REGISTRY APPENDIX

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

Registry Appendix Version 2 dated 5th November, 2024

SUMMARY

This is an Appendix to the REMAP-CAP Core Protocol, which describes the processes to provide an observational dataset of patients with respiratory tract infection who are admitted to hospital. This includes patients who have received an allocation within one or more REMAP-CAP Domain(s) ("platform-randomized") and patients meeting a minimum set of eligibility criteria but not allocated an intervention within a Domain ("registry-only").

The objectives are to describe the characteristics, outcomes, and associations with risk factors for all patients admitted to participating hospitals with respiratory tract infection; to compare the platform-randomized and registry-only populations to assess the representativeness of the randomized study population, to facilitate site feedback and development of domains; and to evaluate long-term outcomes.

Where feasible and practical, data from hospitalized patients with respiratory tract infection will be linked to existing healthcare-related registries and databases in participating countries or regions. These may include the relevant national or regional ICU patient benchmarking registries or databases, and may include other non-ICU patient benchmarking registries, death registries, hospital discharge coding databases, or similar sources. In some countries or regions additional data for Registry-only participants may also be obtained from the clinical record. Registries and databases, methods for linkage, and data to be obtained are specified in a regional addendum.

Exposures (such as baseline risk factors, microbiological causation, and allocation status for randomized patients), outcomes (such as organ support, hospital or longer-term mortality, complications or readmissions) and statistical analyses will be pre-specified in a statistical analysis plan developed for each registry project.

REMAP-CAP: Registry Appendix Summary	
Population	Patients allocated to an intervention within one or more REMAP-CAP Domains ("platform-randomized") and patients meeting a minimum set of eligibility criteria but not allocated an intervention within a Domain ("registry-only")
Interventions	This appendix specifies only collection of data. It does not specify any interventions.
Inclusions	Hospitalized patients (aged 28 days or older) with an acute respiratory tract infection.
Exclusions	The population may be constrained for specific analyses as specified in each project statistical analysis plan
Outcome measures	Those available from the platform and, where feasible, linked patient benchmarking databases and other routinely collected data sources in each participating country or region.

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1. ABBREVIATIONS

CAP	Community Acquired Pneumonia
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
ICU	Intensive Care Unit
ITSC	International Trial Steering Committee
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix

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 (details of the current statistical analysis plan and models for evaluating randomized treatment effects), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), this Registry Appendix, 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, because the analysis model will change over time in accordance with the domain and intervention trial adaptations, but this information is contained in the Statistical Analysis Appendix. 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 blinded 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 an 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. REGISTRY APPENDIX VERSION

The version of the Registry Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the Registry Working Group on 11 September 2019

Version 2: Approved by the Registry Working Group on 05 November 2024

4. REGISTRY GOVERNANCE

4.1. Registry Working Group

Chair: Dr. Colin McArthur

Members: Associate Professor Sean Bagshaw
Professor Michael Baker
Professor Frank Brunkhorst
Dr. Lennie Derde
Professor David Harrison
Dr. Alex Kazemi
Associate Professor Peter Kruger
Dr. Ed Litton
Dr. Susan Morpeth
Mr. Paul Mouncey
Dr. Srinivas Murthy
Ms. Jane Parker
Associate Professor Rachael Parke
Adjunct Clinical Professor David Pilcher
Professor Kathy Rowan

Mrs. Anne Turner

Professor Steve Webb

Dr. Paul Young

4.2. Contact Details

Chair: Dr. Colin McArthur

Department of Critical Care Medicine

Auckland City Hospital

2 Park Road,

Grafton

Auckland, 1023

NEW ZEALAND

Email colinm@adhb.govt.nz

5. REGISTRY WORKING GROUP AUTHORIZATION

The Registry Working Group have read the appendix and authorize it as the official Registry Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair
Colin McArthur

Date 5th November, 2024

6. BACKGROUND AND RATIONALE

6.1. Definition

This is an appendix to the REMAP-CAP Core Protocol, to provide an observational dataset of patients with respiratory tract infection who are admitted to a hospital that is participating in REMAP-CAP.

6.2. Registry-specific background

All hospitalized patients with a respiratory tract infection form a population of interest for this REMAP, as it is from this population that qualifying patients are assigned treatment within domains.

However, some hospitalized patients with respiratory tract infection will not meet the criteria for inclusion in the platform or any of the available domains. Although basic eligibility screening data is available for the reporting of patient flow consistent with Consolidated Standards of Reporting Trials (CONSORT) guidelines, it is important to understand some wider characteristics of excluded patients who have the disease of interest. This facilitates other aspects of general trial management and interpretation such as the generalizability of results, the identification of selection bias and to provide feedback to sites. For this REMAP, this additional observational data also assists in the refinement of the platform and its existing domains, and in the development of further domains. Furthermore, in combination with the data from participants assigned treatment within the domains and where available, linkage to external data sources, a full descriptive analysis of the entire population of hospitalized patients with respiratory tract infection may be undertaken, including longer-term outcomes.

7. REGISTRY OBJECTIVES

The objectives are to:

1. Describe the characteristics, outcomes and associations with risk factors for hospitalized patients with respiratory tract infection. This may include specific analyses to achieve regional objectives.

2. Describe the characteristics and outcomes of hospitalized patients with respiratory tract infection to compare the platform-randomized participants to the population from which they were drawn.

3. Evaluate long-term outcomes following hospitalization with respiratory tract infection, including the effect of allocation status for randomized patients.

8. STUDY DESIGN

This Registry will be conducted as part of the REMAP-CAP Platform (see Core Protocol).

8.1. Population

The study population for the Registry comprises all patients with an acute respiratory tract infection initially hospitalized at a participating hospital. This population is divided into two mutually exclusive

cohorts: those eligible for the Platform and assigned treatment within one or more REMAP-CAP domains (“Platform-randomized”); and a cohort who are either not platform eligible, or are platform eligible but not assigned treatment within a Domain (“Registry-only”).

8.2. Eligibility criteria

Patients are eligible for the Registry if they meet the following eligibility criteria:

8.2.1. Registry inclusion criteria

1. Hospitalized patient
2. Acute respiratory tract infection
3. Aged ≥ 28 days

8.2.2. Registry exclusion criteria

1. Patients who have declined consent for participation in the Platform.

Some jurisdictions may not require consent to be sought for inclusion in the Registry and inclusion in the registry may also be constrained as specified in region-specific addenda.

8.3. Interventions

The Registry specifies no interventions and only collects data previously obtained and recorded for clinical care and administration.

8.4. Data points

Patients meeting the Registry inclusion criteria and none of the Registry exclusion criteria (Section 8.2) may be linked to existing healthcare-related registries and databases to obtain additional data. These may include the relevant national or regional ICU patient benchmarking registry or database (which enrolls all patients admitted to all participating ICUs), and may include one or more of other non-ICU patient benchmarking registries, death registries, and hospital discharge coding databases. Linkage may be performed using national or local patient identifiers in accordance with national and local data governance requirements. In some countries or regions additional data for Registry-only participants may be obtained from the clinical record using a Registry-only CRF.

Country or region-specific data sources and methods for data linkage are described in the addendum (Section 14).

9. STUDY CONDUCT

9.1. Registry-specific data collection

Platform-randomized cohort:

- Case Report Form data collected as part of their participation in the Platform, as specified in core protocol documents and relevant DSAs.
- Data linkages to healthcare-related registries and databases as specified in regional addendum.
  Additional registry-only CRF variables (in some regions, as specified in the regional addendum).

Registry-only cohort:

- Registry-only CRF variables (in some regions as specified in the regional addendum).
- Data linkages to healthcare-related registries and databases as specified in the regional addendum.

10.STATISTICAL CONSIDERATIONS

This is a prospectively defined observational cohort study with retrospective data linkage and collection. The population is hospitalized patients with acute respiratory tract infection. Exposures (such as baseline risk factors, microbiological causation, and allocation status for randomized patients), outcomes (such as hospital or longer-term mortality, complications or readmissions) and statistical analyses will be pre-specified in a statistical analysis plan developed for each registry project.

11. ETHICAL CONSIDERATIONS

11.1. Principles

This observational study utilizes retrospective linkage of existing clinical data and routinely collected healthcare and administrative data only. There are no interventions. Risk to participants is therefore

very low, and primarily relate to the secure handling of data and regional/local data sovereignty considerations. Data linkage will be undertaken utilizing the minimum individual identifiers and only obtaining the variables relevant to the study.

11.2. Consent

Country-specific requirements for consent to research involving observational data will be submitted for health research ethical and regulatory approval as appropriate at each participating site. In view of the low-risk nature of this study, applications for approval may include a waiver of participant consent for registry-only patients. For platform-randomized patients, information related to additional data collection by record linkage will be incorporated within the consent process for such patients. Patients who are platform-randomized but withdraw from the trial may also withdraw from the registry components outlined in this appendix. Ethical issues that are specific to a participating country are outlined in the regional addendum.

12. GOVERNANCE ISSUES

12.1. Funding of Registry

Regional or local funding may support specific Registry data collection and analyses.

Registry participation may be supported with payments to sites, depending on the resources available and workload required for participation in each specific country or region.

12.2. Registry-specific declarations of interest

All members of the International Trial Steering Committee maintain a registry of interests. These are updated periodically and publicly accessible on the study website.

13.UNITED KINGDOM REGISTRY ADDENDUM

13.1. Data sources

13.1.1. Registry Case Report Form

Registry CRF data will not be collected at United Kingdom (UK) sites.

13.1.2. Intensive Care National Audit & Research Centre (ICNARC) Case Mix Programme (CMP) Database

All adult general critical care units in England, Northern Ireland and Wales that are participating in REMAP-CAP submit data on all admissions to the ICNARC CMP Database. Each admission to critical care is allocated a unique 'CMP admission number (CMP ADNO)'. Data submitted to the CMP Database includes information related to dates and times of ICU admission(s), admission diagnoses, physiological and treatment data from the first 24 hours of ICU admission used to calculate severity of illness scores, provision of organ support, survival status at hospital discharge, and, for survivors, discharge destination (corresponding to the data outlined in section 8.4.2). Patients meeting the entry criteria specified in this Appendix will be linked to the CMP Database record for the same patient by the submission to the REMAP-CAP database of the 'CMP ADNO' with linkage supplemented, where appropriate, by additional variables such as hospital and critical care admission dates and times. Patient's NHS number will be obtained from the CMP Database to facilitate identification of further admissions to critical care and record linkage to other databases.

13.1.3. NHS England and NHS Wales Informatics Service

NHS England has responsibility for collecting data from across health and social care in England. Data held includes civil registrations for England and Wales and Hospital Episode Statistics (HES) for details of all admissions, outpatient appointments and Accident and Emergency attendances at NHS hospitals in England. The NHS Wales Informatics Service (NWIS) holds details of all admissions, outpatient appointments and Accident and Emergency attendances at NHS hospitals in Wales in the Patient Episode Database for Wales (PEDW). For REMAP-CAP registry patients, longer term survival including date of death after hospital discharge, will therefore be obtained through data linkage to NHS England. Subsequent hospital readmissions will be determined in England from data linkage to HES via NHS England and for Wales via data linkage to PEDW via NWIS.

13.2. Ethical issues and approvals

At critical care units in England, Northern Ireland and Wales, data collection and submission to the CMP occurs without provision of consent. The CMP provides quality assessment information to participating ICUs by benchmarking their risk-adjusted performance (i.e. adjusted for age, diagnosis, and severity of illness) against all other participating ICUs. The CMP operates under Section 251 of the NHS Act 2006 permitting the use of patient identifiable data without consent for specified purposes. In addition, to approval from the Health Research Authority (HRA) and research ethics committee, study specific section 251 approval from the HRA Confidentiality Advisory Group will be sought in order to access patient information without consent for the purposes of the Registry.

All “platform-randomized” patients will be approached using the consent procedures for participation in the interventional domains. For “Registry-only” patients, information regarding the processing of data, including how to opt-out, for the Registry will be made available by the participating units. It is not practicable to obtain consent as many participants will not be competent to consent and those who are competent will have or be recovering from critical illness. In addition, many patients will be identified retrospectively after discharge from the ICU. All data will be handled in a secure manner and will preserve participant confidentiality.