 7 days) versus placebo	Clinical cure at day 7 unchanged was late failure (>72 hours) ↑with prednisolone
(Meijvis et al., 2011)	Bicenter RCT (n=304), CAP Dexamethasone (5 mg daily for 4 days) versus placebo	↓hospital LOS
(Chen et al., 2011)	Meta-analysis (6 RCTs, n=437), CAP	↑resolution of symptoms ↑clinical stability ↓rate of relapse
(Nie et al., 2012)	Meta-analysis (9 RCTs, n= 1001), CAP	No change in mortality overall ↓mortality in severe CAP
(Shafiq et al., 2013)	Meta-analysis (8 RCTs, n=1119), CAP	↓hospital LOS, No change in mortality
(Cheng et al., 2014)	Meta-analysis (4 RCTs, n=264), severe CAP	↓hospital LOS, ↓mortality

(Confalonieri et al., 2005)	Multicenter RCT (n=46), severe CAP Hydrocortisone (200 mg bolus + infusion (10 mg/hour) for 7 days) versus placebo	Increased PaO2/FiO2, higher chest radiograph score, lower CRP, delayed septic shock, reduced hospital LOS and mortality
(Garcia-Vidal et al., 2007)	Retrospective observational study patients with severe CAP, systemic steroids	Reduction in mortality
(Snijders et al., 2010)	Single center RCT (n=230), CAP Prednisolone (40mg daily for 7 days) versus placebo	Clinical cure at day 7 unchanged Late failure (>72 hours) increased with prednisolone
(Meijvis et al., 2011)	Bicenter RCT (n=304), CAP Dexamethasone (5 mg daily for 4 days) versus placebo	Reduced hospital LOS
(Chen et al., 2011)	Meta-analysis (6 RCTs, n=437), CAP	Faster resolution of symptoms Faster clinical stability Lower rate of relapse

	(Torres et al., 2015)	Multicenter RCT (n=120), CAP Methylprednisolone (0.5 mg/ kg 12 hourly for 5 days) versus placebo	↓treatment failure, No difference for in-hospital mortality	**(Nie et al., 2012)**	Meta-analysis (9 RCTs, n= 1001), CAP	No change in mortality overall Reduced mortality in severe CAP	
	(Blum et al., 2015)	Multicenter RCT (n=785), CAP Prednisolone (50mg daily for 7 days) versus placebo	↓time to clinical stability	**(Shafiq et al., 2013)**	Meta-analysis (8 RCTs, n=1119), CAP	Reduced hospital LOS, No change in mortality	
	(Siemieniuk et al., 2015)	Meta-analysis (12 RCTs, n= 1974), CAP	↓all-cause mortality, ↓mechanical ventilation and ↓ARDS, ↓time to clinical stability, ↓duration of hospitalization	**(Cheng et al., 2014)**	Meta-analysis (4 RCTs, n=264), severe CAP	Reduced hospital LOS and mortality	
	(Wan et al., 2016)	Meta-analysis (9 RCTs, n=1667)	No effect on mortality in CAP and Severe CAP, ↓ARDS	**(Torres et al., 2015)**	Multicenter RCT (n=120), CAP Methylprednisolone (0.5 mg/ kg 12 hourly for 5 days) versus placebo	Less treatment failure, No difference for in-hospital mortality	
				(Blum et al., 2015)	Multicenter RCT (n=785), CAP Prednisolone (50mg daily for 7 days) versus placebo	Reduced time to clinical stability	
				(Siemieniuk et al., 2015)	Meta-analysis (12 RCTs, n= 1974), CAP	Reduced all-cause mortality, mechanical ventilation and ARDS, reduced time to clinical stability, shorter	

				duration of hospitalization	
		(Wan et al., 2016)	Meta-analysis (9 RCTs, n=1667)	No effect on mortality in CAP and Severe CAP, less ARDS	
6.2.5 Role of corticosteroids in CAP secondary to influenza Page 18	6.2.6. Corticosteroids in severe CAP secondary to influenza It has been noted that almost one third of patients admitted to an ICU with 2009 H1N1 pandemic influenza received corticosteroids (Falagas et al., 2010) as either a primary therapy or as a rescue therapy for patients with severe ARDS. (Kumar et al., 2009, Dominguez-Cherit et al., 2009) This widespread use occurred despite there being little evidence of the efficacy and safety of corticosteroids in CAP secondary to influenza. A systematic review and meta-analysis (nine cohort studies (n = 1405) and 14 case-control studies (n = 4700)) showed an increased mortality with corticosteroid treatment in influenza H1N1 infection.	6.2.5 Role of corticosteroids in CAP secondary to influenza The role of corticosteroids in patients with CAP caused by or occurring in association with influenza infection has been a longstanding controversy. Existing evidence is derived predominantly from observational studies. During the 2009 H1N1 influenza pandemic, among patients admitted to an ICU, approximately one third of patients received corticosteroids (Falagas et al., 2010) as either a primary therapy or as a rescue therapy for patients with severe ARDS. (Kumar et al., 2009, Dominguez-Cherit et al., 2009) This widespread use occurred despite the absence of any evidence from RCTs regarding the effectiveness of	Paragraph 6.2.6 deleted and replaced with 6.2.5 Summary of background in relation to effectiveness of systemic steroids in CAP caused by influenza. Relevant because of addition of influenza strata, now allows evaluation of

	(Zhang et al., 2015) However, it is likely that severity of illness will be a confounding factor in observational studies that evaluate this question and it is always uncertain if confounding due to this course has been adjusted for adequately. There have been no RCTs examining the effects of corticosteroids (versus no corticosteroids) in patients who are critically ill due to CAP caused by influenza. A particular feature of this REMAP trial is that it can respond to event such as pandemics, a Pandemic Influenza DSA for corticosteroids will address this question.	corticosteroids in CAP secondary to influenza. A systematic review and meta-analysis (nine cohort studies, n = 1405, and 14 case-control studies, n = 4700) and a recent secondary analysis of a Spanish cohort study, using propensity matching, showed increased mortality with corticosteroid treatment in influenza H1N1 infection. (Zhang et al., 2015, Moreno et al., 2018) However, it is likely that severity of illness will be a confounding factor in these studies and commonly, in studies enrolling patients who are critically ill, adjustment of confounding may be inadequate. As such, the role of corticosteroids in patients with severe CAP secondary to influenza remains uncertain and both beneficial or harmful effects are possible.	this question within the platform.
6.2.6 Role of Ccorticosteroids in Acute Respiratory Distress Syndrome Page 19	ARDS is common in the critically ill and severe CAP is a common primary etiological factor for its development. Several studies have evaluated the effects of corticosteroids in the particularly severely lung injured group (i.e. ARDS) of patients severe CAP in the ICU. Meduri, et al, 1998 conducted a small (n=24) double blind placebo controlled RCT where patients with severe ARDS who failed to improve by day 7 of respiratory failure were randomized to receive methylprednisolone versus placebo. (Meduri et al., 1998) This study demonstrated that corticosteroid treatment reduced ICU mortality,	ARDS is common in the critically ill and severe CAP is a common primary etiological factor for its development. Several studies have evaluated the effects of corticosteroids in patients with ARDS including patients with severe CAP. Meduri and colleagues conducted a small (n=24) double blind placebo controlled RCT where patients with severe ARDS who failed to improve by day 7 of respiratory failure were randomized to receive methylprednisolone versus placebo. (Meduri et al., 1998) This study demonstrated that corticosteroid treatment reduced ICU mortality, improved oxygenation and reduced	Clarification for grammar.

	improved oxygenation and reduced the Multiple Organ Dysfunction Score (MODS). (Meduri et al., 1998) However, this study was very small and it is also important to note that there were differences in baseline characteristics between groups. (Meduri et al., 1998) A subsequent larger Acute Respiratory Distress Syndrome Clinical Trial Network (ARDSNet) study randomized (n=180) patients with late ARDS (day 7 to 28) to receive methylprednisolone or placebo. This study demonstrated no difference in 60- day mortality but an increased death rate in those commenced on steroids after 2 weeks. (Steinberg et al., 2006) There was no increase in nosocomial infections but a trend towards increased neuromyopathy and an increased number of ventilator-free days (VFDs), ICU-free days and shock-free days in the first 28 days after treatment. (Steinberg et al., 2006). A recent single center randomized controlled trial (n=197) study of severe sepsis induced ARDS demonstrated that patients randomized to receive hydrocortisone (50mg, IV 6hourly) was significantly associated with improved pulmonary physiology (partial pressure of oxygen in arterial blood and fraction of inspired oxygen concentration ratio (P:F ratio), lung injury score) but had no survival benefit. (Tongyoo et al., 2016)	the Multiple Organ Dysfunction Score (MODS). (Meduri et al., 1998) The sample size of this study was small and it is also important to note that there were marked differences in baseline characteristics between groups. (Meduri et al., 1998) A subsequent Acute Respiratory Distress Syndrome Clinical Trial Network (ARDSNet) study randomized (n=180) patients with late ARDS (day 7 to 28) to receive methylprednisolone or placebo. This study demonstrated no difference in 60 day mortality but an increased death rate in those commenced on steroids after 2 weeks. (Steinberg et al., 2006) There was no increase in nosocomial infections but a trend towards increased neuromyopathy and an increased number of ventilator-free days (VFDs), ICU-free days and shock-free days in the first 28 days after treatment. (Steinberg et al., 2006). A recent single center randomized controlled trial (n=197) study of severe sepsis induced ARDS demonstrated that patients randomized to receive hydrocortisone (50mg, IV 6hourly) was associated with significantly improved pulmonary physiology (partial pressure of oxygen in arterial blood and fraction of inspired oxygen concentration ratio (P:F ratio), lung injury score) but had no survival benefit. (Tongyoo et al., 2016) These findings have variably been interpreted to mean	

	These findings have variably been interpreted to mean either “current evidence does not support the efficacy of steroids in ARDS” (Agarwal et al., 2007) or “prolonged glucocorticoid treatment substantially and significantly improves meaningful patient-centered outcome variables and has a distinct survival benefit”. (Meduri et al., 2007) Reflecting this apparent controversy the recent LUNG-SAFE study reported low levels of usage of corticosteroid in ARDS globally. (Bellani et al., 2016) It is clear that equipoise exists to randomize severe CAP patients who develop ARDS to receive corticosteroids (or not).	either “current evidence does not support the efficacy of steroids in ARDS” (Agarwal et al., 2007) or “prolonged glucocorticoid treatment substantially and significantly improves meaningful patient-centered outcome variables and has a distinct survival benefit”. (Meduri et al., 2007) Reflecting this apparent controversy the recent LUNG-SAFE study reported low levels of usage of corticosteroid in ARDS globally. (Bellani et al., 2016) It is clear that there is uncertainty if patients with severe CAP who develop ARDS should receive corticosteroids.	
6.2.7 Corticosteroid-associated complications in critical illness Page 20	Blank	The complications associated with the systemic use of corticosteroids treatment have been well described. The duration of administration of corticosteroids in patients with severe CAP is short (up-to a week) and, as a consequence, long-term complications of corticosteroid administration, such as diabetes mellitus, weight gain, and osteoporosis are not considered to be likely. However, risks associated with the short-term use in patients with severe CAP include in increased risk of nosocomial infection (due to the immunosuppressive effect of corticosteroids), hyperglycemia (which can be treated with insulin), and myopathy, which may lead to prolongation of the period of mechanical ventilation and weakness during	Moved from previous location

		the recovery phase after critical illness. It remains uncertain, in critically ill CAP patients, what is the overall effect of these potential complications on patient-centered outcomes, including survival.	
6.2.8 Definitively addressing the role of corticosteroids in severe CAP is a priority Page 21	6.2.8 The need for a large trial to definitively address the role of corticosteroids in severe CAP is a priority. Although the recent RCTs and meta-analyses have increased our knowledge regarding the potential usefulness and safety of corticosteroids in severe CAP, more studies are needed to clarify the effect of corticosteroids on mortality. Moreover, it is possible that there may be differential treatment effect in defined sub-groups of patients (i.e. shocked or not). Reliable treatment recommendations can only be raised only when large multi-center RCTs are conducted with sufficient statistical power to detect a difference in mortality. (Cheng et al., 2014)	6.2.8 Definitively addressing the role of corticosteroids in severe CAP. As outlined above, despite RCTs and meta-analyses, more studies are needed to clarify the effect of corticosteroids on mortality. The most important clinical questions are: • For patients with CAP who develop septic shock, does administration of hydrocortisone affect mortality and, if so, does duration of therapy influence this effect? • For patients with CAP but who do not develop septic shock does administration of hydrocortisone affect mortality? • For patients with influenza infection and CAP does hydrocortisone affect mortality?	Summary of background to better outline the clinical questions that are capable of being evaluated within the platform.
SECTION 7 DOMAIN OBJECTIVES	**Original text**	**New Text**	**Reason**
Page 21	The objective of this domain is to determine the effectiveness of hydrocortisone for the treatment of severe CAP. The interventions that will be compared are:	The objective of this domain is to determine the effectiveness of different strategies of corticosteroid utilization in the treatment of severe CAP. We hypothesize that the probability of all-cause mortality	Addition of new (third) intervention. Rationale outlined above.

	1. Hydrocortisone IV, 50 milligrams every 6 hours for up-to 7 days 2. No hydrocortisone We hypothesize that the probability of all-cause mortality at 90 days will be different in patients who are randomized to receive corticosteroids. We hypothesize that the treatment effect of corticosteroids is different depending on the presence or absence of shock at the time of enrollment (strata-by-intervention interaction). We hypothesize that the treatment effect of corticosteroids is different depending on the duration of concomitant treatment with a macrolide. This is an intervention by intervention interaction between this domain and the Macrolide Duration Domain. We hypothesize that the treatment effect of corticosteroids is different depending on the concomitant antibiotic that is administered. This is an intervention by intervention interaction between this domain and the Antibiotic Domain.	at 90 days after enrollment will differ based on the allocated corticosteroid strategy. The following interventions will be available: • No corticosteroid (hydrocortisone is not prescribed; no other corticosteroid is permitted; no administration of a placebo) • Fixed duration hydrocortisone (IV hydrocortisone 50mg every 6 hours for 7 days) • Shock-dependent duration hydrocortisone (IV hydrocortisone 50mg every 6 hours while in septic shock) We hypothesize that the treatment effect of different corticosteroid strategies is different depending on the presence or absence of shock at the time of enrollment (strata-by-intervention interaction). We hypothesize that the treatment effect of different corticosteroid strategies is different depending on the presence or absence of influenza infection at the time of enrollment (strata-by-intervention interaction). We hypothesize that the treatment effect of different corticosteroid strategies is different depending on allocation status in the Antiviral Domain. This is a	Modification of hypotheses to take into account application of influenza strata within the statistical model. Specification of evaluation of potential interaction between the new antiviral

		treatment-by-treatment interaction between the interventions in the Corticosteroid Domain and the Antiviral Domain. The analytic structure of this domain enables several questions to be addressed. First, is the effect of corticosteroids for CAP general to all of CAP, or different in the subset with shock? Second, is the effect of corticosteroids for CAP general to all of CAP, or different in the subset with influenza? Third, is the effect of corticosteroids different when titrated to the period where the patient is clinically in septic shock, rather than by administering a fixed one-week course?	domain and this domain. Summary of how analytic structure of the domain, and the statistical model, allows evaluation of the relevant questions outlined in the summary section of the background.
SECTION 8 TRIAL DESIGN	**Original text**	**New Text**	**Reason**
Page 22	This domain will be conducted as part of a REMAP trial (see Core Protocol Section 7).	This domain will be conducted as part of a REMAP-CAP trial (see Core Protocol Section 7).	Administrative change to use study nomenclature
8.2 Eligibility criteria Page 22	Patients are eligible for this domain if they meet all of the REMAP-level inclusion and none of the REMAP-level exclusion criteria (see Core Protocol Section 7.4). Patients who are eligible for the REMAP may have conditions that may exclude them from the Corticosteroid Domain.	Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria (see Core Protocol Section 7.4). Patients eligible for the REMAP may have conditions that exclude them from the Corticosteroid Domain.	Administrative changes to use study nomenclature and correct grammar errors. *REMAP-level* changed to *platform-level*.

			The words *who are* and *may* deleted
8.2.1 Domain inclusion criteria Page 23	Blank	8.2.1 Domain inclusion criteria Nil	Added to clarify that there are no domain inclusion criteria and to standardize with other DSAs.
8.2.2 Domain exclusion criteria Page 23	8.2.1 Exclusion criteria from this domain 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 other than CAP (or severe sepsis) such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven Pneumocystis jiroveci pneumonia • Have received an immunomodulatory dose of systemic corticosteroid therapy in the 24 hours prior to the time of enrollment. An immunomodulatory dose is defined as >20mg of hydrocortisone, >5mg prednisone, >4mg methylprednisolone or >0.8mg dexamethasone per 24 hours. • The treating clinician believes that participation in the domain would not be in the best interests of the	8.2.2 Domain exclusion criteria Patients will be excluded from this domain if they have any of the following: • Known hypersensitivity to hydrocortisone • Intention to prescribe systemic corticosteroids for a reason that is unrelated to the current episode of CAP (or direct complications of CAP), such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven Pneumocystis jiroveci pneumonia • More than 24 hours have elapsed since ICU admission • The treating clinician believes that participation in the domain would not be in the best interests of the patient	Change in nomenclature of heading to standardize with other DSAs. Clarification that intention better describes the exclusion criteria Addition of time window to replace previous administration of systemic corticosteroids.

	patient		
8.2.3 Intervention exclusion criteria Page 23	Blank	8.2.3 Intervention exclusion criteria Nil	Added to clarify that there are no intervention exclusion criteria and standardize with other DSAs.
8.3 Interventions Page 23	Patients will be randomly assigned to receive one of the following open-label study interventions. 1. Hydrocortisone IV, 50 mg every 6 hours for up-to 7 days. 2. No hydrocortisone (i.e. hydrocortisone is not prescribed during the subsequent 7 days and there is no administration of a placebo) 8.3.1. Timing to initiation of corticosteroids In patients randomized to receive hydrocortisone, administration should commence immediately after the allocation status is revealed, which is at the time of enrollment. The scientific validity of the study and patient welfare, as a consequence of Response Adaptive Randomization (RAR), is enhanced by immediate commencement of treatment according to the patient's allocation status as this maximizes separation between	8.3.1 Corticosteroid strategy interventions Patients will be randomly assigned to receive one of the following open-label study interventions. Patients allocated to the no corticosteroid intervention are not to receive any systemic corticosteroid, including hydrocortisone, for this episode of CAP and its direct complications up until study day 28. There is no administration of placebo. If a patient has been receiving any corticosteroid for CAP or its direct complications prior to enrollment, this medication must be ceased. Administration of a systemic corticosteroid, including hydrocortisone, is permitted only for the treatment of new illnesses that develop in the course of a patient's ICU stay, such as asthma or treatment of an allergic reaction. All use of systemic corticosteroids is recorded and the reason for any administration is documented.	New heading, to standardize with other DSAs Better specification of the existing interventions to deal with ambiguity that had been identified in start-up meetings.

	interventions. Duration of administration of corticosteroids Hydrocortisone will be prescribed for 7 days at the time of enrollment or until discharge from hospital, if hospital discharge occurs before 7 days have elapsed. For patients who are discharged from the ICU before 7 days, it is the responsibility of ICU staff to prescribe hydrocortisone for administration for a total of 7 days. However, it is not the responsibility of ICU medical or research staff to ensure continuation of the study drug after discharge from the ICU.	Patients allocated to the fixed-duration hydrocortisone intervention are to be prescribed a course of hydrocortisone 50mg IV every 6 hours for 7 days only. Administration is to commence immediately after the allocation status is revealed at the time of enrollment on study day 1. The 7-day course will be administered until at least the end of study day 7 and no longer than the end of study day 8. From completion of the 7-day course onwards, patients allocated to this intervention are not to receive any systemic corticosteroid, including hydrocortisone, for this episode of CAP and its direct complications up until study day 28. Administration of a systemic corticosteroid, including hydrocortisone, after completion of the 7-day course is permitted only for the treatment of new illnesses that develop in the course of a patient's ICU stay, such as asthma or treatment of an allergic reaction. All use of systemic corticosteroids is recorded and the reason for any administration from study day 9 onwards is documented. For patients who are discharged from the ICU before the end of the 7-day course of hydrocortisone, it is the responsibility of ICU staff to prescribe hydrocortisone to	

		complete the 7-day course. However, it is not the responsibility of ICU medical or research staff to ensure continuation of the hydrocortisone after discharge from the ICU and it is not a protocol deviation if the course of hydrocortisone is not completed after ICU discharge. Patients allocated to the shock-dependent duration hydrocortisone intervention, will have hydrocortisone, IV 50 mg every 6 hours, commenced if septic shock develops as a result of the patient's initial episode of CAP, up until study day 28. Hydrocortisone is to be commenced as soon as septic shock is diagnosed, including immediately after enrollment if septic shock has already been diagnosed. For the purposes of this intervention, septic shock is defined as administration of any vasopressor by continuous infusion where the treating clinician believes that the vasopressor requirement is caused by CAP and is not being administered for another reason such as untreated hypovolemia or solely to offset the effects of other ICU interventions such as administration of sedation or mechanical ventilation. The exact dose of vasopressor that defines septic shock is not set by the protocol but is based on the treating clinician's judgement. The rationale for avoiding an exact dose is because no particular dose	Detailed description of the new (third) intervention for shock-dependent duration hydrocortisone administration.

		signifies 'shock' unambiguously. Dosage guidance of vasopressor for initiation of corticosteroids for this intervention is described in a separate operational document. Hydrocortisone administration is to cease when the clinician believes that septic shock has resolved. Septic shock would always be regarded as having resolved if vasopressor infusion has not been administered in the preceding 24 hours. A clinician may regard septic shock to have resolved if vasopressor infusion is being administered intermittently or at sufficiently low dose. If, after cessation of hydrocortisone, but during the same ICU admission, there is redevelopment of septic shock due to CAP (as defined above), then hydrocortisone IV 50 mg every 6 hours is to be recommenced until resolution. Hydrocortisone should be ceased prior to ICU discharge. For all patients in this domain who remain in ICU after study day 28, data on the administration of corticosteroids is not collected, and administration of corticosteroids after study day 28 is at the discretion of the treating clinician. The interventions in this domain apply to any ICU readmission, up until study day 28, noting that the criteria	Clarification of the duration of participation.

		related to CAP and its direct complications still apply. If septic shock develops during the first or any subsequent ICU admission for a reason other than CAP, such as nosocomial infection, administration of corticosteroids is at the discretion of the treating clinician.	
8.4 Concomitant care Page 25	Administration of corticosteroids to patients who are enrolled in this domain and allocated to not receive corticosteroids for the 7 days after enrollment is a protocol violation 8.4.1. Implications of allocation status for eligibility in other domains Randomization in this domain has no influence on eligibility to other domains in this REMAP.	New or additional systemic corticosteroids may be administered to any patient who has received an allocation status in this domain for a new clinical indication other than CAP and its direct complications. All use of systemic corticosteroids is recorded and the reason for any new or additional administration is documented. The administration of etomidate after enrollment is not permitted and will be considered a protocol deviation.	Clarification of protocol deviation, reinforcing that administration of systemic corticosteroids for other indications, as required for participant safety and best interests, is not a protocol deviation. Addition of requirement to *not administer etomidate* as this agent may result in suppression of endogenous corticosteroid

			production and result in harm to patients not receiving hydrocortisone.
SECTION 9 TRIAL CONDUCT	**Original text**	**New Text**	**Reason**
9.1.1 Clinical data collection Page 27	No additional domain-specific data will be collected for this domain.	Additional domain-specific data will be collected. • Administration of systemic corticosteroids • Administration of etomidate between index hospital admission and randomization, and between randomization and the end of study day 8	Clarification of collection of data on administration of systemic corticosteroids and etomidate.
9.2 Criteria for discontinuation Page 27	Refer to Core Protocol Section 8.7 for discontinuation criteria for the participation in REMAP-CAP.	Refer to Core Protocol Section 8.7 for criteria for the discontinuation of participation in the REMAP-CAP trial.	Administrative changes to correct grammar
9.3.1 Blinding Page 27	Hydrocortisone will be administered on an open-label basis. All appropriate measures, such as notes on paper medication charts or entries into an electronic prescribing system will be used to prevent inadvertent administration of systemic corticosteroids to patients who are randomized to not receive hydrocortisone.	Hydrocortisone will be administered on an open-label basis.	Final sentence removed as redundant, as this information is already included in other sections or operational, or both.
SECTION 10 STATISTICAL CONSIDERATIONS	**Original text**	**New Text**	**Reason**
10.2 Unit-of-analysis and strata Page 28	10.2 Strata	10.2 Unit-of-analysis and strata	Specification that the unit-of-analysis takes

	Both analysis of the treatment effect and the RAR will utilize the stratum of shock in this domain.	There are four units-of-analysis for this domain, specified by the combination of shock and influenza strata status. Analysis and Response Adaptive Randomization are applied by shock and influenza status. The statistical model will permit borrowing between all stratum as specified in Core Protocol Section 7.8.3.3. It is noted that the definition of shock that is specified in the Core Protocol (presence or absence of inotrope or vasopressor infusion at baseline) determines strata status, and not the definition of septic shock that is used to define administration of hydrocortisone in the shock-dependent duration hydrocortisone intervention.	into account both shock and influenza strata. Specification that borrowing between stratum is permitted.
10.3 Timing of revealing of randomization status Page 28	The timing of the revealing of allocation status and administration of interventions is as specified to be Randomization with Immediate Reveal and Initiation (see Section 7.8.3.4 in Core Protocol).	The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal and Initiation (see Section 7.8.3.6 in Core Protocol). For patients allocated to the shock-dependent duration hydrocortisone intervention, who are not in septic shock at the time of randomization, Immediate Reveal and Initiation is interpreted as intention to commence hydrocortisone if septic shock develops.	Clarification that, at the time of reveal, for the shock-dependent duration intervention, that, if the patient is not in septic shock, the intervention is intention to commence hydrocortisone if shock develops.
10.4 Interactions with interventions in other domains	An a priori interaction with the Antibiotic Domain is considered possible and will be incorporated into the	An a priori interaction with the Antibiotic Domains is not considered possible and will not be incorporated into the	Revision of the treatment-by-

Page 28	statistical models used to analyze this domain. An a priori interaction with the Macrolide Duration Domain is considered possible and will be incorporated into the statistical models used to analyze this domain.	statistical models used to analyze this domain. An a priori interaction with the Macrolide Duration Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain. An a priori interaction with the Antiviral Domain is considered possible and will be incorporated into the statistical models used to analyze this domain.	treatment interactions that are incorporated into the statistical model based on input from content experts and to optimize available statistical power.
10.5 Nesting Page 29	Blank	The interventions in this domain will be analyzed without application of nesting. This is because the shock-dependent duration hydrocortisone intervention will be more like the fixed-duration hydrocortisone intervention in patients who develop septic shock and more like the no corticosteroid intervention in patients who do not develop septic shock (i.e. no hydrocortisone is administered). This divergence in potential similarity cannot be accommodated within the statistical model to allow nesting. For reasons of participant safety and relevance to public health, the DSMB are empowered to request a secondary model to be performed which does allow nesting, if the DSMB believes that it is appropriate to do so.	Specification that nesting is not being applied and explanation for why nesting is not possible. Further information that would allow nesting to be applied by DSMB, as appropriate, by

			requesting a nested analysis.
10.6 Threshold odds ratio delta for equivalence Page 29	Blank	10.6 Threshold odds ratio delta for equivalence The threshold odds ratio for equivalence in this domain is that specified in the Core Protocol (Section 7.8.8).	Specification of the default odds ratio for equivalence
10.7 Post-trial Sub-groups Page 29	10.5 Post-trial Sub groups Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of the domain. Sub-groups of interest include: • The causative organism, in patients from whom a microbiological diagnosis for the qualifying pneumonia has been made on the basis of culture or other investigations (nucleic acid testing, urinary antigen testing) based on tests taken before or within 72 hours of admission to hospital.	10.7 Post-trial Sub-groups Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The a priori patient sub-groups of interest are: • All other potentially evaluable treatment-by-treatment interactions with other domains	Addition of previously incorporated treatment-by-treatment interactions as a post-trial sub-group.
SECTION 11 ETHICAL CONSIDERATIONS	**Original text**	**New Text**	**Reason**
11.2 Potential domain-specific adverse events Page 30	Please refer to Core Protocol Section (8.13) for information about safety monitoring and reporting.	Other SAEs should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see Core Protocol Section 8.13)	Updated with Domain-specific SAE information only. Overarching SAE information is in the Core protocol

11.3 Domain-specific consent issues Page 30	Hydrocortisone has been used by clinicians for patients with severe CAP for decades. However, there is substantial variation between clinicians within and between countries and hospitals within countries. This variation in practice occurs, predominantly, because, although there is limited evidence of effectiveness, there remains no high-quality evidence that the use of hydrocortisone improves mortality. If this domain were not part of this REMAP it is reasonable to presume that some, but far from all, patients at sites that are participating in the REMAP would receive corticosteroid treatment but that such treatment decisions would reflect the choice of clinicians making a treatment decision in the absence of high quality evidence. Corticosteroids are not contraindicated in women who are pregnant and patients who are pregnant will not be excluded from this domain.	Hydrocortisone has been used by clinicians for patients with severe CAP for decades. However, there is substantial variation between clinicians within and between countries and hospitals within countries. This variation in practice occurs, predominantly, because the limited high-quality evidence is contradictory. If this domain were not part of this REMAP it is reasonable to presume that some, but far from all, patients at sites that are participating in the REMAP would receive corticosteroid treatment. Corticosteroids are not contraindicated in women who are pregnant and patients who are pregnant will not be excluded from this domain. The choice of which the three interventions are available at any site (i.e. any two or all three interventions) is determined by the participating site. Sites for which standard care is to routinely administer hydrocortisone to patients with septic shock should not participate in the no hydrocortisone intervention. The remaining two interventions administer hydrocortisone to patients who have or develop septic shock, but do so for different durations for which may sites will have clinical equipoise.	Administrative changes to correct grammar and the addition of the final paragraph to improve clarity Description of equipoise issues relevant to the choice of interventions within the domain.
21.1 Funding	The REMAP trial is funded by an Australian National	Funding sources for the REMAP-Cap trial are specified in	Updated with Domain-

Page 31	Health and Medical Research Council project grant (APP1101719), a European Union 7th Framework Programme for Research and Technological Development grant (602525) and a Health Research Council New Zealand Programme grant (16/631).	the Core Protocol Section 2.5. This domain has not received any additional domain-specific funding.	specific funding information only. Overall trial funding information is in the Core protocol
12.2. Funding of domain interventions and outcome measures Page 31	12.2. Funding of domain interventions	12.2. Funding of domain interventions and outcome measures	Administrative changes for consistency across all protocol appendices

5.4. Appendices

5.4.1. REMAP-CAP Statistical Analysis Appendix Version 3, dated 24 August 2019

Section	Original text	New Text	Reason
Front page and whole document header	REMAP-CAP Statistical Analysis Appendix Version 2 dated 12 December 2017	REMAP-CAP Statistical Analysis Appendix Version 3 dated 24 August 2018	Administrative change to version and date
SECTION 1. ABBREVIATIONS	**Original text**	**New Text**	**Reason**
Page 4.	DSA Domain-Specific Appendix DSMB Data Safety and Monitoring Board ISIG International Statistics Interest Group ITSC International Trial Steering Committee ITT Intention To Treat MCMC Markov Chain Monte Carlo mITT Modified Intention To Treat NDLM Normal Dynamic Linear Model P:F ratio Ratio of Partial Pressure of Oxygen in Arterial Blood and Fraction of Inspired Oxygen Concentration PP Per Protocol RAR Response Adaptive Randomization REMAP Randomized, Embedded, Multifactorial Adaptive Platform trial REMAP-CAP Randomized, Embedded,	CAP Community-Acquired Pneumonia DSA Domain-Specific Appendix DSMB Data Safety and Monitoring Board ISIG International Statistics Interest Group ITSC International Trial Steering Committee ITT Intention To Treat MCMC Markov Chain Monte Carlo mITT Modified Intention To Treat NDLM Normal Dynamic Linear Model P:F ratio Ratio of Partial Pressure of Oxygen in Arterial Blood and Fraction of Inspired Oxygen Concentration PP Per Protocol RAR Response Adaptive Randomization REMAP Randomized, Embedded, Multifactorial Adaptive Platform trial	Updated with all abbreviations used in this version of the document

	Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia SAC Statistical Analysis Committee Severe CAP Severe Community-Acquired Pneumonia	REMAP-CAP Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia SAC Statistical Analysis Committee ~~Severe CAP Severe Community-Acquired Pneumonia~~	
SECTION 2. STATISTICAL ANALYSIS APPENDIX PROTOCOL VERSION	**Original text**	**New Text**	**Reason**
2.1 Version History Page 5.	Version 1: Approved by the International Trial Steering Committee (ITSC) on 7 November 2016 Version 1.1: Approved by the ITSC on dated 12 April 2017 Version 2: Approved by the ITSC on 12 December 2017	Version 1: Approved by the International Trial Steering Committee (ITSC) on 7 November 2016 Version 1.1: Approved by the ITSC on dated 12 April 2017 Version 2: Approved by the ITSC on 12 December 2017 Version 3: Approved by the ITSC on 24 August 2019	Updated with new version details
SECTION 3. INTRODUCTION	**Original text**	**New Text**	**Reason**
Page 5.	The purpose of this section of the protocol is to describe the statistical methods that will be used to analyse data within this randomized, embedded, multifactorial adaptive platform trial (REMAP). It is written for statisticians and may not be accessible to individuals without training in statistics. This appendix should be	Blank	This introductory paragraph has been removed from the updated version of this document.

	read in conjunction with the Core Protocol. Within the REMAP, two or more interventions within a domain are evaluated and statistical models are used to determine if interventions are superior, inferior or equivalent. The reaching of superiority, inferiority, or equivalence is termed a Platform Conclusion. At any given time, a Platform Conclusion may be reached for one or more, including all, strata. A Platform Conclusion may be reached at different time points in different strata. A Platform Conclusion will follow a Statistical Trigger, which is the model reaching a predetermined threshold for a decision. The criteria for a Statistical Threshold are set out in this Core Protocol (7.8.6 to 7.8.9), although additional details that are relevant to determination of equivalence within a specific domain are described in Domain Specific Appendices (DSAs).		
	The trial design is built as a process – with the possibility of multiple treatment options (interventions) within multiple domains being investigated. The trial design is built prospectively to be flexible. These flexible aspects are designed and planned and are part of the protocol design. In this report, we describe the detail of the prospective design. In contrast to many clinical trial designs, where there is a single or a small number of	This trial design is built as a process – with the possibility of multiple interventions within multiple domains and multiple patient groups being investigated. The trial design is built prospectively to be flexible. These flexible aspects are designed and planned and are part of the protocol. In this report, we describe the details of the prospective statistical design. In contrast to many clinical trial designs, where there is a single	Clarification of terminology.

	fixed treatment options, this REMAP is designed generically to incorporate a flexible number of treatments, with the possibility of these numbers evolving as the science evolves. This adaptive design report describes the design in the most generality possible, and thus applies for all imaginable trial design states. The foundational aspects of the treatments are the defined treatment *domains*, with the individual interventions within these *domains*. A collection of interventions assigned for a patient is a treatment *regimen*. Patients will be classified into *strata*. These strata are used to determine allowable treatment assignments and ultimately to identify optimal interventions. Each of these are allowed to evolve throughout the perpetual REMAP. These evolutionary aspects are described. The adaptations in the design are controlled by a statistical model. This statistical model is described in the section entitled "Statistical Modeling" (Section 5). The model is created to evolve as the domains, interventions, and subgroups evolve. The section entitled "Trial adaptation and stopping criteria and guidelines for interventions" (Section 6) describes the adaptations in this REMAP. These include the timing	intervention or a small number of interventions, this REMAP is designed generically so that it may incorporate a flexible number of interventions, with the possibility of these numbers evolving as the science evolves. This statistical analysis plan describes the statistical design in the most general way possible, and thus applies for all imaginable trial design states. The current trial design state is described a separate document, Current Statistical Modeling. Similar interventions are grouped within *domains*. Each patient is randomized to a single intervention from each domain. This set of randomized interventions across the domains is the patient's *regimen*. Patients are also grouped into *strata* and into disease *states*. The efficacy of the interventions may vary by strata. Optimal interventions will be identified by strata. Some interventions may only be administered to patients in certain disease states. The specific domains, interventions, strata, and states being investigated in REMAP are allowed to evolve throughout the perpetual nature of this trial. These evolutionary aspects are described. The adaptations in the design are controlled by a statistical model. This statistical model is described in the section entitled "Statistical Modeling" (Section 5).	Explains creation of operational document to describe the Current Model.

	of adaptive analyses, the Response Adaptive Randomization (RAR) within strata, and the requirements for declaration of superiority, inferiority, or equivalence of interventions within strata. The Simulations Appendix presents a range of simulations based on the starting assumptions of the trial to understand the operating characteristics of the design. This includes simulating from various assumptions of treatment effects and observing the behavior of the trial design: for example, the rate of determining superiority or inferiority of interventions, the number of patients assigned to each regimen and intervention, and the number of treatment failures during a course of the trial.	The modeling can expand and contract to accommodate the number of domains, interventions, strata, and states being evaluated at any time. The section entitled "Trial adaptation and stopping criteria and guidelines for interventions" (Section 9) describes the adaptations in this REMAP. These include the timing of adaptive analyses, the Response Adaptive Randomization (RAR), and the requirements for declaration of superiority, inferiority, or equivalence of interventions. A separate document, The Current Statistical Modeling document, describes the current domains, interventions, strata, states and specifies the current statistical modeling. Another separate document, the Simulations Appendix, presents a range of simulation-based operating characteristics based on the current state of the trial. This includes simulating from various assumptions of treatment effects and observing the behavior of the trial design: for example, the number of patients assigned to each intervention, and the probability of declaring interventions superior, inferior, or equivalent by strata.	
SECTION 4. STRUCTURE OF THE TRIAL	**Original text**	**New Text**	**Reason**
4.1 Primary Endpoint Page 7.	The primary endpoint for the trial is all-cause mortality at 90 days. Each patient will be defined as a failure	The primary endpoint for the trial is all-cause mortality at 90 days. This is considered as a dichotomous	This section has been moved from section 4.5 in

	(mortality within 90 days of enrollment) or success (not a failure). We label the outcome for a patient as *Y*, where *Y*=1 is defined as a failure (death within 90 days) and *Y*=0 is a patient success.	endpoint where outcomes will be failure (mortality within 90 days of enrollment) or success (not a failure). We label the outcome for a patient as *Y*, where *Y*=1 is defined as a failure (death within 90 days) and *Y*=0 is a patient success.	the previous version, to 4.1. Clarification that primary endpoint will be treated as dichotomous.
4.2 Domains Page 7.	For the purposes of a REMAP, a **domain** defines a specific set of competing treatments within a common clinical mode. Each domain has a set of mutually exclusive and exhaustive **interventions**. That is, every eligible patient will be allocated one and only one of the available interventions within a domain. We label each domain with a letter; A, B, C, … The interventions within a domain are labeled with a subscript index, for example, in domain A, the k_A interventions are $A_1, A_2, \ldots, A_{k_A}$. It is expected that the number of domains, and the interventions within domains will expand or contract as the trial progresses.	For the purposes of REMAP, a **domain** defines a specific set of competing treatments within a common clinical mode. Each domain has a set of mutually exclusive and exhaustive **interventions**. Every eligible patient will be randomized to one and only one of the available interventions from each domain. We label the domains as *d* = 1, 2,…, *D*. A specific domain may also be referred to by a letter: A, B, C, …. Interventions within a domain are labeled with a subscript index, *j*. Therefore, d_j refers to intervention *j* within domain *d*. There are j = 1, …, J_d interventions in each domain *d*. It is expected that the number of domains, and the number of interventions within each domain will expand or contract as the trial progresses.	Clarification of terminology.
4.3 Regimens Page 7.	Every patient will be assigned a set of interventions, exactly one from each domain. The set of interventions are referred to as a treatment regimen. Each patient in the trial will be assigned a treatment regimen, thus	Every patient will be randomized to set of interventions, exactly one from each domain. The set of interventions are referred to as a regimen. All possible combinations define the set of available arms in the trial. We label a	Clarification to differentiate randomization from assignment.

	these are the available arms in the trial. We label a regimen *r*, as the pairing of interventions. As an example, assuming 4 domains, a regimen would be…	regimen as *r*. As an example, assuming 4 domains denoted as domain A, B, C, and D, a regimen would be…	
4.3 Regimens Page 7.	For ease of notation we refer to the arm assigned, *t*, by the index of each intervention, sequentially, for each domain, so equivalently, the regimen assignment is labelled as *t* = (*a, b , c, d).*	Blank	Removal of redundant section.
4.4 Strata Page 8.	There are multiple covariates within this REMAP, but some of these covariates are treated as possibly prognostic – that is the treatment effect may vary across these covariates. We label these prospectively defined subgroups in which the treatment effect is modeled as possibly varying across them as strata. Patients will be classified by membership in different **stratum**. Stratum membership for a patient will be defined by a set of dichotomous baseline characteristics. Let x_1, …, x_J be the set of *J* indicator variables that define strata. The number of unique strata (or sub-groups) is 2^J. Initially in the trial there is one covariate, "Shock" (x_1) to define strata. We label the groups as g=1,2, for the pairs (x_1=0) and (x_1=1), respectively. The model allows for the expansion or modification of	There are multiple covariates within this REMAP to describe patients' baseline characteristics, but some of these covariates are treated as possibly prognostic in that the treatment effect may vary across these covariates. We label these select covariates as prospectively defined strata and the treatment effect of an intervention is modeled as possibly varying across the strata. Within each stratum, patients will be grouped in a dichotomous manner. If a strata is defined as an ordinal-type variable, then dichotomous indicator variables according to the desired contrasts will be defined. Therefore, let x_1, …, x_K be the set of *K* dichotomous indicator variables that define the different strata. The number of unique strata (or sub-groups) is 2^K. We label the dichotomous groups in each stratum as g=1,2. For	Amended to acknowledge that strata membership will be determined by information that relates to patients' at the time of eligibility (i.e. baseline). Clarification that strata membership will be treated in a dichotomous manner. Addition of an example of how strata membership

	stratum definitions as the trial progresses. The description here is expandable when strata are defined by a dichotomous factorial structure. The trial is designed to be expandable in this way. Thus, the initial *J*=1 interventions that define strata could expand if the science dictates this.	example, the trial will begin with a single stratum – shock. Therefore, shock is strata x_1. Within this stratum, patients will either not be in shock (g = 1) or will be in shock (g = 2). The number of strata may be expanded, or the existing strata may be modified as the trial progresses. The description here is expandable when strata are defined by a dichotomous structure.	will be notated. Acknowledgement that the number of strata is not fixed, and that new strata may be added or current strata modified as the trial progresses.
4.5 State Page 8.	The different states within the REMAP are used to define possible eligibility of the patient for different domains at different times in the trial and as a covariate of analysis within the Bayesian statistical model for adjusting the disease severity.	The different states within the REMAP are used to define possible eligibility of the patient for different domains at different times in the trial and as a covariate of analysis within the statistical model to adjust for disease severity.	Correction of Grammar
4.5 State Page 8.	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.	A state is a set of mutually exclusive categories, defined by characteristics of a patient, and states are dynamic in that they can change for a single patient, at different time-points, during the patient's participation in the REMAP.	Inclusion of the concept of State.
4.5 State Page 8.	The number of state variables and the number of states within the REMAP may be varied, depending on the impact of the number of states on statistical power, as determined by simulations. The same states may be shared by one or more domains but may be different in	The number of state variables and the number of states within the REMAP may be varied, depending on the impact of the number of states on statistical power, as determined by simulations. The *a priori* defined states that are used may be changed during the life of the	Removal of redundant text

	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 and, if this occurs, will result in amendment of one or both of the Core Protocol or DSAs. The states are modeled as additive covariates within the statistical model. We label the different states as s=1,…,S.	REMAP as knowledge is accumulated. The states are modeled as additive covariates within the statistical model. We label the different states as s=1,…,S.	
4.6 Randomization Page 9.	Randomization assignment is done for a patient at baseline. Randomization is based on the individual strata for the patient. The randomization probability for different regimens may vary depending on the stratum of the patient. All randomization is done based on the full regimen, not on individual interventions. describes the response adaptive randomization allocation procedure. There are some interventions that are specific to defined states of the patient. Some of the patients will not be in states initially that require an intervention from a domain. For example, a domain may be specific	Randomization assignments are performed for patients at baseline. Randomization is performed separately by strata in that the randomization probabilities to the interventions may vary depending on the group membership of the patient within the strata. Patients are randomized to a full regimen, and not to individual interventions within the domains. Section 9.6 describes the response adaptive randomization allocation procedure. However, there may be domains where the therapy is specific to a certain disease state. Some patients will not be in disease states that require the interventions from	Rewriting without change in meaning to improve clarity.

	to a more severe disease state. Initially the patient may not be in that severe disease state. Randomization at baseline will assign all interventions, even for those domains in which a patient's state does not require an intervention from that domain. Each domain will be treated differently in the timing of revealing the randomization. Some domains will employ an *immediate* reveal at baseline. For these immediate reveal domains the randomization will be treated in an intent-to-treat fashion for the primary analysis. Some domains will employ *delayed reveal*, in which the randomization is revealed only when the patient achieves the state that defines the need for the domain. The revealing of the domain will be tracked and the model will censor appropriately those that do not have a revealed intervention for a domain. In the case of delayed reveal the specific modeling of the intervention effects and modeling the time varying aspects of states will be custom to that domain.	a particular domain. For example, a domain may be specific to a more severe disease state. Initially the patient may not be in that severe disease state but could transition to that disease state. Randomization at baseline will assign an intervention in each domain regardless of disease state. However, the domains may differ in the timing of when the randomization assignment is revealed. Some domains will employ an *immediate* reveal at baseline. For these immediate reveal domains the randomization will be treated in an intent-to-treat fashion for the primary analysis in that all patients will be included in the analysis of that domain. Some domains may employ *deferred reveal*, in which the randomization assignment is revealed based on an initial eligibility criterion at the time of randomization but the information to assess that eligibility criterion only becomes known after some time. These domains will be treated analogously to the immediate reveal domains for analysis. Finally, some domains will employ *delayed reveal*, in which the randomization is revealed only for patients in the disease states, or who progress to the disease states, that require that domain. The revealing of the domain will be tracked and the analysis of delayed reveal domains will censor from the analysis	Addition of deferred reveal (see amendments to Core Protocol for explanation)

		the patients that did have that randomization assignment revealed. In the case of interventions within a delayed reveal domain, the specific modeling of the intervention effects and modeling the time varying aspects of states will be custom to that domain and will be prespecified in a separate document, Current Statistical Modeling.	
SECTION 5. STATISTICAL MODELING	**Original text**	**New Text**	**Reason**
Page 10.	Inferences in this trial are based on a Bayesian statistical model, which estimates the probability of all-cause mortality at 90 days (primary endpoint) of the combinations of interventions (known as a posterior probability distribution), taking into account the evidence accumulated during the trial (based on data on the outcomes of participants) and an assumed prior knowledge (known as a prior distribution). This differs from conventional (frequentist) trials where inferences are based on a likelihood of observed outcomes against a null hypothesis. The statistical model takes into account the variation in outcomes by region (country), age, pre-specified strata, temporal changes, treatment effects effects,	Inferences in this trial are based on a Bayesian statistical model, which estimates the posterior probability of all-cause mortality at 90 days (primary endpoint) for each regimen based on the evidence that has accumulated during the trial in terms of the observed 90-day mortality outcomes and assumed prior knowledge in the form of a prior distribution. This differs from conventional (frequentist) analysis methods where inferences are based on a likelihood of observed outcomes against a null hypothesis. The statistical model takes into account the variation in outcomes by region, strata, disease states, age group, and time since the start of the trial. The model estimates treatment effects for each intervention as	Rewriting without change in meaning to improve clarity. Reorganization from previous version of Statistical Appendix to reflect changes in statistical approach (see amendments to Core Protocol for explanation)

	interactions between treatment and strata, and interactions between interventions across different domains.	well as determines if these treatment effects vary by strata and if treatment effects of individual interventions in one domain vary when paired with interventions from other domains. Let • R = region • s = disease state • k = strata and g_k = the yes/no dichotomous status within strata k where g_k = 1 means the strata condition is “no” and g_k = 2 means the strata condition is “yes” • age = age group • T = era measured in 13-week increments since the start of the trial • d = domain and d_j is intervention j within domain d We model the log odds of the probability of 90-day all-cause mortality, π, as	

		$$\log\left(\frac{\pi}{1-\pi}\right) = \sum_{R=1}^{R} \nu_R + \sum_{k=1}^{K}\sum_{s=1}^{S} \alpha_{s,g_k} + \sum_{age=1}^{AGE} \lambda_{age} + \sum_{T=1}^{T} \theta_T + \sum_{d=1}^{D}\sum_{j=1}^{J_d} \beta_{d_j} + \sum_{k=1}^{K}\sum_{d=1}^{D}\sum_{j=1}^{J_d} I(g_k = 2)\gamma_{kd_j} + \sum_{d=1}^{D}\sum_{j=1}^{J_d}\sum_{d'=d+1}^{D}\sum_{j'=1}^{J'_{d'}} \delta_{d_j d'_{j'}}$$ The interpretation of each term in the model is: ν_R is the covariate that adjusts for region. There is one ν_R term estimated for each R = 1,…,R where R = 1 is the referent group and the remaining terms estimate the increase or decrease in mortality associated with region α_{s,g_k} is the covariate that adjusts for both strata and disease state. For each strata *k* where k = 1,…K, there is one term for every pairwise combination of *s* = 1,…,*S* and g_k = 1,2. The referent by strata *k* is when both s = 1 and g_k = 1. The remaining terms then estimate the increase or decrease in mortality associated with the strata and disease state combinations. When s = 1 (the referent disease state) this term estimates the increase or decrease in mortality associated with the strata	

		condition (g_k = 2 versus g_k = 1). For g_k = 1 (the referent strata group) this term estimates the increase or decrease in mortality associated with disease state (s = 2,…,S versus s = 1). When both s > 1 and g_k = 2 this term estimates the additional effect of the strata condition (g_k = 2) in each of the disease states. λ_{age} is the covariate that adjusts for age group. Age will be modeled as categorical age groups. There is one λ_{age} term for each age group being modeled. The referent will be a middle age group and the remaining terms estimate the increase or decrease in mortality associated with the other age group categories. θ_T is the covariate that adjusts for time since the start of the trial. There is one term for each T = 1,…,T where each represents an era, or a 13-week period of calendar time. The trial era in which the analysis is being conducted (the most current era) will be the referent and every other θ_T then represents the increase or decrease in mortality associated with calendar time since the start of the trial. β_{d_j} are the terms that estimate the main effects of each	

		intervention. There is one β_{d_j} term for each intervention in each domain. Intervention j = 1 in domain d = 1 is the referent and every other β_{d_j} estimates the relative increase or decrease in mortality associated with each other intervention in the trial. γ_{kd_j} are the terms that estimate intervention by strata interactions. There is one term for every pairwise combination between the k = 1,…, K strata in the trial and the j = 1,…,J_d interventions across all d = 1,…D domains in the trial. We define $I(g_k = 2)$ as an indicator variable for g_k = 2 in strata k. Therefore, this term estimates the increase or decrease in morality associated with an intervention when g_k = 2 (strata condition is "yes") versus when g_k = 1 (strata condition is "no"). $\delta_{d_j d'_{j'}}$ are the terms that estimate the intervention by intervention interactions. There is one term for every pairwise combination between all the interventions j = 1,…, J_d in one domain all interventions $j' = 1,\ldots, J_{d'}$ in every other domain. These terms estimate the increase or decrease in the effectiveness of each intervention when it is paired with another intervention from	

		another domain. As described above, there may be two types of domains. There will be immediate reveal domains that investigate interventions that do not depend on disease state and the randomization assignments in these domains can be made known immediately. There may be delayed reveal domains that investigate interventions that are appropriate only for patients in certain disease states that evolve within patients during the trial. The randomization assignment can be made known only to patients in these disease states. Therefore, there will be three groups of patients relative to a delayed reveal domain: 1. The randomization is never revealed because the patient is never in an eligible disease state 2. The patient enters the trial in the eligible disease state and the randomization assignment is effectively immediately revealed 3. The patient transitions to the eligible disease state after the initial randomization and the randomization status is a delayed reveal We define a model that includes terms for the	

		treatments in both immediate and delayed reveal domains. However, there will be no interaction terms estimated with the interventions in the delayed reveal domains and any other domains. This model will be fit based on all randomized patients where patients are included in the model based on the initial disease state they are in at the time they are randomized. The efficacy of delayed reveal domains among patients who transition to the eligible disease state (group 3 above) will be modeled through a "sub-model" that only informs the relative efficacy of the interventions within the delayed reveal domain. The sub-model will include adjustment for the covariates of region, age and era, and will include the main effect terms for the interventions in the delayed reveal domain. The sub-model will be dependent on the primary model in that the estimation of the sub-model will be conditional upon the estimates of region, age, and era from the primary model.	
5.1 Modeling Covariates for ineligibilities for interventions and/or domains Page 13.	In order to present the modelling details we refer to the domains as *d*=1,2,..,D and intervention *j* in domain *d*. as f_{dj} (factor). Let *R* be the region that a patient is enrolled (we use a generic term region, R, where typically this is a site, but may be a cluster of sites, etc). Let *T* be the time	The modeling of the primary endpoint is a logistic regression form: $$\log\left(\frac{\pi}{1-\pi}\right) = f(R,k,s,age,T,d,j).$$ In order to add covariates in the model, for sensitivity or exploration they will be added as (possibly multiple	Reorganization from previous version of Statistical Appendix to reflect changes in statistical approach (see

	interval (era) in which a patient is enrolled. The eras will be sequential "buckets" of 13-week time periods from the start of the trial, *T*=1,2,3,.... The age of the subject will be treated with four age intervals, age=1 is 40-years old or less, age=2 is 41-to-65, age=3 is 66-to-75, and age=4 is 76-or-older. We model the probability of death, π, for a patient with group membership determined by their shock classification x_1, (and the resulting *g*), region *R*, time interval of enrollment *T*, age group, and treatment regimen assignment *t*. The state to which a patient is in is critical to the probability of mortality. We model the probability of mortality as a function of the state of the patient. We describe the model in tiers based on state. There are 3 states defined in the trial, 1) patient is not ventilated 2) patient is ventilated via an endotracheal tube but not severely hypoxic (ratio of partial pressure of oxygen in arterial blood and fraction of inspired oxygen concentration (P:F) ≥ 200), and 3) patient is ventilated via an endotracheal tube and is severely hypoxic (P:F < 200). We refer to these states as *s*=1, 2, and 3, respectively. If a patient starts in state 1 or 2 and progresses to state 3 during the trial, we model this	covariates): $$\log\left(\frac{\pi}{1-\pi}\right) = f(R,k,s,age,T,d,j) + \zeta Z$$ where *Z* is a normalized covariate and ζ is the model coefficient. Individual patients may enter the trial ineligible to one or more individual interventions within a domain or one or more domains. If a patient is ineligible for one or more interventions within a domain but there are at least two interventions for which the patient is eligible to be randomized among then the patient is allocated an intervention from among the eligible interventions and the data for such a patient is included in the full analysis set and a covariate indicating ineligibility to the interventions will be fit. If a patient is ineligible for an entire domain then an indicator for the domain ineligibility is created and a covariate, *Z*, for this ineligibility is created. No treatment allocation variable nor interactions for this patient are included in the model. The coefficients for all covariates for these ineligibility interventions/domains will have the following priors: $$[\zeta] \sim N(0, 10^2).$$ A list of all models, model terms, and their prior	amendments to Core Protocol for explanation)

	state of progressing during the trial as state 4. This appendix presents the details for the following starting domain structure. There are four domains, ventilator, antibiotic, steroids, and extended macrolide. The ventilator domain will employ delayed reveal if a patient is in state 1 or 2 initially and progresses to state 3 (this time transition is referred to as state 4). The ventilator domain is ideal for this delayed reveal because we model the interventions without interactions with the other domains. The extended macrolide is defined a extending the use of the macrolide to 14 days instead of 3 days. This domain will employ immediate reveal and the treatment effects will be modeled with an intent-to-treat model. We model the efficacy of the ventilator interventions (d=1) as independent of the remaining domains, Antibiotic (d=2), Steroid (d=3), and Macrolide (d=4). We model the interaction between each of the interventions in different domains, except the ventilator domain which is modeled without interactions to other domains. If a patient enters the trial in State s=3, then all interventions are revealed and the model for the	distributions specific to the current state of the trial are provided in a separate document. All models will be fit using Markov Chain Monte Carlo (MCMC) methods.	

	probability of mortality is $$\log\left(\frac{\pi}{1-\pi}|x_1, s, R, T, t\right) = \nu_R + \alpha_{g,s} + \lambda_{age} + \theta_T + \sum_{d=1}^{D} \beta_{dt_j} + \sum_{d=2}^{D} x_1 \gamma_{jdt_d} + \sum_{i=2}^{D} \sum_{j=i+1}^{D} \delta_{ij}\left(f_{it_i}, f_{jt_j}\right).$$ The first term, ν_R, is the parameter for the region in which a patient is enrolled. It is expected that the rate of mortality, conditional on group, will vary across regions. These parameters allow the simultaneous estimation of the risk of each region. The $\alpha_{g,s}$ for *g*=1,2, *s*=1,2,3, 4 are the parameters for the risk of each strata and state. The λ_{age} for *age*=1,2,3,4 are the parameters for the covariate adjustment to risk for based on the age grouping.		

	The θ_T for *T*=1,2,3,… are the parameters for the risk of each time period (referred to as eras) during the course of the trial. These parameters allow the estimate of the relative risk changing over time during the course of the trial. This is a common estimate for all groups. The β_{dj} for *d*=1,…,*D*, and *j*=1,…, k_d are the global treatment effect parameters for each intervention. These parameters capture the relative risk of each intervention for patients in all strata. The γ_{idj} for *i*=1,2; *d*=1,…,*D*; and *j*=1,…, k_d are the treatment effect parameters for each intervention, isolated to patients with $x_1 = 1$ (shock). These parameters capture the relative risk for each intervention, isolated to patients with the indicator of shock. These parameters characterize the interaction between an intervention and the shock stratum. The $\delta_{f_{di}f_{lj}}$ for $d \neq l$; and *i*=1,…, k_d; *j*=1,…, k_l are the global two-way interaction effects between all (non-ventilator) treatment interventions in different domains. These parameters capture the relative risk of combining two interventions from different domains together. If a patient enters the trial in States 1 or 2 (off ventilator		

	or ventilated but not with severe hypoxia) then the ventilator allocation status will not be revealed and the model does not inform on the efficacy of the ventilator domain. The probability of mortality for a patient is modeled as $\log\left(\frac{\pi}{1-\pi}|x_1, E, R, T, t\right)$ $= \nu_R + \alpha_{g,E} + \lambda_{age} + \theta_T + \sum_{d=2}^{D} \beta_{dt_j}$ $+ \sum_{d=2}^{D} x_1 \gamma_{jdt_d} + \sum_{i=2}^{D} \sum_{j=i+1}^{D} \delta_{ij}\left(f_{it_i}, f_{jt_j}\right)$ Therefore, the odds-ratio effect of each intervention in these states of *s*=1 or *s*=2 are the same as in state *s*=3. The severity of patients is modeled through the strata by state additive effects, α. The interaction of an intervention and the stratum "shock" is modeled for non-ventilator domains. If a patient progresses during the trial from states *s*=1 or *s*=2 to state *s*=3 then the ventilator randomization is revealed, delayed. We model the severity of a patient the transitions to state s=3 after randomization differently than one that starts the trial in state 3. For		

	modeling purposes, we refer to state s=4 as a patient who has transitioned after randomization to state s=3. The following sub model is fit for estimating the parameters of the ventilator domain. In the following sub-model the parameters of region, age, and era are conditioned on from the above model, only the state by strata parameters and the ventilator domain intervention parameters are fit in the sub-model. $\log\left(\frac{\pi}{1-\pi}|x_1, E, R, T, t\right)$ $= \nu_R + \alpha_{g,E} + \lambda_{age} + \theta_T + \sum_{d=2}^{D} \beta_{dt_j}$ In this sub-model the classification of the variable x_1, shock status, will be based on the baseline group. The model is fit using Markov Chain Monte Carlo (MCMC) methods.		
SECTION 6. MISSING DATA	**Original text**	**New Text**	**Reason**
Page 16.	Blank	There will be no imputation of missing primary endpoint values. Patients with missing values for the primary endpoint will be excluded from the modeling. If randomization assignment or reveal of randomization assignment is missing, the patient	Addition of new section to clarify how missing data will be managed statistically

		will be assumed to be ineligible for that domain. Patients with unknown region, age, or era may have these covariates imputed. Where possible, missing values will be calculated based on other available data. Otherwise, the mean value will be imputed for missing values. If strata or state is missing for a subject, it will be multiply imputed in the Bayesian algorithm. This multiple imputation will be based on the primary outcome variable and each of the variables in the model through the Bayesian posterior distribution. An important aspect of this model is a prior distribution of the missing strata or state. In some cases, this may be a specified prior (such as having a sleeping strata become active in which the status of the previous patients' strata status was never collected. The prior probability may be quite small in the case of a new pandemic). If there is no scientifically informed prior distribution then the relative frequency of the strata or state in the region and era will be used as the prior distribution for each state.	

SECTION 7. MODEL PRIORS	Original text	New Text	Reason
7.1 Region Effects Page 17.	The hyper-prior distributions have a mean estimate of 0, which is the same as the baseline, Region 1, and a prior mean of 0.20^2 for the standard deviation across countries	The hyper-prior distributions have a mean estimate of 0, which is the same as the baseline, Region 1, and a prior centered at 0.20^2 for the standard deviation across countries	Replacement of term mean with more appropriate term centered
7.2 Stata and State Effects Page 17.	For every strata and state combination a single parameter captures the relative severity of the population. For identifiability we restrict the parameter for g=1 and s=1 (non-shock, not ventilated) to be set at 0. The prior distributions for the parameters are set as fixed priors with weak prior distributions $[\alpha_{g,s}] \sim N(0,10^2), g = 1,2;$ s=1,2,3,4 (excluding the pair g=1, s=1)	For every strata and state combination a single parameter captures the relative severity of the population. For identifiability we restrict the parameter for g_k =1 and s=1 to be set at 0. Thus, for the shock stratum, g_1 = 1 and s = 1 corresponds to non-shock, not ventilated. The prior distributions for the parameters are set as fixed priors with weak prior distributions.	Modification of model to take into account additional strata.
7.3 Time (Era) Effects Page 18.	For identifiability, the era parameter for the most recent time period, θ_{N_T}, is considered the baseline and is set to 0. For every previous era, the prior distributions for the parameters are modelled with a first-order normal dynamic linear model (NDLM).	The time eras will be sequential "buckets" of 13-week time periods measured from the start of the trial. For identifiability, the era parameter for the most recent time period, θ_T is considered the baseline and is set to 0. For every previous era, the prior distributions for the parameters are modelled with a first-order normal dynamic linear model (NDLM).	Clarification of how time eras will be defined.
7.3 Time (Era) Effects Page 18.	The drift parameter τ_T is the variance component that creates the amount of borrowing from one era to the	The drift parameter τ_T^2 is the variance component that creates the amount of borrowing from one era to the	Notation for drift parameter updated

	next.	next.	
7.5 Intervention Common Effects Page 18 – 19.	Each intervention parameter β_{dj} for *d*=1,…,*D*; *j*=1,…,k_d is considered the relative effect of each intervention. For identifiability, the effect for the first intervention within each domain is set to 0. We set common weak priors for each intervention. In rare circumstances, prior distributions could deviate, the goal of the trial is to determine the relative treatment effects and these will be set for allowing the empirical data to shape the posterior. The priors for each intervention parameter are $[\beta_{dj}] \sim N(0, 10^2), d = 1, \ldots, D; j = 2, \ldots, k_d.$	Each intervention parameter β_{dj} for *d*=1,…,*D*; *j*=1,…, J_d is considered the relative effect of each intervention. For identifiability, the effect for the first intervention within each domain is set to 0. For some domains, there may be sets of interventions that are considered "nested". For these nested interventions, the intervention effects are modeled hierarchically, which allows borrowing among the intervention effect estimates for the interventions within the nest. Each domain-specific appendix will specify which interventions, if any, will be considered nested for the model. For all non-nested interventions, the intervention effects are given weak independent priors: $[\beta_{d_j}] \sim N(0, 10^2).$ For the set of nested interventions within a domain, the prior for interventions within the nest is $[\beta_{d_j}] \sim N(\mu_\beta, \tau_\beta^2),$	Updating description of model to take into account nested interventions (see Core Protocol for explanation and rationale)

		With hierarchical priors $[\mu_\beta] \sim N(0, 10^2); [\tau_\beta^2] \sim IG(0.125, 0.00281).$ For the set of nested interventions within a domain, the hyperparameters are selected such that the prior for τ_β is centered at 0.15 with weight 0.25. For non-nested interventions, the intervention effects are modeled separately, corresponding to large τ_β^2. For the purpose of assessing statistical triggers that lead to platform decisions, the analysis will be repeated, with nested interventions pooled together ($\tau_\beta^2 = 0$). However, the model with hierarchically modeled nested interventions will be the primary model that drives the adaptive randomization.	
7.6 Intervention by Strata Effects	7.6 Intervention by Covariate Effects	7.6 Intervention by Strata Effects	Heading updated
Page 19.	For the interaction parameters, we set more informative prior distributions. It is anticipated that there may be interactions between stratum membership and the different inventions (this defines the strata variables), but in general expected to be small. We set common priors for each intervention by stratum factor interventions with a relatively smaller variance and	It is anticipated that there may be interactions between stratum membership and some interventions, but in general expected to be small. The protocol enumerates three choices for modelling the intervention by strata interaction terms. These choices are described in the protocol as the "gamma	Updating of statistical model to explain operation of unit-of-

	mean 0. The priors for each interaction parameter are $[\gamma_{idj}] \sim N(0, 0.15^2), i = 1,2;\ d = 1, \ldots, D; j = 2, \ldots, k_d$ For reference, on the log-odds scale (in which the parameter γ are) an effect of 0.15 is an odds-ratio of 1.16, which would make a probability of 0.20 increase to 0.225. These prior values were selected by the ITSC in evaluating the model behavior versus possible scenarios	parameter" though they actually refer to choices for the standard deviation of the prior distribution for the interaction parameter. Each domain-specific appendix will pre-specify which of the following options is selected for each intervention-strata pair within that domain: • On one extreme, the interaction parameter may be set to zero, $\gamma_{kd_j} = 0$, forcing the model to estimate no interaction; thus, the treatment effect of the intervention is not permitted to differ between strata. • On the opposite extreme, the interaction parameter may be given a weak prior, $[\gamma_{kd_j}] \sim N(0, 10^2)$ which is described in the protocol as gamma = infinity. This prior spreads its mass over the real line. • Finally, the prior for the interaction parameter may be selected as $[\gamma_{kd_j}] \sim N(0, 0.15^2)$ which has a standard deviation of 0.15 (referred to as gamma = 0.15 in the protocol). This prior places most of	analysis which allows strata structure to differ between domains. See amendments to Core Protocol for explanation and rationale.

		its mass on small values, effectively shrinking the estimate of the interaction towards zero. For reference, on the log-odds scale (in which the parameter γ are) an effect of 0.15 is an odds-ratio of 1.16, which would make a probability of 0.20 increase to 0.225. This prior standard deviation value was selected by the ITSC in evaluating the model behavior versus possible scenarios	
7.7 Intervention by Intervention Interactions Page 20 – 21.	For the intervention-by-intervention interaction parameters we set more informative prior distributions. It is anticipated that there may be interactions between interventions, but that these would be likely, relatively small. In order to prevent model overfitting, without strong empirical information, we create stronger prior distributions around 0 (no interaction). The priors for each possible two-way interaction parameter are $[\delta_{ij}(f_i, f_j)] \sim N(0, 0.05^2), i \neq j, f_i = 1, .., k_i; f_j = 1, \dots, k_j.$ For reference, on the log-odds scale (in which the parameter δ are) an effect of 0.05 is an odds-ratio of 1.05, which would make a probability of 0.20 increase to 0.208. These prior values were selected by the ITSC in evaluating the model behavior versus possible	It is anticipated that there may be interactions between some interventions, but that these would likely be relatively small. For all two-way interaction parameters, three choices are available for modeling purposes. These choices are described in the protocol as the "lambda parameter" though they actually refer to choices for the standard deviation of the prior distribution for the interaction parameter. One of the following options will be pre-specified for each intervention-intervention pair: • The model may force no interaction between a pair of interventions by setting the interaction parameter equal to zero. That is, $\delta_{d_j,d'_{j'}} = 0$ for the interaction between intervention j in domain d and intervention j' in domain d'	Updating of statistical model as to whether interaction will be evaluated between interventions in different domains. See amendments to Core Protocol for explanation and rationale

	scenarios.	(where $d \neq d'$). In the protocol, this option is written as lambda = 0. • On the opposite extreme, the interaction term may be given a weak prior: $\left[\delta_{d_j,d'_{j'}}\right] \sim N(0, 10^2)$ which is described in the protocol as lambda = infinity. • Finally, the prior for the interaction parameter may be selected as $\left[\delta_{d_j,d'_{j'}}\right] \sim N(0, 0.05^2)$ For reference, on the log-odds scale (in which the parameter δ are) an effect of 0.05 is an odds-ratio of 1.05, which would make a probability of 0.20 increase to 0.208. These prior values were selected by the ITSC in evaluating the model behavior versus possible scenarios.	
SECTION 8. STATISTICAL QUANTITIES	**Original text**	**New Text**	**Reason**
Page 22.	The following statistical quantities are used in the design of the trial. The posterior distribution of the model parameters is calculated using MCMC. The algorithm allows the generating of M (100,000) draws from the joint posterior distribution. The following posterior quantities are calculated during the MCMC algorithm.	The following statistical quantities are used in the design of the trial. The posterior distribution of the model parameters is calculated using MCMC. The algorithm allows the generating of at least M (100,000) draws from the joint posterior distribution. The following posterior quantities are calculated during the	

	For each regimen, r, we define π_r as the probability of mortality, and $\pi_r^{(m)}$ as the probability of mortality for regimen *r*, for the *m*th draw from the MCMC algorithm.	MCMC algorithm. For each regimen, r, we define π_{r,g_k} as the relative effectiveness of the regimen, for group *g* within strata *k*. Similarly, $\pi_{r,g_k}^{(m)}$ as the relative effectiveness of regimen *r* for group *g* within strata *k*, for the *m*th draw from the MCMC algorithm.	Modification to nomenclature with no change to meaning of content
8.1 Probability of Optimal Regimen Page 22.	Let $O_g(r)$ be the posterior probability that a regimen, *r*, is the optimal regimen within subgroup *g*. For the *m*=1,…,*M* draws from the posterior, the frequency of draws in which each unique regimen, *r*, is optimal in group *g*, is tracked.	Let $O_{gk}(r)$ be the posterior probability that a regimen, *r*, is the optimal regimen for group *g* within strata *k*. For the *m*=1,…,*M* draws from the posterior, the frequency of draws in which each unique regimen, *r*, is optimal in group g_k, is tracked.	Modified to include strata membership.
8.1 Probability of Optimal Regimen Page 22.	$O_g(r) = \frac{1}{M}\sum_{m=1}^{M} I\left[\pi_{r,g} > \pi_{j,g} \text{ for all } j \neq r\right]$	$O_{g_k}(r) = \frac{1}{M}\sum_{m=1}^{M} I\left[\pi_{r,g_k} < \pi_{q,g_k} \text{ for all } q \neq r\right]$	Formula for posterior probability that a regimen is the optimal regimen updated
8.2 Probability of Optimal Intervention Page 23.	While $O_g(r)$ tracks the posterior probability, a regimen is optimal, we also track the probability that an intervention is in the optimal regimen. We refer to the posterior probability an intervention *i*, from domain *d*, is in the optimal regimen in group *g*, as $\lambda_g(d,i)$: $\lambda_g(d,i) = \frac{1}{M}\sum_{m=1}^{M} I\left[r_d = i \mid \pi_{r,g} > \pi_{j,g} \text{ for all } j \neq r\right]$	While $O_{g_k}(r)$ tracks the posterior probability that a regimen is optimal, we also track the probability that an individual intervention is in the optimal regimen. We refer to the posterior probability an intervention *j*, from domain *d*, is in the optimal regimen for group g_k, as $\Lambda_{g_k}(d_j)$: $\Lambda_{g_k}(d_j) = \frac{1}{M}\sum_{m=1}^{M} I\left[d_j \in r \mid \pi_{r,g_k} < \pi_{q,g_k} \text{ for all } q \neq r\right]$.	Modification to nomenclature with no change to meaning of content
SECTION 9. TRIAL ADAPTATION	**Original text**	**New Text**	**Reason**

AND STOPPING CRITERIA AND GUIDELINES FOR INTERVENTIONS			
Page 23.	The trial is designed to be perpetual and that it can continue studying severe community-acquired pneumonia (severe CAP), with no designated end	The trial is designed to be perpetual and continue studying severe community-acquired pneumonia (severe CAP), with no designated end	Correction of grammar
Page 23.	The goals of the trial are to both treat patients effectively while also investigating the relative benefit of different interventions, within different types of patients.	The goals of the trial are to both treat patients effectively while also investigating the relative benefit of different interventions, within different groups of patients.	Correction of terminology
Page 23.	First, there will be a starting status to the number of domains and the interventions within a domain. These aspects are expected to change during the course of the REMAP trial. Domains can be added or removed, and interventions can be added or removed based on external information. The trial design is specified generically for the number of domains and interventions within a domain, so that the trial functions seamlessly, based on predefined rules, as the trial evolves. Each section below describes aspects of the trial design that will evolve in a predetermined fashion based on accruing empirical information.	First, there will be a starting status with regard to strata, domains, and the interventions within a domain. These aspects are expected to change during the course of the REMAP trial. Strata can be added or removed. Similarly, domains can be added or removed, and interventions within the domains can be added or removed based on internal or external information. The trial design is generic in terms of the number of strata, domains, and interventions within a domain, so that the trial functions seamlessly, based on predefined rules, as the questions being evaluated within the trial evolve. Each section below describes aspects of the trial design that will evolve in a predetermined fashion based on accruing empirical information.	Clarification to reflect Core Protocol (noting this relates to unamended aspects of the Core Protocol)

Section 9.1 Data Sources Page 24.	All patients in the perpetual trial will become a part of the accruing data in the trial. There will be a set of patients in the primary analysis set. All patients in the primary analysis set will remain in the set for as long as the trial is running.	All patients in the perpetual trial will become a part of the accruing data in the trial. There will be a set of patients in the primary analysis population. All patients in the primary analysis population will remain in that population for as long as the trial is running.	Clarification of terminology
9.2 Primary Analysis Population	9.2 Primary Analysis Set	9.2 Primary Analysis Population	Heading changed to reflect terminology change
Page 24.	The primary analysis set will consist of all patients that are randomized to at least one of the interventions. The primary analysis set will be used for all efficacy endpoints and will be determined in accord with the intention to treat (ITT) principle and will comprise all patients, analyzed by the regimen to which they were randomized and their stratum membership as notified at the time of randomization. Other analysis sets may be used in supportive analyses of efficacy endpoints (when a Public Disclosure has been triggered) and in the analyses of domain-specific safety endpoints	The primary analysis population will consist of all patients that are randomized to at least one of the interventions and at least one intervention is revealed. The primary analysis population will be used for all efficacy endpoints and will be determined in accord with the intention to treat (ITT) principle and will comprise all randomized patients, analyzed by the regimen to which they were randomized and their stratum membership as determined at the time of randomization. Other analysis populations may be used in supportive analyses of efficacy endpoints (when a Public Disclosure has been triggered) and in the analyses of domain-specific safety endpoints	Clarification to reflect Core Protocol (noting this relates to unamended aspects of the Core Protocol)
9.3 Adaptive Analyses Page 24.	Adaptive Analyses will be conducted frequently throughout the trial process. The first adaptive analysis	Adaptive analyses will be conducted frequently throughout the trial process. The first adaptive analysis	Removal of reference to section 6.3.1 and 6.3.2 in

	will occur when there are a significant number of patients with 90 day outcome data (Section 6.3.1). After that first adaptive analysis, they will be repeated monthly, perpetually, for the remainder of the trial. A regular time period (e.g. first of the month) will be selected and this will trigger the running of an adaptive analysis. These adaptive analyses will consist of all currently available data being analyzed according to the trial model (Section 6.3.2).	will occur when there are a significant number of patients with 90 day outcome data. After that first adaptive analysis, they will be planned to be repeated monthly, perpetually, for the remainder of the trial. Interim analyses may be skipped if, due to seasonal variations, enrollment is slow and little new information has accrued during the month. A regular time period (e.g. first of the month) will be selected and this will trigger the running of an adaptive analysis. These adaptive analyses will consist of all currently available data being analyzed according to the current trial model.	previous version. It is acknowledged that there may be periods during this trial wherein recruitment may be slower, and therefore interim analyses may be unnecessary.
9.4 Allocation (Response Adaptive Randomization) Page 24.	Sections 6.3.1 and 6.3.2 describe the two states the platform trial can take, with Section 6.3.3 describing the procedure for starting a new intervention.	Blank	This sentence has been removed. It refers to redundant sections of the previous version of this document.
9.6 Response Adaptive Randomization Page 25 - 26.	After the burn-in period RAR will be used for the allocation for each regimen, within each patient stratum. Patients will be enrolled in the trial and randomized to a treatment arm stratified by their strata membership. The randomization for each patient is based on the probability that each regimen is the optimal regimen for a patient within the same strata,	After the burn-in period RAR will be used for the allocation for each regimen. Allocation to the regimens will be allowed to vary across the patient groups defined by the strata. Patients will be enrolled in the trial and randomized to a regimen according to the group they belong to within each strata. The randomization for each patient is based on the probability that each	Clarification to reflect Core Protocol (noting this relates to unamended aspects of the Core Protocol)

	but balanced by the sample size for that regimen. This balancing creates better learning about the optimal regimen by allowing a less aggressive randomization when there are differential sample sizes in each intervention. We refer to this scheme as maximizing the information about the optimal regimen within a stratum. The randomization for a patient within strata *g* is proportional to $$q_{r,g} \propto \sqrt{\frac{O_g(r)}{n_{r,g}+1}}.$$ Multiple normalizations are done to create the final randomization probabilities. The following steps are carried out. 1. Each randomization probability is normalized to sum to 1 by dividing by the sum of quantities over all regimens. 2. Any single intervention with a sum of probabilities across all regimens within a stratum less than 10% will be increased to sum to the floor randomization per intervention of 0.10	regimen is the optimal regimen for a patient within that patient strata, but balanced by the sample size already allocated to that regimen. This balancing creates better learning about the optimal regimen by allowing a less aggressive randomization to regimens that already have a larger number of patients allocated. We refer to this scheme as maximizing the information about the optimal regimen within a stratum. The randomization for a patient in group *g* within strata *k* is proportional to $$\rho_{r,g_k} \propto \sqrt{\frac{O_{g_k}(r)}{n_{r,g_k}+1}}.$$ Where $O_{g_k}(r)$ is the probability that regimen *r* is optimal for patients in group *g* of strata k and n_{r,g_k} is the total number of patients in group *g* of strata *k* who have already been allocated to regimen *r*. Multiple normalizations are done to create the final randomization probabilities. The following steps are carried out. 1. Each randomization probability is normalized to sum to 1 by dividing by the sum of quantities over all regimens.	

	a. A nuisance parameter φ to the odds ratio for each intervention meeting the less than 10% criterion will be added to the randomizations and the values of φ creating a minimum of 10% for each intervention will be fit and all randomization probabilities updated. The result is a set of randomization probabilities for each regimen, within each stratum.	2. Any single intervention with a sum of probabilities across all regimens within a stratum less than 10% will be increased to sum to the floor randomization per intervention of 0.10. Note that a minimum randomization of 10% implies a maximum randomization probability of 90% a. A nuisance parameter (φ) will be added to the odds ratio for each intervention that does not achieve at least a 10% randomization probability. The value of φ will be selected to create a minimum randomization probability of 10% for each intervention. The result is a set of randomization probabilities for each regimen, for each group as defined by the strata.	
9.7 Introduction of new interventions Page 26.	While this REMAP is running, if a new intervention is started then the randomization will be "blocked" for the new intervention in order to guarantee a set burn-in sample size. If there are k_d interventions in a domain after the new intervention is started, then a fixed allocation of $1/k_d$ will be used to all patients to be	While this REMAP is running, if a new intervention is started then the randomization will be "blocked" for the new intervention in order to guarantee an initial sample size. If there are Jd interventions in a domain after the new intervention is started, then a fixed allocation of $1/Jd$ will be used to allocate patients to the new	Clarification to reflect Core Protocol (noting this relates to unamended aspects of the Core Protocol)

	allocated to the new intervention for its respective domain. The remaining $1-\frac{1}{k_d}$ probability will be allocated using the RAR, ignoring the new intervention. This burn-in for each intervention will last until 25 patients have been allocated to the new intervention. At this point the static randomization will be removed and full adaptive randomization for all regimens is carried out.	intervention. The remaining $1-\frac{1}{J_d}$ probability will be allocated to the other interventions using the RAR. This burn-in for each intervention will last until 25 patients have been allocated to the new intervention. At that point this restriction will be removed and adaptive randomization to all regimens will be carried out.	
9.9 Intervention Superiority Page 27.	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 subgroup, $\lambda_g(d,i) > 0.99$, and there are at least 250 patients randomized to that intervention in that stratum, then that intervention, within that domain, will be deemed as being superior within that stratum, triggering a Public Disclosure. At that point, the remaining interventions in the domain will be halted for inferiority. All patients will then be allocated to the superior intervention (still randomized to interventions from remaining domains) until any new interventions are added to the domain of the superior intervention.	At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being the optimal intervention for a strata group, $\Lambda_{g_k}(d_j) > 0.99$, and there are at least 250 patients randomized to that intervention in that strata group, then that intervention, within that domain, will be deemed as being superior within that strata group, triggering a Public Disclosure. At that point, the remaining interventions in the domain will be halted for inferiority for that strata group. All future patients in that strata group will then be allocated to that superior intervention and randomized to interventions in the other domains. This will continue until new interventions are added to the domain that contains the superior intervention.	Clarification to reflect Core Protocol (noting this relates to unamended aspects of the Core Protocol)
9.10 Intervention Inferiority Page 27.	At any adaptive analysis, if a single intervention has less than a 0.01/(k_d–1) posterior probability of being a	At any adaptive analysis, if a single intervention has less than a 0.01/(J_d–1) posterior probability of being the	Clarification to reflect Core Protocol (noting this

	member of the optimal regimen, for a stratum, $\lambda_g(d,i) < 0.01$, then that intervention will be deemed as being inferior within that domain, for that stratum, triggering a report to the Data Safety and Monitoring Board (DSMB). The DSMB then makes a judgment on whether a Platform Conclusion has been reached and triggering a Public Disclosure. At that point the intervention will not be randomized to any more patients within that domain for patients in that stratum. When simultaneous superiority/inferiority occurs (for example when there are 2 interventions they are always simultaneous), then the result will be released as an intervention demonstrating superiority.	optimal intervention for a strata group $\Lambda_{g_k}(d_j) < 0.01$, then that intervention will be deemed as being inferior within that domain, for that strata group, triggering a report to the Data Safety and Monitoring Board (DSMB). The DSMB then makes a judgment on whether a Platform Conclusion has been reached and whether to trigger a Public Disclosure. If so, no additional patients in that strata group will be randomized to that intervention. When simultaneous superiority/inferiority occurs (for example when there are 2 interventions they are always simultaneous), then the result will be released as an intervention demonstrating superiority.	relates to unamended aspects of the Core Protocol)
9.11 Intervention Equivalence Page 28.	If the ITSC deems it desirable for two or more interventions within a domain then an equivalency condition will be set up for the interventions, as well as a δ difference of equivalence. If the two interventions within the domain have at least a 0.90 probability of having a mortality rate within δ% for any stratum (or strata) then this result will be communicated to the ITSC and they will take the appropriate action (Public Disclosure, removal of one intervention, no action). There is no automatic adaptation when this occurs.	If the two interventions within the domain have at least a 90% posterior probability that the odds ratio comparing the two within any stratum is between 1/1.2, and 1.2, the two interventions will be considered equivalent for that stratum. This result will be communicated to the ITSC and they will take the appropriate action (Public Disclosure, removal of one intervention, no action). There is no automatic adaptation when this occurs.	Updating of statistical appendix to reflect changes to evaluation of equivalence. See amendments to Core Protocol for explanation and rationale.

SECTION 10. OPERATING CHARACTERISTICS	**Original text**	**New Text**	**Reason**
	Given the complexity of the trial design, adaptations, and modeling complex clinical trial simulations have been created to explore the behavior and operating characteristics of the design. The cut-points, priors, and model have been optimized through this process. The simulations of the behavior of the design will change if new domains or interventions are added to the platform trial. The simulations are detailed in the Simulations Appendix to this Statistical Appendix. As interventions or domains are removed from the REMAP new simulations will not be conducted, but if new domains, interventions, states, or stratum are added then the simulations and the Simulations Appendix will be updated. Existing simulations indicate that when a single intervention in a domain with two interventions is beneficial, with a constant benefit for all patients, 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 patients. The timing of these	Blank	Section removed. This information will be contained in an operational document.

	conclusions of superiority have a median time of less than 2000 patients. 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%.		

5.5. Other Protocol Documents

5.5.1. REMAP-CAP Protocol Summary Version 3, dated 11 September 2019

The Protocol Summary for the REMAP-CAP trial has been updated in line with the changes outlined elsewhere in this document. A version of the Protocol Summary will be provided with tracked changes; however, a summary of changes to the Protocol Summary is not included here as this document does not contain any information that is not included in other protocol documents.