Domain-Specific Appendix:

MACROLIDE DURATION DOMAIN

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

Macrolide Duration Domain-Specific Appendix Version 4 dated 5th November, 2024

In this domain, participants meeting Platform entry criteria with community-acquired pneumonia who have been allocated to receive a macrolide-containing intervention within an Antibiotic Domain of this Platform will be randomized to receive one of two interventions depending on availability and acceptability:

- 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

This domain includes patients aged 18 years or older.

This domain is available in the following States and Strata:

Age Stratum	≥ 18 years old	
Illness Severity State	Moderate State	Severe State
Domain-specific strata	N/A	N/A
Interventions specified in this DSA	N/A	• Standard duration macrolide (3-5 days) • Extended duration macrolide (for 14 days)
Interventions submitted for approval in this jurisdiction	N/A	☐ Standard duration macrolide (3-5 days) ☐ Extended duration macrolide (for 14 days)

Macrolide Duration Domain Summary	
Interventions	The following interventions and specified in this domain: • Standard course macrolide discontinued after 3 to 5 days • Extended course macrolide for 14 days
Timing of Reveal	Randomization with Deferred Reveal and Initiation.
Population	This domain will be offered to the following patient categories: • Adult Age Stratum • Severe Illness Severity State
Domain-Specific Inclusions	Patients are eligible for this domain if: • Patient has been allocated to a macrolide-containing intervention within an Antibiotic Domain within this Platform.
Domain-Specific Exclusions	Domain exclusions: • 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 endpoint: as specified in core protocol documents. Secondary endpoints: refer to Core Protocol documents 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 documents
Platform Conclusions	The following Platform Conclusions are possible for this domain: • Superiority of extended course macrolide intervention compared to standard course macrolide intervention • Inferiority of extended course macrolide intervention compared to standard course macrolide intervention • Futility of extended course macrolide intervention compared to standard course macrolide intervention
Unit-of-analysis and Strata	There is a single unit-of-analysis in this domain, corresponding to all patients who receive an allocation in this domain. No other strata contribute to the unit-of-analysis for this domain. Response Adaptive Randomization will be applied.
Evaluable treatment-by-treatment Interactions	No interactions will be evaluated with any other domains.
Nesting	None.

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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, 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 (principles and details of statistical analysis and models); a Patient, Pathogen and Disease Appendix to the Core Protocol (PANDA); 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 the relevant 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 Statistical Design Team 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.

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

Version 4: Approved by the Macrolide Duration DSWG on 05 November 2024

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

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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. Signed on behalf of the committee,

Chair
Allen Cheng

Date 5th November, 2024

6. BACKGROUND AND RATIONALE

6.1. *Domain definition*

This is a domain to test the effectiveness of different durations of macrolide administration for hospitalized patients with severe community-acquired pneumonia (CAP) who have received and allocation to a macrolide-containing intervention in an Antibiotic Domain of this Platform.

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). The optimal duration of antibiotic therapy for atypical pathogens has not been established as trials of patients with severe community acquired pneumonia have not generally included significant numbers of patients with legionella, *Mycoplasma pneumonia*, *Chlamydophila (Chlamydia) pneumonia, or Chlamydophila (Chlamydia) psittaci*). Guidelines are conflicting and recommend at least 7-10 days of azithromycin for legionellosis, but some recommend longer (of up to 21 days) in some clinical scenarios and where other macrolides or fluoroquinolones are used (eTG, Viasus, Amsden). ATS/IDSA guidelines do not make specific recommendations for atypical pathogens but recommend a minimum of 5 days of treatment for all patients with pneumonia (Metlay et al., 2019).

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., 2009b, Lim et al., 2015, Lim et al., 2009a)	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, Metlay et al., 2019)	1. Cefotaxime, ceftriaxone, ampicillin-sulbactam or ceftaroline AND either (a) azithromycin or clarithromycin (b) Levofloxacin or moxifloxacin	Additional antibiotics recommended if MRSA or Pseudomonas aeruginosa previously isolated
Australia (Antibiotic Expert Groups, 2014)	1. Ceftriaxone AND azithromycin	1. Moxifloxacin
Canada (Mandell et al., 2000, Mandell et al., 2022)	β-lactam plus a macrolide OR β-lactam plus a fluoroquinolone	
Swedish guidelines (Spindler et al., 2012, Athlin et al., 2018)	1. Cefotaxime AND macrolide 2. Benzylpenicillin AND respiratory fluoroquinolone	
Europe European Society of Clinical Microbiology and Infectious Diseases / European Respiratory Society (Woodhead et al., 2011, Martin-Loeches et al., 2023)	beta-lactam antibiotic plus a macrolide [agents not specified]	beta-lactam antibiotic plus a fluoroquinolone [agents not specified]
Netherlands Dutch Working Party on Antibiotic Policy / Dutch Association of Chest Physicians (Wiersinga et al., 2012, Wiersinga et al., 2018)	1. Moxifloxacin 2. Cefuroxime or Ceftriaxone or Cefotaxime AND Ciprofloxacin	

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. 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 for hospitalized patients with severe community-acquired pneumonia, who have received an allocation to a macrolide-containing intervention in an Antibiotic Domain of this Platform.

We hypothesize that the primary endpoint specified in relevant Core Protocol documents 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, or hospital discharge, whichever occurs first
- Extended course macrolide for 14 days or hospital discharge, whichever occurs first

8. TRIAL DESIGN

8.1. *Population*

8.1.1. Age Strata

This domain is available to patients who are in the Adult Age Stratum, as defined in Core Protocol Documents.

8.1.2. Illness Severity State

This domain is available for patients who are in the Severe Illness Severity State, as defined in Core Protocol Documents.

8.1.3. Domain-Specific Strata

Domain-specific strata are not applied to patients at the time of assessment for this domain.

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 as specified in relevant Core Protocol documents. Patients eligible for the Platform may have conditions that exclude them from the Macrolide Duration Domain.

8.2.1. Domain inclusion criteria

Patients are eligible for this domain only if they have been allocated a macrolide-containing intervention within an Antibiotic Domain of this Platform. In this regard, the Macrolide Duration Domain sits within the macrolide-containing interventions of Antibiotic Domain(s) within this Platform.

8.2.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- 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

Reveal of allocation in the Macrolide Duration Domain is only possible before the end of Study Day 5 after randomization to a macrolide-containing intervention within an Antibiotic Domain of this Platform.

8.2.3. Intervention exclusion criteria

There are no intervention-specific exclusion criteria for this domain.

8.3. *Interventions*

8.3.1. Macrolide intervention

Patients will be randomly assigned to receive one of the following open-label study interventions. Macrolide therapy will be commenced following reveal of allocation to a macrolide-containing

intervention in an Antibiotic Domain of this Platform. The duration of macrolide therapy will then be determined by allocation in this domain.

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

8.3.2. Macrolide administration and dosing

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

- Initial intravenous (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.

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

8.3.3. Duration of administration of macrolide

Reveal of allocation status can occur at any time before the end of Study Day 5 after randomization to a macrolide-containing intervention within an Antibiotic Domain of this Platform, as soon as sufficient information is available to confirm eligibility. If reveal of allocation 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 of allocation occurs after Study Day 3, and the patient is allocated to standard course macrolide, discontinued immediately. If the patient is allocated to extended course macrolide, macrolide therapy should be prescribed to Study Day 14, irrespective of the timing of reveal.

For participants discharged from hospital before the end of the allocated course of macrolide therapy, macrolides should be discontinued at hospital discharge.

8.3.4. Discontinuation of study intervention

If, at any time after reveal of allocation, 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.

Macrolide therapy should be discontinued if there is development of an SAE which, in the opinion of the treating clinician, could be related to participation in this domain. The study interventions can be temporarily or permanently discontinued at any time by the treating clinician if doing so is regarded as being 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 during the intervention period and prior to discontinuation of continuous ECG monitoring.

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. All other treatment that is not specified by assignment within the Platform will be determined by the treating clinician.

8.5. *Endpoints*

8.5.1. Primary endpoint

The primary endpoint for this domain is the primary outcome specified in Core Protocol.

8.5.2. Secondary endpoints

All secondary endpoints as specified in the Core Protocol.

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

- Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital
- Serious Adverse Events (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

9.3. *Criteria for discontinuation*

Refer to Core Protocol documents for criteria for the discontinuation of participation in this trial.

9.4. *Blinding*

All interventions will be administered on an open-label basis.

10. STATISTICAL CONSIDERATIONS

10.1. *Domain-specific stopping rules*

The following Platform Conclusions are possible in this domain:

- Superiority of extended course macrolide as compared to standard course macrolide
- Inferiority of extended course macrolide as compared to standard course macrolide
- Futility of extended course macrolide as compared to standard course macrolide

A harm threshold is not necessary in this domain, as a futility trigger will be achieved before harm thresholds in the setting of regular adaptive analyses.

In all other respects the stopping rules for this domain are those outlined in the Core Protocol.

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, although this may be modified as an operational decision as specified in the Current State document.

10.3. *Application of Response-Adaptive Randomization*

Response-adaptive randomization will be applied for this domain.

10.4. *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 once the results of microbiological testing to establish domain eligibility are available, or if prospective agreement to participate is required for this domain.

10.5. *Interactions with interventions in other domains*

Interactions with all other domains are either not evaluable or not considered possible and will not be incorporated into the statistical model or models in which this domain is evaluated.

If an interaction is specified with a future domain, it is sufficient for the interaction to be specified only in the DSA of such a future domain.

10.6. *Nesting*

Nesting is not applicable to this domain.

10.7. *Threshold probability for superiority, inferiority, and futility*

The threshold probability for statistical triggers for superiority, inferiority, and futility are those specified in the Core Protocol.

10.8. *Informative priors*

This domain will launch with priors that are uninformative for main effects.

10.9. *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
- Age
- Chronic Obstructive Pulmonary Disease (COPD)
- Azithromycin versus other macrolides
- Influenza strata
- All potentially evaluable treatment-by-treatment interactions with other domains

If there are potentially important results within one or more of these pre-specified post-platform conclusion subgroups, after the occurrence of a pre-specified threshold for the unit-of-analysis described above, this domain may re-start (new stage) without necessarily requiring a subsequent amendment with eligibility restricted to a sub-group with possible beneficial treatment effect. This will be an operational decision of the ITSC, as advised by the DSWG.

Heterogeneity of treatment effect may also be evaluated by multiple methods including machine learning techniques (such as causal forest).

11. ETHICAL CONSIDERATIONS

11.1. *Data Safety and Monitoring Board*

The DSMB is convened under the guidance provided in the Core Protocol and DSMB Charter. The statistical triggers that apply to this domain are specified in this DSA. If requested by the DSMB, domain-specific safety secondary endpoints will be provided to the DSMB as part of the regular safety reports.

11.2. *Potential domain-specific adverse events*

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

The occurrence of the following should be screened for and reported as SAEs for all participants in this domain, irrespective of intervention allocation:

- 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 relevant Core Protocol documents).

11.3. *Domain risk assessment*

Participating sites will have reviewed the interventions in this domain and their clinical appropriateness for evaluation in this population. Clinicians may choose not to enroll individual patients if they feel that participation is not in patient's best interests, and safety criteria are used to exclude patients from this domain for appropriate clinical reasons. The risks and benefits of participation will be outlined in local consent documentation.

If, at any stage, external evidence of harm or definitive evidence of absence of effectiveness in hospitalized patients emerges for one or more interventions specified in this domain, the ITSC, as advised by the DSWG, may remove the intervention(s) prior to declaration of a Platform Conclusion. If this occurs, presentation and publication of results that relate to the intervention will occur, so as to contribute additional weight of evidence in the public domain.

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 three to five 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.

11.4. *Domain-specific consent issues*

For patients who are not competent to consent, and where permitted in accordance with local jurisdictional requirements, entry into this domain is preferred to be via waiver-of-consent or some form of delayed consent. In any jurisdiction in which prospective agreement is necessary, reveal of assignment status will only occur after prospective agreement has been obtained.

During a pandemic visiting by relatives of affected patients may not be possible. In such situations, alternative methods for confirming consent including electronic and telephone communication, as permitted by an appropriate ethical review body, may be acceptable methods for confirming agreement to participate in this (and other) domains of the platform.

12.GOVERNANCE ISSUES

12.1. *Funding of domain*

Funding sources for the Platform are specified in the Core Protocol documents. This domain has not received any additional domain-specific funding but such funding, from any source, may be obtained during the life-time of the domain.

12.2. *Funding of domain interventions and outcome measures*

Domain interventions will be provided by participating hospitals. The interventions specified in this domain are part of the spectrum of standard care and are known to be inexpensive.

12.3. *Domain-specific declarations of interest*

A registry of interests for all members of the International Trial Steering Committee is maintained and is publicly available on the trial 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.

ATHLIN, S., LIDMAN, C., LUNDQVIST, A., NAUCLER, P., NILSSON, A. C., SPINDLER, C., STRALIN, K. & HEDLUND, J. 2018. Management of community-acquired pneumonia in immunocompetent adults: updated Swedish guidelines 2017. *Infect Dis (Lond),* 50**,** 247-272.

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. 2009a. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax,* 64 Suppl 3**,** iii1-55.

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

LIM, W. S., SMITH, D. L., WISE, M. P. & WELHAM, S. A. 2015. British Thoracic Society community acquired pneumonia guideline and the NICE pneumonia guideline: how they fit together. *BMJ Open Respir Res,* 2**,** e000091.

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.

MANDELL, L. A., ZHANEL, G. G., ROTSTEIN, C., MUSCEDERE, J., LOEB, M. & JOHNSTONE, J. 2022. Community-Acquired Pneumonia in Canada During Coronavirus Disease 2019. *Open Forum Infect Dis,* 9**,** ofac043.

MARTIN-LOECHES, I., TORRES, A., NAGAVCI, B., ALIBERTI, S., ANTONELLI, M., BASSETTI, M., BOS, L., CHALMERS, J. D., DERDE, L., DE WAELE, J., GARNACHO-MONTERO, J., KOLLEF, M., LUNA, C., MENENDEZ, R., NIEDERMAN, M., PONOMAREV, D., RESTREPO, M., RIGAU, D., SCHULTZ, M. J., WEISS, E., WELTE, T. & WUNDERINK, R. 2023. ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia. *Eur Respir J,* 61.

METLAY, J. P., WATERER, G. W., LONG, A. C., ANZUETO, A., BROZEK, J., CROTHERS, K., COOLEY, L. A., DEAN, N. C., FINE, M. J., FLANDERS, S. A., GRIFFIN, M. R., METERSKY, M. L., MUSHER, D. M., RESTREPO, M. I. & WHITNEY, C. G. 2019. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med,* 200**,** e45-e67.

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.

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.

WIERSINGA, W. J., BONTEN, M. J., BOERSMA, W. G., JONKERS, R. E., ALEVA, R. M., KULLBERG, B. J., SCHOUTEN, J. A., DEGENER, J. E., VAN DE GARDE, E. M. W., VERHEIJ, T. J., SACHS, A. P. E. & PRINS, J. M. 2018. Management of community-acquired pneumonia in adults: 2016 guideline update from the Dutch Working Party on Antibiotic Policy (SWAB) and Dutch Association of Chest Physicians (NVALT). *Neth J Med,* 76**,** 4-13.

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.