



Region-Specific Appendix:
UNITED STATES

**Randomized, Embedded, Multifactorial
Adaptive Platform trial for Community-
Acquired Pneumonia (REMAP-CAP): COVID-19
(REMAP-CAP:covid, or REMAP-COVID)**

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1. ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
eCRF	Electronic Case Report Form
EC	Ethics Committee
ICH-GCP	International Conference on Harmonization-Good Clinical Practice
IIG	International Interest Group
IRB	Institutional Review Board
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
IV	Intravenous
RCC	Regional Coordinating Center
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
US RCC	American Regional Coordinating Center
US RMC	American Regional Management Committee

2. PROTOCOL APPENDIX STRUCTURE

The structure of a REMAP 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 REMAP protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see section entitled 'Glossary' of applicable Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The REMAP 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). Additionally, any of the adjustments made in the protocol as described in the section entitled 'Amendments' of the applicable Core Protocol or a change in the

statistical evaluation concept will be considered as a substantial amendment of the protocol and will be provided as such to the Ethics Committee (EC) for approval and will only be implemented when approval is obtained from EC.

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.

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).

3. RELATIONSHIP BETWEEN REMAP-CAP AND REMAP-COVID

REMAP-CAP is a large on-going international adaptive platform trial specifically designed to run in both inter-pandemic and pandemic periods, focusing on optimizing care for patients with severe pneumonia.

For sites participating solely in the enrollment of COVID-19 patients, the REMAP-COVID core protocol and its associated domain-specific appendices will govern these activities. While based on the REMAP-CAP core protocol, the REMAP-COVID core protocol removes any information not relevant to the study of COVID-19 patients. The REMAP-COVID core protocol provides background information about COVID-19 and incorporates the design concepts of the REMAP-CAP core protocol pandemic appendix. The REMAP-COVID core protocol also broadens the enrollment criteria to include hospitalized patients with COVID-19 (depending upon the domain) and expands co-enrollment discussion.

3.1. Region-Specific Protocol version

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

3.2. Version History

Version 1: Approved by the U.S. Regional Management Committee (US RMC) on March 30, 2020.

4. U.S. REGION

The US region comprises sites in the United States. These sites may be a part of a trial network (as outlined in Section 10.7 of this RSA), multi-hospital health care systems, or independent hospitals.

5. U.S. STUDY ADMINISTRATION STRUCTURE

5.1. *Coordinating center and data management*

The initial Regional Coordinating Center (RCC) of REMAP-CAP in the United States (US RCC) is a joint collaboration of the sponsor, GCAR (Global Coalition for Adaptive Research) and the CRISMA Center, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. Sites may join the US region either as individual sites or as part of existing research networks. In instances where sites join as existing networks, the coordinating centers of these networks will function in a federated relationship, either as sub-RCCs or in parallel to the Pitt RCC, for data management issues, and under GCAR for overall contractual issues. The Pitt RCC will have predominant responsibility for the coordination of trial activities all UPMC owned, managed, and controlled sites. The Pitt RCC will also supervise clinical trial activities at those sites that are not affiliated with established trial networks, while GCAR will assist with contracting and central IRB approval region-wide.

5.1.1. Responsibilities

The joint Pitt/GCAR RCC is responsible for the following aspects of study management in the United States, consistent with the scope of responsibility as outlined in Section 4.1 of this RSA:

- 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
- 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 regulatory affairs

- Management of study set up including assistance with Institutional Review Board (IRB) applications
- Initiation, monitoring and close-out site visits
- Organization of investigator meetings
- Serious adverse event notification to DSMB and American regulatory authorities.
- Coordination of data entry and feedback of data enquiries
- 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

5.2. U.S. Regional Management Committee

5.2.1. Responsibilities

The US RMC is responsible for the following aspects of study management in the United States:

- Liaison with the staff of each US RCC
- Funding applications to and negotiations and communications with funding bodies located in the United States, or located in other countries, but for which funding will be used to support trial activities in the US 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
- 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

5.2.2. Members

Executive Director and Chief Investigator in the United States

Derek C. Angus, MD, MPH, FRCP

Co-chairs

Brian Alexander, MD

Christopher W. Seymour, MD, MSc

Members

Jennifer Vates, MS-RA

Meredith Buxton, PhD

Membership to be expanded

5.3. Contact Details

Executive Director and Chief Investigator

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5.3.1. Coordinating Center

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University of Pittsburgh
CRISMA Center
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5.3.2. Project Management

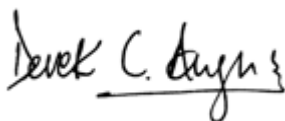
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6. U.S. REGIONAL MANAGEMENT COMMITTEE AUTHORISATION

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

US Executive Director

Derek Angus



Date

30 March 2020

7. TRIAL REGISTRATION

Participation in this trial and involvement of sites in the United States is registered at ClinicalTrials.gov. The registration number is [NCT02735707](#).

8. FUNDING OF REGION

8.1. Sources of funding

In the United States, funding has been received from UPMC health system for recruitment internally at all UPMC hospitals (>40) and to support a U.S. regional coordinating center. Additional funds are being pursued.

8.2. Site costs

Participating U.S. sites will bear any costs associated with their involvement in REMAP-COVID.

8.3. Sponsors

For the purposes of REMAP-COVID, the sponsor in the United States is the Global Coalition for Adaptive Research (GCAR).

8.4. 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.

8.5. Insurance

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

9. 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 the United States. Some interventions may not be implemented at all participating sites within the region.

10. TRIAL DESIGN

10.1. Study setting

As described in the Study Setting section of the applicable Core Protocol.

10.2. Interventions

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

10.2.1. Full REMAP-CAP platform

10.2.1.1. Antibiotic Domain

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

10.2.1.2. Macrolide Duration Domain

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

10.2.1.3. Corticosteroid Domain

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

10.2.1.4. Ventilation Domain

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

10.2.1.5. Registry

Site(s) participation in the Registry is optional within the United States. Participation is possible where there is an existing healthcare-related registry or database, which routinely captures data on the entire study population specified for the Registry.

The study population specified for the Registry comprises adult patients admitted to an ICU for CAP. 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 those who are either platform ineligible or platform eligible but not assigned treatment within one or more REMAP-CAP domains (“Registry-only”).

The purpose of the Registry is to provide limited information on all patients admitted to an ICU with CAP so that the characteristics of patients who are randomized within the Platform (“Platform-randomized”) can be compared with the patients with CAP admitted to an ICU at participating sites (“Registry-only”). Registry data will overlap with, but will not be more extensive than, the minimum dataset collected for patients who are randomized within the Platform.

The Registry does not specify any interventions and only utilizes the routine data captured for administration and clinical care.

10.2.2. REMAP-COVID

10.2.2.1. COVID-19 Antiviral Domain

The COVID-19 antiviral domain will be offered to any site in this region.

10.2.2.2. COVID-19 Corticosteroid Domain

The COVID-19 corticosteroid domain will be offered to any site in this region.

10.2.2.3. COVID-19 Targeted Immuno-Modulatory Domain

The COVID-19 targeted immune-modulatory domain, when available, will be offered to any site in this region.

10.3. Endpoints

Data will be collected for the endpoints as described in the section entitled 'Endpoints' in the applicable Core Protocol and DSAs.

10.4. Co-enrollment

As described in the section entitled 'Co-enrollment with other trials' of the applicable Core Protocol.

10.5. Criteria for termination of the trial

It is anticipated that after inclusion of the initially planned sample size, the study would continue to include additional participants and test additional domains and/or interventions until one of the following occurs:

- As applicable to the relevant Core Protocol, CAP and COVID-19 are no longer deemed to be a public health problem
- The effectiveness and/or cost-effectiveness of all interventions are known and there are no new plausible interventions to test

There is no current estimated end date for recruitment in United States.

11. TRIAL CONDUCT

11.1. Recruitment and embedding

As described in the section entitled 'Recruitment of participating including embedding' of the applicable Core Protocol.

11.2. Treatment allocation

Except to the extent outlined in Section 12 of this RSA, central randomization will occur online and be managed and operated by SPIRAL Web Solutions Ltd with servers in the United States.

11.3. 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. Although the default is

the provision of open-label treatments, the blinding of treatment status is not precluded within the REMAP. Whether interventions are open-label or blinded will be specified in DSAs.

11.4. *Unblinding of allocation status*

Unblinding of any blinded treatment by site research staff or the treating clinician should only occur only when it is deemed that knowledge of the actual treatment is essential for further management of the participant. A system for emergency unblinding will be provided in a future DSA of any domain that includes interventions that are administered in a blinded fashion. Any unblinding process will ensure that the investigator can directly and rapidly unblind in an emergency situation. All unblindings and reasons as they occur will be documented in the CRF. Unblinding should not necessarily be a reason for study drug discontinuation.

11.5. *Data collection*

Data collection will be as outlined in the section entitled 'Data collection' of the applicable Core Protocol. The collection of data at day 90 will be mandatory, the collection of data from time-points after day 90 will be voluntary in this region.

11.6. *Data management*

Except as outlined in Section 12 of this RSA, data used to establish eligibility will be entered into a secure, password protected web based CRF designed by SPRIAL Web Solutions Ltd, using a server located in the United States.

The Project Managers and the RCC will coordinate data entry and data management.

11.7. *Trial group linkage / participation*

The participation of established trial networks is recognized as one method for facilitating high quality trial conduct. Networks that are based in the United States will be approached to determine their interest in contributing as partners to the study.

11.8. *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.

11.9. Quality assurance and monitoring

11.9.1. Quality assurance

As described in the section entitled 'Quality assurance and monitoring' of the applicable Core Protocol.

11.9.2. Monitoring

The study will use a monitoring plan that is developed on a risk-based approach. Details can be found in the monitoring plan.

A representative of each RCC or a local representative at request of the applicable RCC will monitor the study. Monitoring will be conducted by quality control reviews of protocol compliance, data queries and safety reporting.

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 monitor for these visits during the course of the study and at the completion of the study as needed.

11.10. Safety reporting

Safety reporting will occur as outlined in the section entitled 'Safety monitoring and reporting' of the applicable Core Protocol.

All Serious Adverse Events (SAE) will be recorded in the electronic Case Report Form (eCRF) and intermittently monitored by the Sponsor. Complications of the underlying critical illness and its treatment do not require specific SAE reporting as the trial endpoints are designed to measure the

vast majority of events. These will be monitored by the sponsor both centrally and on-site through sourced data verification. However, any SAE that is considered by the site-investigator to be attributable to a study intervention or study participation should be reported as detailed below. All SAEs must be reported immediately to the coordinating center within a maximum of 24-hours of the investigators becoming aware of the event. Personal data must be pseudonymized before transmission using the randomization number of the person concerned.

Only SAEs that occur between randomization and hospital discharge censored at day 90 need to be recorded.

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

Sites will be provided with contact information for SAE reporting before recruitment commences.

11.11. *Contraceptive advice*

If any trial drugs require specific contraceptive advice in this trial population, the details will be provided in the relevant Domain Specific Appendix.

12. ETHICAL CONSIDERATIONS

12.1. *Ethical and regulatory issues*

The trial will be conducted in accordance with applicable federal law and regulation. Research ethics and regulatory authorities' approvals will be obtained prior to the start of the study at each institution from the responsible local or central IRB. As expedited initiation of the trial is desired, sites shall use the Western Institutional Review Board (WIRB) to the extent legally permissible and in accordance with site policy/procedure. 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 trial design, including new domain specific appendices or serious adverse events are also reported to the IRB as required by that committee and all relevant regulatory authorities.

13. MODIFICATIONS SPECIFIC TO A NETWORK IN THE UNITED STATES

13.1. Introduction

This section identifies any issue that is different within a specific network in the United States to vary the protocol in that network from what is specified elsewhere in this RSA or the Core Protocol or both.

13.2. UPMC

13.2.1. Data Collection

UPMC has developed an integrated Electronic Health Record (EHR) platform to facilitate the automated collection of medical record information to fulfill study data requirements. REMAP-CAP data will be collected using UPMC's embedded EHR system. This data will be made available for incorporation into the aggregate dataset to permit interim analyses.

13.2.2. Treatment Allocation

Interfacing with its integrated EHR platform, UPMC will randomize REMAP-CAP patients through a Berry Consultants' randomization table located behind its institutional firewall.