Domain-Specific Appendix: ANTIBIOTIC DOMAIN

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

Antibiotic Domain-Specific Appendix Version 1 dated 7 November 2016

Summary

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:

- Ceftriaxone + Macrolide
- Moxifloxacin or Levofloxacin
- Piperacillin-tazobactam + Macrolide
- Ceftaroline + Macrolide
- Amoxicillin-clavulanate + Macrolide

At this participating site the following interventions have been selected within this domain:

<table>
<tr><th colspan="3">Beta-lactam and Macrolide Options</th></tr>
<tr><td>Beta-Lactam interventions for this site</td><td></td><td>Combined with one IV macrolide option and one enteral option chosen by site</td></tr>
<tr><td>☐ Ceftriaxone</td><td rowspan="4">One of beta-lactam interventions (randomized) combined with an Intravenous (IV) option and an enteral option</td><td rowspan="2">☐ IV Azithromycin
☐ IV Clarithromycin
☐ IV Erythromycin
☐ No IV preparation</td></tr>
<tr><td>☐ Piperacillin-tazobactam</td></tr>
<tr><td>☐ Ceftaroline</td><td rowspan="2">☐ Enteral Azithromycin
☐ Enteral Clarithromycin
☐ Enteral Roxithromycin</td></tr>
<tr><td>☐ Amoxicillin-clavulanate</td></tr>
<tr><th colspan="3">Respiratory Fluroquinolone Options</th></tr>
<tr><td>☐ Moxifloxacin</td><td></td><td></td></tr>
<tr><td>☐ Levofloxacin</td><td></td><td></td></tr>
</table>

REMAP-CAP: Antibiotic Domain Summary	
Interventions	• Ceftriaxone + Macrolide • Moxifloxacin or Levofloxacin • Piperacillin-tazobactam + Macrolide • Ceftaroline + Macrolide • Amoxicillin-clavulanate + Macrolide
Strata	Analysis permits analysis strata (shock) by intervention interaction
Evaluable Interactions	Intervention-intervention interactions will be evaluated between interventions in this domain that include a beta-lactam antibiotic and interventions in the Macrolide Duration Domain and between interventions in this domain and the corticosteroid domain.
Timing of Reveal	Randomization with Immediate Reveal and Initiation
Inclusions	Inclusion criteria are the same as the REMAP see Core Protocol Section 7.4.1

Domain Specific Exclusions	Domain exclusions:
	• Received more than 48-hours of intravenous antibiotic treatment for this index illness
	• More than 24-hours has elapsed since becoming eligible for this domain
	• Known hypersensitivity to all of the study drugs in the site randomization schedule
	• A specific antibiotic choice is indicated, for example:
	  ○ Suspected or proven concomitant infection such as meningitis
	  ○ Suspected 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 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

Intervention-Level Exclusions	• Known non-serious hypersensitivity to penicillins (excluded from excluded from interventions that include piperacillin and amoxicillin) • Known non-serious hypersensitivity to cephalosporins (excluded from interventions that include ceftriaxone and ceftaroline) • Known serious hypersensitivity to beta-lactams including penicillins or cephalosporins (excluded from interventions that include piperacillin, amoxicillin, ceftriaxone, ceftaroline) • Known hypersensitivity to moxifloxacin or levofloxacin (moxifloxacin/levofloxacin intervention) • Known hypersensitivity to macrolide option (excluded from all interventions that comprise a beta-lactam macrolide combination) • Pregnancy (excluded from moxifloxacin or levofloxacin and ceftaroline interventions)

Outcome measures	Primary REMAP endpoint: occurrence of death during the index hospital admission censored 60-days from the date of enrolment. Secondary REMAP endpoints refer to Core Protocol Section 7.6.2 Secondary domain endpoints (during index hospitalization censored 60-days from the date of enrolment): 1. Microbiological failure (persistent bacteremia >72-hours after commencement of antibiotics or isolation of any clinically relevant bacteria from pleural specimens) 2. Super-infection (isolation of clinically relevant bacteria from blood cultures or pleural specimens >48-hours after commencement of antibiotics not present on admission) 3. Multi-Resistant Organisms (MRO) colonization/infection: Isolation of multi-drug resistant (MDR) bacteria from clinical or screening specimens including vancomycin resistant enterococci (VRE), MRSA, extended spectrum beta-lactamase (ESBL)-producing enterobacteriacae, carbapenem resistant enterobacteriacae (CRE). 4. *Clostridium difficile (C. difficile)* illness based on detection from faeces using current standard of care diagnostics used at site Serious adverse event (SAE) related to study treatment,

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1. ABBREVIATIONS

ATS	American Thoracic Society
CAP	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
eGRF	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
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

2. PROTOCOL APPENDIX STRUCTURE

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

3. ANTIBIOTIC DOMAIN-SPECIFIC APPENDIX VERSION

The version of the Antibiotic Domain-Specific Appendix is in this documents header and on the cover page.

3.1. Version history

Version 1: Approved by the Antibiotic Domain-Specific Working Group (DSWG) on 7 November 2016

4. ANTIBIOTIC DOMAIN GOVERNANCE

4.1. Domain members

Chair:

Professor Allen Cheng

Members:

Professor Richard Beasley
Professor Marc Bonten
Dr. Lennie Derde
Dr. Robert Fowler
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

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4.2. Contact Details

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5. ANTIBIOTIC DOMAIN SPECIFIC WORKING GROUP AUTHORIZATION

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

Chair

Date 7th November 2016

Allen Cheng

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP to test the effectiveness and incidence of defined adverse events of different empiric antibiotic treatments in patients with severe community-acquired pneumonia (severe 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 community-acquired pneumonia (CAP). In patients with sepsis (including pneumonia) who have organ dysfunction the International Surviving Sepsis Campaign Guidelines recommend initiation of antibiotics within 60 minutes of presentation. (Dellinger et al., 2013)

6.2.1. Microbiology of CAP

In the majority of cases of CAP, no microbiological diagnosis is made. (Charles et al., 2008) In patients in whom a microbiological diagnosis is made, the most commonly isolated organism is *Streptococcus pneumoniae.* Other bacteria that cause CAP include *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, and a range of gram-negative organisms. Although studies have demonstrated that clinical features are not specific to bacterial aetiology, the so-called "atypical" pathogens include Legionella species, *Mycoplasma pneumoniae*, and *Chlamydiphila pneumoniae*. Since the advent of sensitive nucleic acid tests, there is an increasing recognition of the role of viral pathogens, particularly influenza viruses and respiratory syncytial virus (RSV), either as the primary pathogen or associated with secondary bacterial pneumonia. (Musher and Thorner, 2014) 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.

Many studies have characterised the microbiological cause of infection in patients with severe CAP and a summary of these has been reported previously. (Lim et al., 2009, Mandell et al., 2007, Musher et al., 2013, Wiersinga et al., 2012, Woodhead et al., 2011) While there are clinically significant differences between studies in healthcare delivery (including criteria for hospital and ICU admission), the population under study and other epidemiological features, and study methodology, the distribution of identified pathogens is remarkably consistent in temperate developed countries. The results of studies that have reported the microbiology findings in patients with CAP are outlined in Table 1.

Table 1: Distribution of identified pathogens in hospitalized patients with CAP in selected studies

Type of organisms	Australia (2004-2008) (Charles et al., 2008)	Europe (Woodhead, 2002)	United States (Musher et al., 2013)
Gram positive bacteria	*Streptococcus pneumoniae (13.9%)*	*Streptococcus pneumoniae (25.9%)*	*Streptococcus pneumoniae (24.7%)*

	Staphylococcus aureus (1.2%)	*Staphylococcus aureus (1.4%)*	*Staphylococcus aureus (3.5%)*
Gram negative bacteria	*Haemophilus influenzae (5.1%)* *Pseudomonas aeruginosa (1.6%)* *Enterobacteriaecae (1.5%)* *Moraxella catarrhalis (0.8%)*	*Haemophilus influenza (4.0%)* *Moraxella catarrhalis (2.5%)* *Gram-negative enteric bacteria (2.7%)*	*Haemophilus influenza (4.6%)* *Pseudomonas aeruginosa (2.3%)* *Klebsiella pneumoniae (0.8%)* *Escherichia coli (0.8%)* *Moraxella (0.4%)*
"Atypical"	*Mycoplasma pneumoniae (8.8%)* *Legionella (3.4%)* *Chlamydophila species (1.7%)*	*Legionella* spp. *(4.9%)* *Mycoplasma pneumoniae (7.5%)* *Chlamydia pneumoniae (7.0%)* *Chlamydia psittaci (1.9%)*	
Viral pathogens	*Influenza (7.7%)* *Picornaviruses (5.2%)* *RSV (1.9%)*	*Viruses (10.9%)*	*Rhinovirus (10%)* *Coronavirus (2.7%)* *Parainfluenza virus (1.5%)* *RSV (1.2%)* *hMPV (1.2%)* *Influenza (0.4%)*
Other	*Other pathogens (2.3%)* *Unknown (54.4%)*	*Coxiella burnetii (0.8%)* *Other pathogens (2.2%)* *Unknown (43.8%)*	*Other pathogens (6.9%)* *Unknown (45.9%)*

** More than one pathogen detected in 8.5% of patients, including both a viral and bacterial pathogen in 5.3%*

Drug resistant pathogens are an increasing concern globally. Macrolide resistant pneumococci are of little clinical relevance in patients treated with beta-lactams (Cheng and Jenney, 2016) and it appears that poor outcomes linked to penicillin resistant pneumococci (Tleyjeh et al., 2006) are likely to be attributed to age, underlying disease and severity of illness rather than treatment failure.

(Moroney et al., 2001, Yu et al., 2003) Of greater concern is the advent of community-acquired methicillin resistant Staphylococcus aureus, particularly those associated with the Panton Valentine leucocidin. (Rubinstein et al., 2008)

6.2.2. Guidelines recommend a number of different antibiotic treatment options

A "respiratory" quinolone (moxifloxacin or levofloxacin) or combination antimicrobial therapy with a beta-lactam and a macrolide, are both recommended empiric treatment for CAP in national and international guidelines. (Mandell et al., 2000, Mandell et al., 2007, Woodhead et al., 2011) Data, mostly from retrospective observational analyses, report that guideline-concordant therapy is associated with a mortality benefit in CAP (Baudel et al., 2009, Frei et al., 2010), but whether one of these options results in a lower mortality than the other remains an open question. It has been suggested that fluoroquinolone treatment may be optimal for pneumonia due to *Legionella* spp, but randomized clinical trial data are lacking. (Asadi et al., 2012) A summary of different recommendations in guidelines for the treatment of severe CAP is displayed in Table 2.

Table 2: 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)**	Co-amoxiclav AND macrolide (clarithromycin)	Cefuroxime OR ceftriaxone AND clarithromycin
United States Infectious Diseases Society of America (IDSA)/ the American Thoracic Society (ATS) (Mandell et al., 2007)	cefotaxime, ceftriaxone, or ampicillin-sulbactam AND Either azithromycin; or a fluoroquinolone	respiratory fluoroquinolone and aztreonam
Australia **(Antibiotic Expert Groups, 2014)**	ceftriaxone AND azithromycin	moxifloxacin
Canada **(Mandell et al., 2000)**	Moxifloxacin or levofloxacin	Cefuroxime OR ceftriaxone or beta-lactam/beta-lactamase inhibitor AND intravenous (IV) macrolide
Swedish guidelines (Spindler et al., 2012)	Cephalosporin AND macrolide OR benzylpenicillin AND fluoroquinolone	

Europe **European Society of Clinical Microbiology and Infectious Diseases / European Respiratory Society (Woodhead et al., 2011)**	Non-antipseudomonal 3rd generation cephalosporin AND macrolide OR (moxifloxacin OR levofloxacin) AND/OR Non-antipseudomonal 3rd generation cephalosporin	

The most studied interventions for pneumonia have involved antibiotic interventions. A 2008 systematic review that compared respiratory quinolones with beta-lactam/macrolide combinations identified 23 clinical trials that enrolled 7885 patients. (Vardakas et al., 2008) A higher proportion of patients treated with fluoroquinolones had treatment success (defined as clinical cure or improvement) compared with comparator-treated patients (primarily beta-lactam and/or macrolides), but there were no significant differences in mortality, and the majority of patients in these studies did not have severe pneumonia and were not treated an ICU.

Clinical trials adding a macrolide to beta-lactams have not definitively demonstrated clinical benefit. One trial found a shorter time to clinical stability in patients with severe pneumonia although the difference in this small trial was not statistically significant. (Garin et al., 2014) Additionally, there were no differences in other groups or outcomes including length of stay or mortality. A recent cluster randomized trial of beta-lactam monotherapy, beta-lactam/macrolide combination therapy, or fluoroquinolone monotherapy in patients with moderate severity CAP (who were not admitted to ICU at the time of randomization) did not find any differences in mortality or hospital length of stay associated with any strategy. (Postma et al., 2015) A systematic review of antibiotic treatments recommended in the IDSA/ATS guideline did not find any conclusive evidence that "atypical" coverage was associated with better outcomes in clinical trials, although an association was found between treatments that included macrolides or quinolones in lower quality observational studies. (Lee et al., 2016)

Most of these studies were performed in hospitalized patients with CAP where the mortality was relatively low and statistical power limited. Although the available evidence suggests that patients with moderate/severe pneumonia may benefit from atypical coverage, the choice of beta-lactam and whether atypical coverage should include a macrolide or a quinolone in severe CAP remains an open question.

6.2.3. There is a diversity of antibiotics used in clinical practice

Current guidelines recommend a number of different antibiotic treatment options and it is likely that others options are also being used at individual hospitals or by individual clinicians.

A survey of Australian and New Zealand ICU specialists indicates that more than 95% administer a beta-lactam antibiotic in combination with azithromycin (a macrolide) for empiric therapy but there is substantial variation in the choice of beta-lactam. The majority of patients receive ceftriaxone, as recommended in Australian guidelines, but one third of ICU specialists use piperacillin-tazobactam (unpublished data from the REMAP-CAP investigators). Although piperacillin-tazobactam has wider microbiological coverage, it penetrates less well into lung tissue, is less potent against pneumococci (the commonest cause of severe CAP), and is predicted to impose increased selection for resistant organisms. (Sime et al., 2012)

In New Zealand, IV amoxicillin-clavulanate and cefuroxime (both not available currently in Australia as IV formulations) are also used widely. A 2013 study found that both second/third generation cephalosporins (58%) and co-amoxiclav (36%) were used in patients with severe pneumonia defined by CURB-65 score. (Aikman et al., 2013)

In Europe, practice also varies; third generation cephalosporins are also commonly used, but 4th generation cephalosporins, carbapenems and combination beta-lactam/beta-lactam inhibitor use is reported with both levofloxacin or macrolides. (Martin-Loeches et al., 2011, Mol et al., 2005)

6.2.4. New antibiotics may be more effective but data are limited.

Ceftaroline is an antibiotic, newly licensed for CAP in a range of countries, with a similar spectrum of activity to ceftriaxone, but with the additional advantage of being active against methicillin-resistant *Staphylococcus aureus*. In some Randomized Controlled Trials (RCTs) of patients with moderate severity CAP, ceftaroline was superior to ceftriaxone in achieving clinical cure. (File et al., 2011, Low et al., 2011) Recent high-profile reviews and guidelines list ceftaroline as a recommended first-line choice for severe CAP, even though the evidence is derived from non- critically ill patients. (Eccles et al., 2014, Musher and Thorner, 2014) Ceftaroline is ~500 times more expensive than ceftriaxone currently.

6.2.5. Both the efficacy as well as adverse effects of antibiotics need to be considered

RCTs that compare antibiotics to treat infections in ICU patients have demonstrated unexpected differences in mortality. For example, doripenem was associated with a higher mortality than imipenem in patients with ventilator associated pneumonia (Kollef et al., 2012, Yahav et al., 2011) Moreover, the choice of agent may influence the risk of nosocomial superinfection including *Clostridium difficile (C. difficile)*. Despite the ubiquity of the agents used to treat severe CAP in clinical practice there have been no RCTs powered to detect differences in clinically relevant endpoints between groups receiving different antibiotics primarily in critically ill patients. It is imperative that the comparative effectiveness of alternative beta-lactam agents and the role of respiratory quinolones is established, including any differences in acquisition of resistant organisms and *C. difficile.*

6.2.6. All antibiotics used in CAP have a well-established safety profile

Ceftriaxone, piperacillin-tazobactam, amoxicillin-clavulanate, moxifloxacin and levofloxacin have a long history of use for pneumonia as well as for other indications and are regarded as having a good safety profile. The pharmacokinetics of all drugs may be altered in critically ill patients due to pathophysiological changes including altered volumes of distribution, augmented renal clearance, renal failure and hepatic failure. (Roberts and Lipman, 2009)

Both immediate and delayed hypersensitivity have been described with ceftriaxone, piperacillin-tazobactam, amoxicillin-clavulanate and moxifloxacin, and include rare cases of anaphylaxis, Stevens-Johnson syndrome and toxic epidermal necrolysis. Diarrhea, including that due to *C. difficile*, is a recognized complication of all antibiotic therapy.

Pipericillin-tazobactam and moxifloxacin have been associated with hematological abnormalities, including agranulocytosis, hemolytic anemia and pancytopenia. Amoxicillin-clavulanate has been associated with cholestasis and hepatitis. Moxifloxacin has been associated with a prolonged QT interval and arrhythmias. Pipericillin-tazobactam, ceftaroline and moxifloxacin have been associated with seizures but this is uncommon when doses within current clinical practice guidelines.

6.2.7. Transition from empiric to targeted antibiotic therapy

Microbiological tests identify a causative organism in less than 50% of patients with CAP. (Jain et al., 2015) It is almost always the case that empiric antibiotic therapy is commenced before a microbiological diagnosis is available. Standard practice and international guidelines recommend that where a causative organism is identified and antibiotic susceptibilities are available that an antibiotic with a narrow spectrum of action that is active against the infecting organism is substituted for the initial empiric therapy. This domain tests only empiric therapy and the domain intervention is considered complete once microbiological test results are available that can guide appropriate targeted antibiotic therapy or, in the absence of identification of a causative organism for which its antimicrobial susceptibility is known, that sufficient time and clinical improvement have occurred to warrant cessation or de-escalation of initial empiric therapy.

7. DOMAIN OBJECTIVES

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 60-day mortality 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
- 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 enrolment (intervention by stratum 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 a treatment by treatment interaction between the beta-lactam antibiotic options in this domain and the macrolide duration domain (i.e. the macrolide duration domain is nested within this domain 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 a treatment by treatment interaction between the antibiotic domain and the corticosteroid domain.

Each participating site has the option to opt-in to two or more interventions to be included in the site randomization schedule depending on local clinical preference, usual practice, and the availability of the agent at that site.

8. TRIAL DESIGN

This domain will be conducted as part of a REMAP-CAP trial of CAP (see Core Protocol Section 7). Treatment allocation will be independent from other treatment domains. Treatment allocation will be adaptive, as described in the Core Protocol.

8.1. Population

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

8.2. Eligibility criteria

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.

8.2.1. Exclusion criteria from this domain

Patients will be excluded from this domain if they have:

- Received more than 48-hours of IV antibiotic treatment for this index illness
- More than 24-hours has elapsed since becoming eligible for this domain
- Known hypersensitivity to all of the study drugs in the site randomization schedule
- A specific antibiotic choice is indicated, for example:
    - Suspected or proven concomitant infection such as meningitis
    - Suspected 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 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 with suspected MRSA should be included (see below "interventions" Section 8.3).

Melioidosis: Sites in tropical areas (defined in Australia as hospitals located north of a latitude of 21°S) will not randomize to the antibacterial domain during the melioidosis season (defined as the monsoonal period according to local guidelines).

8.2.2. Exclusions from individual interventions

Prior to the study commencement, sites will select which interventions that patients at their site will be allocated to, based on the current standards of care, local epidemiology and regulatory status of antibiotics as outlined below.

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons. In such cases, patients will be randomly allocated a remaining intervention from among those available at that site. An example would include patients with a history of a penicillin hypersensitivity, who may receive a cephalosporin or moxifloxacin. Patients may have multiple intervention exclusions (eg both a penicillin and a cephalosporin hypersensitivity).

Patients who are eligible for only a single intervention at a site (i.e. all other interventions are contraindicated) will be allocated that intervention but data from such patients will not be included in the primary analysis set for this domain. Patients in whom all interventions are contraindicated will be treated according to the current standard of care at the clinicians discretion.

Criteria that exclude a patient from a one or more interventions are:

- Known non-serious hypersensitivity to penicillins will result in exclusion from receiving interventions that include piperacillin and amoxicillin
- Known non-serious hypersensitivity to cephalosporins will result in exclusion from receiving interventions that include ceftriaxone and ceftaroline
- Known serious hypersensitivity to beta-lactams, including penicillins or cephalosporins, will result in exclusion from interventions that include piperacillin, amoxicillin, ceftriaxone, and ceftaroline. These patients are eligible only for the moxifloxacin or levofloxacin intervention.

- Known hypersensitivity to moxifloxacin or levofloxacin will result in exclusion from moxifloxacin or levofloxacin intervention
- Known serious hypersensitivity to the macrolide will result in exclusion from interventions that include piperacillin, amoxicillin, ceftriaxone, and ceftaroline. These patients are eligible only for the moxifloxacin or levofloxacin intervention.
- Known or suspected pregnancy will result in exclusion from moxifloxacin or levofloxacin and ceftaroline interventions. It is normal clinical practice that women admitted who are in an age group in which pregnancy is possible will have a pregnancy test conducted. The results of such tests will be used to determine interpretation of this exclusion criteria.

8.3. Interventions

8.3.1. Antibiotic interventions

Patients will be randomly assigned to receive one of the following study interventions. While it is expected that all sites will participate in the ceftriaxone intervention, each site has the option to opt-in to one or more of the remaining 4 interventions based on local practice and the availability of the antibiotic in the country. For sites that are including the moxifloxacin or levofloxacin intervention it is strongly encouraged that the sites participate in at least one intervention that includes a cephalosporin and one intervention that includes a penicillin so that causal inference by random allocation is possible for patients who have known non-serious intolerance to either cephalosporins or penicillins but not both. All patients receiving ceftriaxone, piperacillin-tazobactam, ceftaroline, or amoxicillin-clavulanate will also receive a macrolide. Patients allocated to the moxifloxacin or levofloxacin intervention will not receive a macrolide or any beta-lactam or monobactam agent.

The choice of macrolide (see front page) will depend on the availability and acceptability of the agents at each site in the following order of preference;

1. IV azithromycin, with switch to enteral azithromycin when appropriate
2. IV clarithromycin, with switch to enteral azithromycin when appropriate
3. Enteral azithromycin
4. Enteral clarithromycin or roxithromycin
5. IV or enteral erythromycin. Sites in which only erythromycin is available are not able to participate in the macrolide duration domain.

Vancomycin, linezolid or other antimicrobials active against MRSA (other than ceftaroline) may be added if MRSA is suspected at the discretion of the treating clinician, irrespective of the intervention to which the participant is allocated.

8.3.2. Recommended antibiotic dosing

The doses specified are recommended minimum doses and may be modified according to local guidelines or practice.

- Ceftriaxone ≥1 gram IV q24h
- Moxifloxacin 400mg IV q24h or Levofloxacin 750mg IV q24h
- Piperacillin-tazobactam ≥4.5 grams IV q8h
- Ceftaroline 600 mg IV q12h
- Amoxicillin-clavulanate ≥1200mg IV q8h

If no local guidelines exist, it is recommended that subsequent doses of antibiotics will be adjusted for estimated renal function (based on estimated Glomerular Filtration Rate (eGFR)) as follows:

Table 3: Minimum doses of antibiotics, by eGFR

Agent	eGFR >50 ml/min	eGFR10-50 ml/min	eGFR <10	Continuous Veno-Venous Hemofiltration (CVVHF)
Ceftriaxone	1g-2g IV daily	1g-2g IV daily	1g IV daily	1g IV daily
Piperacillin-tazobactam	4.5g IV q6h	(eFGR 20-40) 4.5g IV q8h	(eGFR<20) 4.5g IV q12h	4.5g IV q8h
Ceftaroline	600mg IV q12h	400mg IV q12h	200mg IV q12h	400mg IV q12h
Amoxicillin-clavulanate	1200mg IV q8h	1200mg IV q8h	1200mg IV q12h	1200mg IV q8h
Moxifloxacin	400mg IV q24h	400mg IV q24h	400mg IV q24h	400mg IV q24h
Levofloxacin	750mg IV q24h	(eGFR 20-50) 750mg IV load, 750mg IV q48h	(eGFR<20) 750mg IV load, 500mg IV q48hr	750mg IV load, 500mg IV q48hr

8.3.3. Timing of initiation of antibiotics

In keeping with all international guidelines optimized empiric antibiotic treatment should commence as soon as possible. Usual practice for patients admitted to the ICU with severe CAP is either immediate administration of empiric antibiotics, if antibiotics have not already been administered, or initiation of the empiric antibiotic treatment that will be continued during admission to the ICU, even if antibiotics have been administered already. As such, initiation of antibiotic therapy to a patient with severe CAP, within this REMAP should commence immediately after admission to the ICU.

8.3.4. Duration of administration of antibiotics

The duration of empiric antibiotics will be determined by the treating clinician based on daily reviews of the following criteria:

- 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.

8.4. Concomitant care

Additional non-beta-lactam antibacterial agents, such as vancomycin, gentamicin, clindamycin or cotrimoxazole, will be permitted at the discretion of the treating clinician. Other beta-lactams, carbapenems (meropenem, imipenem, doripenem, ertapenem), monobactams (aztreonam) and quinolones are not permitted at study enrolment, but a change to these agents is permitted if clinical cultures are positive for a resistant pathogen that necessitates commencement of one of these agents. Oseltamivir will also be permitted in patients with suspected or confirmed influenza.

Any subsequent change of antibiotics, based on availability of microbiological data, will be permitted at the treating clinician's discretion.

8.4.1. Implications of allocation status for eligibility in other domains

Patients randomized to intervention moxifloxacin will not be included in the macrolide-duration domain in this REMAP.

8.5. Endpoints

8.5.1. Primary endpoint

The primary endpoint for this domain is the REMAP primary outcome (the occurrence of death during the index hospital admission censored 60-days from the date of enrolment) 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 60-days after enrolment) will be:

- Microbiological failure (persistent bacteremia >72-hours after commencement of antibiotics or isolation of any clinically relevant bacteria from pleural specimens)
- Super-infection (isolation of clinically relevant bacteria from blood cultures or pleural specimens >48-hours after commencement of antibiotics not present on admission)
- 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), extended spectrum beta-lactamase (ESBL)-producing enterobacteriacae, carbapenem resistant enterobacteriacae (CRE).
- *C. difficile* illness based on detection from feces using current standard of care diagnostics used at site
- Serious adverse event (SAE) related to study treatment

Data collection will be stratified by the timing of when the culture was taken (within 48-hours of admission or after 48-hours of enrolment).

Table 4: Organisms of interest as baseline or outcome measures

Site	Organisms of interest
Blood, lower respiratory tract (endotracheal suction, bronchoalveolar lavage, sputum), Pleural fluid (e.g.	Staphylococcus aureus Streptococcus pyogenes, or pneumoniae Haemophilus influenzae Moraxella catarrhalis

pleural aspirate, chest drain)	Enterobacteriacae** Acinetobacter spp. Pseudomonas spp.
Multi resistant organisms from any clinical or screening* site	VRE, MRSA, ESBL-producing enterobacteriacae** CRE

*screening specimens include fecal/rectal swabs, swabs of intact skin or nose

**Enterobacteriacae includes *Escherichia coli*, *Klebsiella* spp, *Enterobacter* spp, *Serratia*,

9. TRIAL CONDUCT

9.1. Microbiology

Isolates will be tested for susceptibility to study antibiotics using routine clinical testing. If required specific isolates may be referred for centralized susceptibility testing.

9.2. Domain specific data collection

9.2.1. Clinical data collection

Additional domain specific data will be collected.

- Risk factors for aspiration – chronic neurological disease, recent history of altered conscious state, hazardous alcohol intake
- Details of prior antibiotic administration
- Selected microbiological results before and after 48-hours after enrolment
- Antimicrobial susceptibility results
- *C. difficile* isolation from feces

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 discontinuation criteria for the 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.

9.4. Blinding

9.4.1. Blinding

All antibiotics 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 7.8.9.

10.2. Strata

Both analysis and the Response Adaptive Randomization (RAR) will utilize the stratum of shock in this domain.

10.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is as specified for Randomization with Immediate Reveal and Initiation (see section 7.8.3.4 in Core Protocol)

10.4. Interactions with interventions in other domains

An *a priori* interaction with the macrolide domain is considered possible and will be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the steroid 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.

10.5. Sub-groups

Domain specific post-hoc subgroups will be used in analysis following the conclusion of one or more interventions within the domain. The *a priori* subgroups 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, serology, urinary antigen testing) based on tests taken before or within 48-hours of admission to hospital.
- Patients with risk factors for aspiration pneumonia (chronic neurological disease, recent history of altered conscious state, hazardous alcohol use)
- Elderly (≥65 years) and non-elderly (<65 years) patients
- Chronic Obstructive Pulmonary Disease (COPD)

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, determination of the optimal intervention may be based on secondary endpoints, such as the incidence of *C. difficile* – associated diarrhea or isolation of MRO organisms.

11.2. Potential domain specific adverse events

The antibiotics used in this domain largely have a known toxicity profile. Additionally, it is expected that a high proportion of critically ill patients who will be enrolled in this trial will experience mortality or substantial morbidity.

The following potential adverse outcomes relating to antibiotic therapy will be reported as secondary outcome measures (and do not need to be reported separately as SAEs):

- Progression of infection: deep infection (lung abscess, empyema) or bacteremia
- Acquisition of multi-drug resistant organisms in clinical or screening specimens (including VRE, MRSA, ESBL or CRE)

- *C. difficile* – associated diarrhea

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 intervention or study participation (see Core Protocol Section 8.13).

11.3. Domain-specific consent issues

All the antibiotics to be tested in this domain are approved for this indication or are in common use in many countries for CAP or both. Sites will be able to opt out of interventions for all patients at that site if they believe that an intervention is not part of reasonable care of patients with pneumonia, or are not approved for use in the country, or conflict with local antimicrobial stewardship considerations. Additionally, clinicians may choose not to enroll individual patients if they feel that participation is not the patient's best interests, and safety criteria are used to exclude patients from individual interventions for medical reasons (e.g. hypersensitivity to one or more study drugs).

Where all interventions that are available at the participating site are regarded as being part of the acceptable spectrum of standard care and given the time imperative to commence antibiotics, entry to the study, for participants who are not competent to consent, is preferred to be via waiver-of-consent or some form of delayed consent.

Pregnant women are susceptible to pneumonia and a number of different antibiotics, including amoxicillin-clavulanate and ceftriaxone, are widely used and have a track record of safety in this population. Pregnant women will be excluded from the moxifloxacin and ceftaroline interventions.

Ceftaroline is not in widespread use but is licensed for use for CAP by regulatory agencies in Australia, New Zealand, the European Union and North America but has been recommended as appropriate therapy for patients with severe CAP in high profile reviews. (Jain et al., 2015)

12.GOVERNANCE ISSUES

12.1. Funding of domain

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).

12.2. Funding of domain interventions

Sites that participate in the ceftaroline intervention will have this antibiotic provided by the trial in Australia and New Zealand. Astra Zeneca have indicated in-principle support for the provision of ceftaroline for at least some participating countries (Australia and New Zealand). The contract between the trial Sponsors and Astra Zeneca must meet criteria set out in the Core Protocol for provision of interventions by commercial entities. Arrangements for supply of ceftaroline will be set out in operational documents.

All other antibiotics will be provided by participating hospitals on the basis that if the patient was not participating in the trial, appropriate antibiotics would always have been indicated and provided by the treating hospital.

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.

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