Region-Specific Appendix:

SAUDI ARABIA

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

REMAP-CAP Saudi Arabia Region-Specific Appendix Version 3 dated 23 Nov 2020

THIS STUDY IS SUPPORTED BY THE AUSTRALIAN AND NEW ZEALAND INTENSIVE CARE SOCIETY CLINICAL TRIALS GROUP (ANZICS CTG)

TABLE OF CONTENTS

1. ABBREVIATIONS

ANZ	Australia and New Zealand
ANZIC-RC	Australian and New Zealand Intensive Care Research Centre
ANZICS CORE	Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation
ANZICS CTG	Australian and New Zealand Intensive Care Society Clinical Trials Group
ANZ RCC	Australia and New Zealand Regional Coordinating Center
ANZ RMC	Australia and New Zealand Regional Management Committee
CAP	Community-acquired pneumonia
CRF	Case Report Form
CTA	Clinical Trial Agreement
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
eCRF	Electronic Case Report Form
HRC	Health Research Council
HREC	Human Research Ethics Committee
IIG	International Interest Group
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
IV	Intravenous
NHMRC	National Health and Medical Research Council
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia
RCC	Regional Coordinating Center
RMC	Regional Management Committee
RSA	Region-Specific Appendix
SA	Saudi Arabia
SAE	Serious Adverse Event

2. PROTOCOL APPENDIX STRUCTURE

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

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

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

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

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

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

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

2.1. Region-Specific Protocol version

The version of the Saudi Arabian (SA) RSA is in this document's header and on the cover page.

2.2. Version History

Version 1: Approved by the Australia and New Zealand Regional Management Committee (ANZ RMC) on 12 December 2019

Version 2: Approved by the Australia and New Zealand Regional Management Committee (ANZ RMC) on 04 June 2020

Version 3: Approved by the Australia and New Zealand Regional Management Committee (ANZ RMC) on 23 November 2020

3. SAUDI ARABIAN REGION

The SA region comprises sites in the country of Saudi Arabia.

The countries to which this appendix applies are:

- Saudi Arabia (commenced 2020)

4. SAUDI ARABIAN STUDY ADMINISTRATION STRUCTURE

4.1. Coordinating center and data management

The Regional Coordinating Center (RCC) of REMAP-CAP in Saudi Arabia is the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), Department of Epidemiology and Preventive Medicine, Monash University, as part of the Australian and New Zealand RCC (ANZ RCC). The ANZIC-RC will have predominant responsibility for the region plus management of sites in Saudi Arabia.

4.1.1. Responsibilities

The ANZ RCC is responsible for the following aspects of study management in SA:

- Liaison with the ITSC and other RCCs in relation to data management, Case Report Forms (CRFs), and site management
- CRF design for any region-specific data collection
- Development, maintenance, and administration of the regional database
- Recruitment and selection of sites
- Data management
- Protocol training of site investigators and research coordinators
- Preparation and arrangement of investigator payments
- Management of study set up including assistance with Human Research Ethics Committee (HREC) applications
- Monitoring and close-out site visits
- Organization of investigator meetings
- Serious adverse event notification to DSMB
- Coordination of data entry and feedback of data enquiries
- Administrative assistance to the Regional Management Committee (RMC), Domain-Specific Working Groups (DSWG), Interest Groups (IIG), and the ITSC, as required
- Liaison with other RMCs to develop study documents and materials that are standardized as much as possible

The site (KAMC-RIY) will be responsible for the following aspects of study management in SA:

- Management of study budget and liaison with funding bodies in SA
- Management of regulatory affairs (for example, Therapeutic Goods Administration, etc.)
- Public relations for the study

4.2. Regional Management Committee

4.2.1. Responsibilities

Sites in Saudi Arabia will be managed by the ANZ RMC which will be responsible for the following aspects of study management in SA:

- Liaison with the staff of the ANZ RCC

- Approval of the RSA
- Development and approval of the RSA and study materials for the region
- Development and approval of data management systems for the region
- General study management issues
- Liaison with the ITSC, DSWGs, IIGs, and other RCCs with regard to analysis and interpretation of results, and collaboration on publications and presentations
- Liaison with and reporting to the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG)

The site (KAMC-RIY) will be responsible for the following aspects of study management in SA:

- Funding applications to and negotiations and communications with funding bodies for which funding will be used to support trial activities in the SA region
- Study budget in SA
- Approval and establishment of feasibility of domains and interventions in the region
- Consumer engagement in SA

A representative of the SA region will be invited to join the ANZ RMC.

4.2.2. Members

Chief Investigator in Saudi Arabia

Professor Yaseen Arabi

Executive Director and Chief Investigator in Australia

Professor Steve Webb

Deputy Executive Director and Chief Investigator in New Zealand

Dr. Colin McArthur

Chair

Dr. Shay McGuinness

Members

Professor Allen Cheng

Dr. Lennie Derde

Professor Andrew Forbes

Associate Professor David Gattas

Mr Cameron Green

Associate Professor Stephane Heritier

Ms. Lisa Higgins

Associate Professor Peter Kruger

Dr. Ed Litton

Professor Alistair Nichol

Associate Professor Rachael Parke

Ms. Jane Parker

Associate Professor Jeffrey Presneill

Mr. Tony Trapani

Ms. Anne Turner

Dr. Paul Young

4.3. Contact Details

Chief Investigator in Saudi Arabia

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Chairman, Intensive Care Unit

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SAUDI ARABIA

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Executive Director

Professor Steve Webb

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Email steven.webb@monash.edu

Deputy Executive Director

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Fax +64 9 307 4827
Email colinm@adhb.govt.nz

4.3.1. Coordinating Center

Coordinating Center

The Australian and New Zealand Intensive Care Research Centre
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Email jane.parker@monash.edu
Web http://www.anzicrc.monash.org

4.3.2. Project Management

4.3.2.1. Global Project Manager

Cameron Green

Global Project Manager

The Australian & New Zealand Intensive Care Research Centre

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4.3.2.2. Australia and Saudi Arabia

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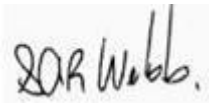
5. ANZ REGIONAL MANAGEMENT COMMITTEE AUTHORIZATION

The ANZ RMC have read the appendix and authorize it as the official SA Regional appendix for the study entitled REMAP-CAP. Signed by on behalf of the committee,

Chief Investigator in Saudi Arabia Yaseen Arabi		Date	23 November 2020
Executive Director Steve Webb		Date	23 November 2020
Deputy Director Colin McArthur		Date	23 November 2020

6. TRIAL REGISTRATION

Participation in this trial and involvement of sites is registered ClinicalTrials.gov. The registration number NCT02735707 and was registered on 12 April 2016.

The Universal Trial Number is: U1111-1189-1653.

7. FUNDING OF REGION

7.1. Sources of funding

In Australia, the trial has been funded by the National Health and Medical Research Council (NHMRC) (APP1101719) for Australian dollars $4,413,145. Funding for the REMAP-CAP study from the NHMRC is for approximately 2000 patients.

7.2. Site costs

Per-patient and any other project-related payments to sites will be as specified in the Clinical Trial Agreement (CTA) between the Sponsor and each site.

7.3. Sponsors

The sponsor in Saudi Arabia is Monash University.

7.4. Role of sponsor

The role of the sponsor is to act as the legal entity for those trial related activities that can only be undertaken by a legal entity. CTAs will be between the sponsor and participating sites. All other activities, including but not limited to trial design, conduct, safety monitoring, and reporting, are the responsibility of trial steering and management committees and working groups, as specified in the Core Protocol and appendices.

7.5. Insurance

The sponsor/investigator has insurance in accordance with the relevant legal requirements in each country.

8. TRIAL BACKGROUND AND RATIONALE

There are no anticipated issues that are specific to the background and rationale in the Core Protocol of the trial in Saudi Arabia. However, some interventions may not be available in all countries or participating sites within the region.

9. TRIAL DESIGN

9.1. Study setting

As described in the Core Protocol Section 7.3.

9.2. Interventions

The RMC will offer all interventions that are available in Saudi Arabia to all participating sites in which the intervention is available and feasible.

9.2.1. Antibiotic Domain

All antibiotics that are specified in the Antibiotic Domain-Specific Appendix that are licensed for use in each country within this region will be made available to any site. Only Ceftriaxone, Piperacillin-tazobactam, and Macrolide antibiotics will be available at KAMC-RIY, Saudi Arabia. Ceftaroline, Moxifloxacin, and Amoxicillin will not be made available in Saudi Arabia.

All antibiotic interventions, except Ceftaroline, are off-patent and will be provided by the hospital (as the hospital would have otherwise been provided by that site). See Section 10.3 for information about distribution of any medications provided by the study.

9.2.2. Macrolide Duration Domain

The macrolide duration domain will be offered to any site in this region.

9.2.3. Corticosteroid Domain

The corticosteroid domain will be offered to any site in this region.

9.2.4. Antiviral Domain

The antiviral domain will be offered to all sites in this region.

9.2.5. Ventilation Domain

The ventilation domain will be offered to all sites in this region.

9.2.6. Registry

Registry participation is not possible at King Abdulaziz Medical City, Riyadh.

9.2.7. COVID-19 Antiviral Therapy Domain

The COVID-19 Antiviral domain will be offered to all sites in this region.

9.2.8. COVID-19 Immune Modulation Therapy Domain

The COVID-19 Immune Modulation domain will be offered to all sites in this region. Only Tocilizumab and Anakinra will be available at KAMC-RIY, Saudi Arabia.

9.2.9. COVID-19 Therapeutic Anticoagulation Domain

The COVID-19 Therapeutic Anticoagulation domain will be offered to all sites in this region.

9.2.10. COVID-19 Antiplatelet Domain

The COVID-19 Antiplatelet domain will be offered to all sites in this region.

9.2.11. COVID-19 Statin Therapy Domain

The COVID-19 Statin Therapy domain will be offered to all sites in this region.

1.1. Endpoints

Data will be collected as set out in the Core Protocol and DSAs. It is mandated in Saudi Arabia that trial endpoints that occur after day 90 are collected at sites in Saudi Arabia.

1.2. Co-enrollment

As described in the Core Protocol Section 7.9.

2. TRIAL CONDUCT

2.1. Recruitment and embedding

As described in the Core Protocol Section 8.3.

2.2. Treatment allocation

Central randomization will occur online and be managed and operated by Spiral Web Solutions Ltd (New Zealand) at https://remapcap.spinnakersoftware.com.

2.3. Distribution of study drug

The processes and management of distribution of any drug provided by the study will be outlined in operational documents and, as required, specified in the CTA.

2.4. Data collection

Data collection will be as outlined in the Core Protocol Section 8.9. The collection of data from time-points after day 90 will be mandatory in this region.

2.5. Data management

Data will be entered into a secure, password protected web based CRF designed by Spiral Web Solutions Ltd (New Zealand). Data entry and data management will be coordinated by the Project Managers and the coordinating centers including programming and data management support.

2.6. Trial group linkage / participation

REMAP-CAP has been accorded 'supported' status by the ANZICS CTG. The RMC is responsible for ensuring that all aspects of the study comply with the requirements of supported status, as set out by the ANZICS CTG. Re-application for supported status will be made for each new domain that is

being considered.

2.7. Site start up and initiation

A site initiation teleconference or visit will be conducted before site activation; at least one routine monitoring visit will be conducted during the recruitment period; and a close out visit. Additional monitoring visits will be planned based on patient inclusion rate or indication. Email and telephone communication will supplement site visits.

Standardized procedures will be in place to educate sites on the trial and trial procedures before site initiation. These include printed material, face-to-face start up meetings, webinars, and on-line study materials.

2.8. Quality assurance and monitoring

2.8.1. Quality assurance

As described in the Core Protocol Section 8.11.

2.8.2. Monitoring

The study will be monitored by a representative of the ANZIC-RC in Saudi Arabia. Monitoring will be conducted by quality control reviews of protocol compliance, data queries and safety reporting. The study will use a monitoring plan that is developed on a risk-based approach. Details can be found in the REMAP-CAP Monitoring Plan.

A monitoring report will be prepared following each visit and reviewed by the management committee if appropriate. A follow up letter will be sent to the principal investigator and research coordinator at the site and will be filed in the site investigator file.

Medical records, any other relevant source documents and the site investigator files must be made available to the ANZIC-RC representative for these monitoring visits during the course of the study and at the completion of the study as needed.

2.9. Safety reporting

Safety reporting will occur as outlined in the Core Protocol Section 8.13.

All Serious Adverse Events (SAEs) will be recorded in the electronic case report form (eCRF). All SAEs must be reported to the coordinating center via the trial website within 72 hours of the investigators becoming aware of the event.

The investigator should notify the Institutional / Ethics Committee of the occurrence of the serious adverse event in accordance with local requirements.

Web address https://remapcap.spinnakersoftware.com

Contact phone numbers for SAE advice:

ANZIC-RC	+61 3 9903 0937

A 24 hour per day contact number for Australia will be provided to all sites before recruitment commences.

3. ETHICAL CONSIDERATIONS

3.1. Ethical and regulatory issues

The trial will be conducted in accordance with legislation in Saudi Arabia. Research ethics approval will be obtained prior to the start of the study at each institution from the responsible local or national HREC. It is the principal investigator's responsibility to ensure that all conditions for approval of the study are met and that amendments to the protocol or SAEs are also reported to the HREC as required by that committee.

3.1.1. Saudi Arabia

Each participating site will submit this protocol and any other relevant study documentation to their responsible institutional review board (IRB). The study shall be carried out in compliance with all the local applicable laws in Kingdom of Saudi Arabia and the international standards applicable for conducting research including, but not limited to, the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants, the provisions of the Declaration of Helsinki, the Guideline for Good Clinical Practice of the International Conference on Harmonization (ICH-GCP), and the requirement of the Ministry of Health in Kingdom of Saudi Arabia.