Region-Specific Appendix:
Canada

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

REMAP-CAP Canada Region-Specific Appendix Version 2 dated 05 July, 2019

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1. ABBREVIATIONS

AHRC	Applied Health Research Centre
CAPTIC	Canadian Adaptive Platform Trial in Intensive Care
CaRCC	Canada Regional Coordinating Centre
CaRMC	Canada Regional Management Committee
CCCTG	Canadian Critical Care Trials Group
CRF	Case Report Form
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
eCRF	Electronic Case Report Form
IIG	International Interest Group
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
IV	Intravenous
RCC	Regional Coordinating Center
REB	Research Ethics Board
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia
RMC	Regional Management Committee
RSA	Regional-Specific Appendix
SAE	Serious Adverse Event

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2. PROTOCOL APPENDIX STRUCTURE

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

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

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

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

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

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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.

At any one time there will be the same current version of the Core Protocol, in all regions, with accompanying Region-Specific and Domain-Specific Appendices that change over time and between regions.

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 Canada RSA is in this document's header and on the cover page.

2.2. Version History

Version 1: Approved by the Canadian regional Management Committee (CaRMC) November 2018

Version 2: Approved by the CaRMC on July 5, 2019

3. CANADA REGION

The Canada region comprises the country of Canada.

4. CANADA STUDY ADMINISTRATION STRUCTURE

4.1. Coordinating center and data management

The Regional Coordinating Center (RCC) of REMAP-CAP in Canada CaRCC is St. Michael's Hospital, Unity Health Toronto. This document outlines the responsibilities of the CaRCC.

4.1.1. Responsibilities

The CaRCC is responsible for the following aspects of study management in Canada:

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- 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
- Management of study budget and liaison with funding bodies
- Recruitment and selection of sites
- Protocol training of site investigators and research coordinators
- Management of study set up including assistance with Research Ethics Board (REB) 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 with Monash University database managers
- Administrative assistance to the RMC, Domain-Specific Working Groups (DSWG), International Interest Groups (IIG), and the ITSC, as required
- Public relations for the study
- Liaison with other RMCs to develop study documents and materials that are standardized as much as possible

4.2. Canada Regional Management Committee

4.2.1. Responsibilities

The CaRMC is responsible for the following aspects of study management in Canada:

- Liaison with the staff of the CaRCC
- Funding applications to and negotiations and communications with funding bodies located in Canada, or located in other countries, but for which funding will be used to support trial activities in the Canada region
- Study budget
- Approval of the RSA
- Approval and establishment of feasibility of domains and interventions in the region
- Development and approval of the RSA and study materials for the region
- Development and approval of data management systems for the region

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- General study management issues
- Consumer engagement
- Liaison with ITSC, DSWGs, IIGs, and other RCCs with regard to analysis and interpretation of results, and collaboration on publications and presentations

4.2.2.Members

Executive Director and Chief Investigator in Canada

John Marshall

Deputy Executive Director

Srinivas Murthy

Members

Sean Bagshaw

Zahra Bhimani

Nick Daneman

Niall Ferguson

Francois Lamontagne

Cheryl Misak

Marlene Santos

4.3. Contact Details

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4.3.1.Coordinating Center

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4.3.2. Project Management

4.3.2.1. CAPTIC Project Management

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5. CANADIAN REGIONAL MANAGEMENT COMMITTEE AUTHORIZATION

Canada REGIONAL MANAGEMENT COMMITTEE AUTHORISATION
The CaRMC have read the appendix and authorize it as the official Canada Region Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Canada Executive Director
John Marshall

Date 05th July 2019

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6. TRIAL REGISTRATION

Participation in this trial and involvement of sites in Canada is registered at ClinicalTrials.gov. The registration number for the international trial is 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

The trial is funded as part of the CAPTIC consortium of the Canadian Institutes of Health Research, Strategy for Patient-Oriented Research (CIHR SPOR) Innovative Clinical Trials Program Operating Grant number 158584.

7.2. Site costs

Per-patient and any other project-related payments to sites will be as specified in the contract between the Sponsor and each site.

7.3. Sponsors

The sponsor in Canada is St. Michael's Hospital, Unity Health Network.

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. Contracts 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.

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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 Canada. 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 Canada to all participating sites in which the intervention is available and feasible

9.2.1. Antibiotic Domain

The antibiotic domain will be offered to any site in Canada for drugs that are available in Canada. All antibiotic strategies that are off-patent will be provided by the treating hospital (as the patient would have always required antibiotic treatment that the hospital would have otherwise provided).

9.2.2. Macrolide Duration Domain

The macrolide duration domain will be offered to any site in Canada. Intravenous (IV) Azithromycin is licensed for use in Canada and enteral Azithromycin is widely used. The IV formulation is not widely used, and not available in all sites. In Canada, enteral Azithromycin or other enteral or parenteral macrolides will be allowed as an alternative to Azithromycin IV, as described in the Macrolide Duration DSA.

9.2.3. Corticosteroid Domain

The steroid 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.

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9.2.5. Ventilation Domain

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

9.2.6. Registry

The registry will only be offered to sites that participate in regional registries.

9.3. Endpoints

Data will be collected as set out in the Core Protocol and DSAs.

9.4. Co-enrollment

As described in the Core Protocol Section 7.9.

10. TRIAL CONDUCT

10.1. Recruitment and embedding

As described in the Core Protocol Section 8.3.

10.2. Treatment allocation

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

10.3. Distribution of study drug

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

10.4. Data collection

Data collection will be as outlined in the Core Protocol Section 8.9. The collection of data from time-points after discharge from the index hospitalization will be voluntary in this region.

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10.5. Data management

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

10.6. Trial group linkage / participation

REMAP-CAP is conducted under the auspices of the Canadian Critical Care Trials Group (CCCTG) and in collaboration with funded initiatives in Europe, Australia, and New Zealand. It is one component of the Canadian Adaptive Platform Trial in Intensive Care (CAPTIC) program that is exploring the wider use of the platform trial model in critical care research.

10.7. Site start up and initiation

A site initiation teleconference or visit will be conducted before site activation; at least 1 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.

10.8. Quality assurance and monitoring

10.8.1. Quality assurance

As described in the Core Protocol Section 8.11.

10.8.2. Monitoring

A representative of CaRCC will monitor the study. Monitoring will be conducted by quality control reviews of protocol compliance, source data verification, data queries and safety reporting.

A monitoring report will be prepared following each visit and reviewed by the RMC 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.

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

10.9. Safety reporting

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

All Serious Adverse Events (SAE) will be recorded in the electronic Case Report Form (eCRF). For sites in Canada, all SAEs must be reported 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.

A 24-hour contact number for Canadian sites will be provided to all sites before recruitment commences.

11.ETHICAL CONSIDERATIONS

11.1. Ethical and regulatory issues

The trial will be conducted in accordance with Canadian legislation. Research ethics approval will be obtained prior to the start of the study at each institution from the responsible local REB. 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 serious adverse events are also reported to the REB as required by that committee.

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