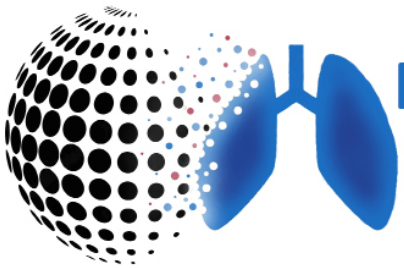

Domain-Specific Appendix:

MACROLIDE DURATION DOMAIN

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

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

Summary

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

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

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

Intravenous: ☐ Azithromycin ☐ Clarithromycin

Enteral: ☐ Azithromycin ☐ Clarithromycin ☐ Roxithromycin

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

TABLE OF CONTENTS

TABLE OF TABLES

1. ABBREVIATIONS

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

2. PROTOCOL APPENDIX STRUCTURE

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

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

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

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

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

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

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

3. MACROLIDE DURATION DOMAIN-SPECIFIC APPENDIX VERSION

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

3.1. *Version history*

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

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

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

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

4. MACROLIDE DURATION DOMAIN GOVERNANCE

4.1. *Domain members*

Chair:

Professor Allen Cheng

Members:

Professor Richard Beasley

Professor Marc Bonten

Dr. Nick Daneman

Dr. Lennie Derde

Dr. Robert Fowler

Associate Professor David Gattas

Professor Anthony Gordon

Mr. Cameron Green

Associate Professor Peter Kruger

Dr. Colin McArthur

Dr. Steve McGloughlin

Dr. Susan Morpeth

Dr. Srinivas Murthy

Professor Alistair Nichol

Professor David Paterson

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4.2. *Contact Details*

Chair:

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5. MACROLIDE DURATION DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

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

Chair
Allen Cheng

Date 10 July 2019

6. BACKGROUND AND RATIONALE

6.1. *Domain definition*

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

6.2. *Domain-specific background*

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

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

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

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

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

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

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

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

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

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

6.2.2. Macrolide antibiotics have anti-inflammatory properties

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

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

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

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

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

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

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

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

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

6.2.6. Macrolide antibiotics safety profile

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

7. DOMAIN OBJECTIVES

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

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

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

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

8. TRIAL DESIGN

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

8.1. *Population*

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

8.2. *Eligibility criteria*

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

8.2.1. Domain inclusion criteria

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

8.2.2. Domain exclusion criteria

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

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

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

8.2.3. Intervention exclusion criteria

Nil.

8.3. *Interventions*

8.3.1. Macrolide intervention

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

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

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

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

8.3.2. Recommended macrolide dosing

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

Table 2: Minimum doses of intravenous or enteral macrolide

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

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

8.3.3. Timing of initiation of intervention

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

8.3.4. Duration of administration of macrolide

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

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

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

8.4. *Concomitant care*

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

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

8.5. *Endpoints*

8.5.1. Primary endpoint

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

8.5.2. Secondary endpoints

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

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

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

9. TRIAL CONDUCT

9.1. *Microbiology*

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

9.2. *Domain-specific data collection*

9.2.1. Clinical data collection

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

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

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

9.3. *Criteria for discontinuation*

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

9.4. *Blinding*

9.4.1. Blinding

Macrolides will be administered on an open-label basis.

9.4.2. Unblinding

Not relevant.

10.STATISTICAL CONSIDERATIONS

10.1. *Domain-specific stopping rules*

If a Platform Conclusion of equivalence in the primary endpoint is demonstrated the DSMB and the ITSC may consider continuation of randomization if clinically relevant differences in secondary endpoints have not been demonstrated and it is considered plausible that clinically relevant differences in one or more secondary endpoints may be capable of being demonstrated. In all other respects the stopping rules for this domain are those outlined in the Core Protocol Sections 7.8.6 to 7.8.9.

10.2. *Unit-of-analysis and strata*

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

10.3. *Timing of revealing of randomization status*

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Deferred Reveal after domain-specific exclusion criteria have been evaluated (see section 7.8.3.6 in Core Protocol).

10.4. *Interactions with interventions in other domains*

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

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

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

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

10.5. *Nesting*

Nesting is not applicable to this domain.

10.6. *Threshold odds ratio delta for equivalence*

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

10.7. *Post-trial Sub-groups*

Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The *a priori* patient sub-groups of interest are:

- A microbiological diagnosis of pneumococcal pneumonia

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

11. ETHICAL CONSIDERATIONS

11.1. *Data Safety and Monitoring Board*

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

11.2. *Potential domain-specific adverse events*

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

Domain-specific harms related to macrolide therapy include:

- Cardiac arrhythmia (particularly torsades de pointes)

- Gastrointestinal intolerance
- Hypersensitivity
- Abnormal liver function

Other SAEs should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see Core Protocol Section 8.13).

11.3. *Domain-specific consent issues*

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

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

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

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

12.GOVERNANCE ISSUES

12.1. *Funding of domain*

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

12.2. *Funding of domain interventions and outcome measures*

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

12.3. *Domain-specific declarations of interest*

All investigators involved in REMAP-CAP maintain a registry of interests on the REMAP-CAP website. These are updated periodically and publicly accessible on the study website.

13.REFERENCES

ALBERT, R. K., CONNETT, J., BAILEY, W. C., CASABURI, R., COOPER, J. A., JR., CRINER, G. J., CURTIS, J. L., DRANSFIELD, M. T., HAN, M. K., LAZARUS, S. C., MAKE, B., MARCHETTI, N., MARTINEZ, F. J., MADINGER, N. E., MCEVOY, C., NIEWOEHNER, D. E., PORSASZ, J., PRICE, C. S., REILLY, J., SCANLON, P. D., SCIURBA, F. C., SCHARF, S. M., WASHKO, G. R., WOODRUFF, P. G., ANTHONISEN, N. R. & NETWORK, C. C. R. 2011. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med,* 365**,** 689-98.

ALTENBURG, J., DE GRAAFF, C. S., STIENSTRA, Y., SLOOS, J. H., VAN HAREN, E. H., KOPPERS, R. J., VAN DER WERF, T. S. & BOERSMA, W. G. 2013. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. *JAMA,* 309**,** 1251-9.

ANSARI, F., ERNTELL, M., GOOSSENS, H. & DAVEY, P. 2009. The European surveillance of antimicrobial consumption (ESAC) point-prevalence survey of antibacterial use in 20 European hospitals in 2006. *Clin Infect Dis,* 49**,** 1496-504.

ANTIBIOTIC EXPERT GROUPS 2014. *Therapeutic Guidelines: antibiotic,* Melbourne, Australia, Therapeutic Guidelines Limited,.

ANTUNES, G., EVANS, S. A., LORDAN, J. L. & FREW, A. J. 2002. Systemic cytokine levels in community-acquired pneumonia and their association with disease severity. *Eur Respir J,* 20**,** 990-5.

CORRIS, P. A., RYAN, V. A., SMALL, T., LORDAN, J., FISHER, A. J., MEACHERY, G., JOHNSON, G. & WARD, C. 2015. A randomised controlled trial of azithromycin therapy in bronchiolitis obliterans syndrome (BOS) post lung transplantation. *Thorax,* 70**,** 442-50.

DELLINGER, R. P., LEVY, M. M., RHODES, A., ANNANE, D., GERLACH, H., OPAL, S. M., SEVRANSKY, J. E., SPRUNG, C. L., DOUGLAS, I. S., JAESCHKE, R., OSBORN, T. M., NUNNALLY, M. E., TOWNSEND, S. R., REINHART, K., KLEINPELL, R. M., ANGUS, D. C., DEUTSCHMAN, C. S., MACHADO, F. R., RUBENFELD, G. D., WEBB, S. A., BEALE, R. J., VINCENT, J. L., MORENO, R. & SURVIVING SEPSIS CAMPAIGN GUIDELINES COMMITTEE INCLUDING THE PEDIATRIC, S. 2013. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med,* 41**,** 580-637.

GARIN, N., GENNE, D., CARBALLO, S., CHUARD, C., EICH, G., HUGLI, O., LAMY, O., NENDAZ, M., PETIGNAT, P. A., PERNEGER, T., RUTSCHMANN, O., SERAVALLI, L., HARBARTH, S. & PERRIER, A. 2014. beta-Lactam monotherapy vs beta-lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. *JAMA Intern Med,* 174**,** 1894-901.

JUURLINK, D. N. 2014. The cardiovascular safety of azithromycin. *CMAJ,* 186**,** 1127-8.

KANOH, S. & RUBIN, B. K. 2010. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. *Clin Microbiol Rev,* 23**,** 590-615.

LEVERT, H., GRESSIER, B., MOUTARD, I., BRUNET, C., DINE, T., LUYCKX, M., CAZIN, M. & CAZIN, J. C. 1998. Azithromycin impact on neutrophil oxidative metabolism depends on exposure time. *Inflammation,* 22**,** 191-201.

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

MANDELL, L. A., MARRIE, T. J., GROSSMAN, R. F., CHOW, A. W., HYLAND, R. H. & CANADIAN, C. A. P. W. G. 2000. Summary of Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Disease Society and the Canadian Thoracic Society. *Can J Infect Dis,* 11**,** 237-48.

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

POSTMA, D. F., VAN WERKHOVEN, C. H., VAN ELDEN, L. J., THIJSEN, S. F., HOEPELMAN, A. I., KLUYTMANS, J. A., BOERSMA, W. G., COMPAIJEN, C. J., VAN DER WALL, E., PRINS, J. M., OOSTERHEERT, J. J. & BONTEN, M. J. 2015. Antibiotic treatment strategies for community-acquired pneumonia in adults. *N.Engl.J.Med.,* 372**,** 1312-1323.

RESTREPO, M. I., FAVERIO, P. & ANZUETO, A. 2013. Long-term prognosis in community-acquired pneumonia. *Curr Opin Infect Dis,* 26**,** 151-8.

RUBIN, B. K., DRUCE, H., RAMIREZ, O. E. & PALMER, R. 1997. Effect of clarithromycin on nasal mucus properties in healthy subjects and in patients with purulent rhinitis. *Am J Respir Crit Care Med,* 155**,** 2018-23.

SCHULTZ, M. J. 2004. Macrolide activities beyond their antimicrobial effects: macrolides in diffuse panbronchiolitis and cystic fibrosis. *J Antimicrob Chemother,* 54**,** 21-8.

SPINDLER, C., STRALIN, K., ERIKSSON, L., HJERDT-GOSCINSKI, G., HOLMBERG, H., LIDMAN, C., NILSSON, A., ORTQVIST, A., HEDLUND, J. & COMMUNITY ACQUIRED PNEUMONIA WORKING GROUP OF THE SWEDISH SOCIETY OF INFECTIOUS, D. 2012. Swedish guidelines on the management of community-acquired pneumonia in immunocompetent adults--Swedish Society of Infectious Diseases 2012. *Scand J Infect Dis,* 44**,** 885-902.

SVANSTROM, H., PASTERNAK, B. & HVIID, A. 2013. Use of azithromycin and death from cardiovascular causes. *N Engl J Med,* 368**,** 1704-12.

TAMAOKI, J. 2004. The effects of macrolides on inflammatory cells. *Chest,* 125**,** 41S-50S; quiz 51S.

TORRES, A., BLASI, F., PEETERMANS, W. E., VIEGI, G. & WELTE, T. 2014. The aetiology and antibiotic management of community-acquired pneumonia in adults in Europe: a literature review. *Eur J Clin Microbiol Infect Dis,* 33**,** 1065-79.

UZUN, S., DJAMIN, R. S., KLUYTMANS, J. A., MULDER, P. G., VAN'T VEER, N. E., ERMENS, A. A., PELLE, A. J., HOOGSTEDEN, H. C., AERTS, J. G. & VAN DER EERDEN, M. M. 2014. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med,* 2**,** 361-8.

VALERY, P. C., MORRIS, P. S., BYRNES, C. A., GRIMWOOD, K., TORZILLO, P. J., BAUERT, P. A., MASTERS, I. B., DIAZ, A., MCCALLUM, G. B., MOBBERLEY, C., TJHUNG, I., HARE, K. M., WARE, R. S. & CHANG, A. B. 2013. Long-term azithromycin for Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis Intervention Study): a multicentre, double-blind, randomised controlled trial. *Lancet Respir Med,* 1**,** 610-20.

VOS, R., VANAUDENAERDE, B. M., VERLEDEN, S. E., DE VLEESCHAUWER, S. I., WILLEMS-WIDYASTUTI, A., VAN RAEMDONCK, D. E., SCHOONIS, A., NAWROT, T. S., DUPONT, L. J. & VERLEDEN, G. M.

2011. A randomised controlled trial of azithromycin to prevent chronic rejection after lung transplantation. *Eur Respir J,* 37**,** 164-72.

WIERSINGA, W. J., BONTEN, M. J., BOERSMA, W. G., JONKERS, R. E., ALEVA, R. M., KULLBERG, B. J., SCHOUTEN, J. A., DEGENER, J. E., JANKNEGT, R., VERHEIJ, T. J., SACHS, A. P. & PRINS, J. M. 2012. SWAB/NVALT (Dutch Working Party on Antibiotic Policy and Dutch Association of Chest Physicians) guidelines on the management of community-acquired pneumonia in adults. *Neth.J.Med.,* 70**,** 90-101.

WILKINSON, M. & WOODHEAD, M. A. 2004. Guidelines for community-acquired pneumonia in the ICU. *Curr.Opin.Crit Care,* 10**,** 59-64.

WOODHEAD, M., BLASI, F., EWIG, S., GARAU, J., HUCHON, G., IEVEN, M., ORTQVIST, A., SCHABERG, T., TORRES, A., VAN DER, H. G., READ, R. & VERHEIJ, T. J. 2011. Guidelines for the management of adult lower respiratory tract infections--full version. *Clin.Microbiol.Infect.,* 17 Suppl 6**,** E1-59.

YANAGIHARA, K., IZUMIKAWA, K., HIGA, F., TATEYAMA, M., TOKIMATSU, I., HIRAMATSU, K., FUJITA, J., KADOTA, J. & KOHNO, S. 2009. Efficacy of azithromycin in the treatment of community-acquired pneumonia, including patients with macrolide-resistant Streptococcus pneumoniae infection. *Intern Med,* 48**,** 527-35.