



Region-Specific Appendix: EUROPE

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

REMAP-CAP European Region-Specific Appendix Version 3 dated 23 August 2019

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1. ABBREVIATIONS

AE	Adverse Event
AMG	Arzneimittelgesetz (German drug law)
CRF	Case Report Form
CA	Competent Authority
CSCC	Center for Sepsis Control & Care
DGIIN	Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
eCRF	Electronic Case Report Form
EC	Ethics Committee
Eu	Europe
EU	European Union
EudraCT	European Clinical Trials Database
Eu RCC	European Regional Coordinating Center
Eu RMC	European Regional Management Committee
GDPR	General Data Protection Regulation
ICH-GCP	International Conference on Harmonization-Good Clinical Practice
ICNARC	The Intensive Care National Audit & Research Centre
IIG	International Interest Group
IRB	Institutional Review Board
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
IV	Intravenous
NET-GER	Network Germany
NFU	Netherlands Federation of University Medical Centres
PREPARE	Platform for European Preparedness Against (Re-)emerging Epidemics
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
UK	United Kingdom
UMC Utrecht	University Medical Center Utrecht
WP8	Work Package 8

Not for IRB submission

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). Additionally, any of the adjustments made in the protocol as described in Section 5.3.7.7 of the 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) and Competent Authority (CA) for approval and will only be implemented when approval is obtained from EC and CA.

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) and the PREPARE Workpackage 5 website (<https://www.prepare-europe.eu/About-us/Workpackages/Workpackage-5>)

2.1. Region-Specific Protocol version

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

2.2. Version History

Version 1: Approved by the Europe Regional Management Committee (Eu RMC) on 20 November 2016

Version 1.1: Approved by the Eu RMC on 09 May 2017

Version 2: Approved by the Eu RMC on 12 December 2017

Version 2.1: Approved by the Eu RMC on 24 May 2018

Version 2.2: Approved by the Eu RMC on 26 October 2018

Version 2.3: Approved by the Eu RMC on 26 March 2019

Version 2.4: Approved by the Eu RMC on 25 April 2019

Version 3.0: Approved by the Eu RMC on 23 August 2019

3. EUROPEAN REGION

The European (Eu) region comprises sites in the 28 European Union (EU) member states, plus sites in other countries that may be added subsequently but does not include any site that is located in any country that is active as part of an existing REMAP-CAP region.

The countries to which this appendix applies are:

- Austria
- Belgium
- Bulgaria
- Croatia
- Cyprus
- Czech Republic
- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- Ireland
- Italy
- Latvia
- Lithuania
- Luxembourg
- Malta
- Netherlands
- Poland
- Portugal
- Romania
- Slovakia
- Slovenia
- Spain
- Sweden

- United Kingdom

4. EUROPEAN STUDY ADMINISTRATION STRUCTURE

4.1. Coordinating center and data management

The Regional Coordinating Center (RCC) of REMAP-CAP in Europe (Eu RCC) is the University Medical Center Utrecht (UMC Utrecht), Department Julius Center for Health Sciences and Primary Care. This document outlines the responsibilities of the UMC Utrecht. The UMC Utrecht will have predominant responsibility for the region plus management of sites in all 28 EU member states and associated countries, as described above, and any countries that joins the EU as member state or associated countries in the future.

4.1.1. Responsibilities

The Eu RCC is responsible for the following aspects of study management in Europe:

- 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 (in cooperation with Work Package 8 (WP8) of Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE) and SPIRAL Web Solutions Ltd.)
- 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 EU 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

4.2. European Regional Management Committee

4.2.1. Responsibilities

The Eu RMC is responsible for the following aspects of study management in Europe:

- Liaison with the staff of the Eu RCC
- Funding applications to and negotiations and communications with funding bodies located in EU, or located in other countries, but for which funding will be used to support trial activities in the Eu 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, DSWG, 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 Europe

Professor Marc Bonten

Co-chairs

Professor Marc Bonten

Dr. Lennie Derde

Members

Dr. Farah Al-Beidh

Professor Derek Angus
Ms. Wilma van Bentum-Puijk
Dr. Scott Berry
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Professor Herman Goossens
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5. Eu REGIONAL MANAGEMENT COMMITTEE AUTHORISATION

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

Eu Executive Director
Marc Bonten



Date 23 August, 2019

6. TRIAL REGISTRATION

Participation in this trial and involvement of sites in Europe is registered at ClinicalTrials.gov. The registration number is [NCT02735707](#) and was registered on 12 April 2016.

Additionally, this study is registered at European Clinical Trials Database (EudraCT). The registration number is 2015-002340-14 and was registered on 20 May 2015.

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

7. FUNDING OF REGION

7.1. Sources of funding

The PREPARE consortium is funded by the EU, FP7-HEALTH-2013-INNOVATION-1, grant number 602525. Within the PREPARE consortium, funding for the REMAP-CAP study is included for approximately 4000 patients.

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 Europe is the University Medical Center Utrecht.

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.

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 Europe. 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 Europe 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 this region. 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 this region. Intravenous (IV) Azithromycin is licensed for use in Europe and oral Azithromycin is widely used. The IV formulation is not widely used, and not available in all sites. In Europe, 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

This antiviral domain will be offered to any site in this region.

9.2.5. Ventilation Domain

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

9.2.6. Registry

Site(s) participation in the Registry is optional within the EU. Participation is possible by countries, or by regions within countries, 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.

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.

9.5. 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:

- CAP is 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

Current estimated end date for recruitment in Europe is 31st January 2021. The last patient last follow-up in Europe would be 6 months later and would be the end date of the trial in Europe.

10. TRIAL CONDUCT

10.1. Recruitment and embedding

As described in the Core Protocol Section 8.3.

10.2. Pregnancy testing and breastfeeding

For specifically identified countries in the EU, according to local requirements, pregnancy testing is mandatory for female patients of childbearing age. This is necessary because in such countries

pregnancy will be a platform-level exclusion criteria, i.e. excludes a patient from receiving a randomization allocation in all domains, but does not exclude the patient from the registry.

For specifically identified countries in the EU, according to local requirements, breastfeeding is also a platform-level exclusion criteria, i.e. excludes a patient from receiving a randomization allocation in all domains, but does not exclude the patient from the registry.

Countries to which this requirement applies will be listed in operational documents.

10.3. Treatment allocation

Central randomization will occur online and be managed and operated by SPIRAL Web Solutions Ltd.. Data management and transfer will comply with GDPR requirements in the country in which a site is located.

10.4. 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.

10.5. 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.

10.6. Data collection

Data collection will be as outlined in the Core Protocol Section 8.9. 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.

10.7. Data management

Data used to establish eligibility will be entered into a secure, password protected web based CRF designed by SPIRAL Web Solutions Ltd., in New Zealand, using a server located in Australia. All allocations and all other data collected in the trial will be entered into a secure, password protected web based CRF designed by WP8 of PREPARE, ResearchOnline 2, Located in the Netherlands. Each subject will be allocated a unique trial number that is used as the common identifier in both databases. Data management and transfer will comply with GDPR requirements in the country in which a site is located. The Project Managers and the coordinating center will coordinate data entry and data management.

10.8. Trial group linkage / participation

The participation of established trial networks is recognized as one method for facilitating high quality trial conduct. The COMBACTE network will facilitate the identification of suitable sites to participate in the trial.

In the United Kingdom (UK), The Intensive Care National Audit & Research Centre (ICNARC) and Imperial College London will jointly coordinate the identification and participation of suitable sites.

In Germany, the Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin (DGIIN) / Center for Sepsis Control & Care (CSCC) network will facilitate the identification and participation of suitable sites.

Additional networks that are based in Europe will be approached to determine their interest in contributing as partners to the study.

10.9. 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.

10.10. Quality assurance and monitoring

10.10.1. Quality assurance

As described in the Core Protocol Section 8.11.

10.10.2. Monitoring

The study will use a monitoring plan that is developed on a risk-based approach, as described by the Netherlands Federation of University Medical Centres (NFU). Details can be found in the monitoring plan.

A representative of the UMC Utrecht or a local representative at request of the UMC Utrecht 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.

10.11. 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) 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. For sites in Europe, all SAEs must be reported immediately to the coordinating center (UMC Utrecht) via email (prepare_icu@umcutrecht.nl) 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 / EC of the occurrence of the serious adverse event in accordance with local requirements.

Web address www.researchonline.org

Contact phone numbers for SAE advice:

UMC Utrecht +31 (0) 6 27 74 44 77

10.12. 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 and the relevant Summary of Patient Characteristics referred to.

11. ETHICAL CONSIDERATIONS

11.1. Ethical and regulatory issues

The trial will be conducted in accordance with EU and national legislation relevant in each European country. Research ethics and regulatory authorities' approvals will be obtained prior to the start of the study at each institution from the responsible local or national IRB and relevant CA. 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.

12. MODIFICATIONS SPECIFIC TO A NETWORK IN EUROPE

12.1. Introduction

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

12.2. Network Germany (NET-GER)

12.2.1. Recruitment numbers

The initial planned enrollment in NET-GER will be 600 participants.

12.2.2. Repeat enrollment

A patient who has been enrolled previously in REMAP-CAP is not eligible for re-enrolment in any second or subsequent episode of CAP.

12.2.3. Process for obtaining consent

As outlined in Core Protocol and in the Antibiotic and Corticosteroid DSAs, some interventions specified in this REMAP meet the requirement for emergency indication (§ 41 para. 2 Arzneimittelgesetz (AMG)) that apply to patients who are unable to consent for themselves and, if necessary, without a declaration of consent from the legal representative.

The process for establishing participation in Germany for a patient who is not competent to consent is outlined below.

Wherever possible, a presumed will of the patient has to be asked for (contact close relatives or existing legal representative). The legal representative is asked for consent. The legal representative is a person with participant's power of attorney or a person appointed by the court.

If consent cannot be obtained directly from a legal representative or the legal representative is unavailable, a patient's inability to consent and the urgency of participating in the study must be confirmed by an independent consultant physician. Once this is established by the independent consultant physician, a patient may then be enrolled. To be eligible as an independent consultant physician, the physician must not have any involvement with the trial, must not hold an appointment at the institution that is conducting the trial and must not be a member of the team that is providing care to the patient. The consultant independent physician must document the relevant findings and conclusions in writing.

If a patient is enrolled by a determination by an independent consultant physician, the patient's legal representative must be approached to ask for a subsequent declaration of consent or a legal representative has to be appointed by the court.

It is the responsibility of the site investigator to identify promptly a suitable person to act as the legal representative and if required submit an application to the appropriate court as soon as possible after randomization. The legal representative can withdraw the participant from the trial at any time. However, data collected before this time will continue to be available and utilized in the analysis of the trial.

When an enrolled participant regains competency, their participation should be explained and an opportunity provided to the participant to provide their ongoing consent. The patient can withdraw from participation from the trial at any time. However, data collected before this time will continue to be available and utilized in the analysis of the trial.

Patients or their legal representatives can withdraw their consent at any time and without giving reasons and can cancel participation in the study. In such a case, the patient is asked to state the reason for termination, but is advised that this is not necessary to do so. Information as to when and in which study arm a patient was randomized as well as the withdrawal of their consent and time of withdrawal must be documented. In this situation, the patient must also be informed that stored data may be further used, if necessary, to:

- determine the effects of the medicinal product to be tested; and
- ensure that the legitimate interests of the participant are not prejudiced.

12.2.4. (Serious) Adverse Events

Contrary to the Core Protocol 8.13, the following applies to Germany without exception:

12.2.4.1. Definitions

According to GCP-V § 3 (31), an Adverse Event (AE) is any adverse event that occurs to a subject who has been administered an investigational product and is not necessarily causally related to that treatment. According to ICH-GCP, these may be signs of disease (including e.g. abnormal laboratory values), diseases or symptoms associated with the use of an investigational product. This is independent of whether the event is causally related to the investigational product or not.

According to GCP-V § 3 (31), a Serious Adverse Event (SAE) or a Serious Adverse Reaction (SAR) is any adverse event or adverse reaction that is fatal, life-threatening, requires hospitalization or prolongation of treatment, results in permanent or serious disability or disability, or results in congenital anomaly or birth defect.

12.2.4.2. *Documentation and Reporting*

The documentation and notification obligations according to GCP-V §12 (4) - (6) shall be strictly observed.

All adverse non-serious and serious events must be recorded completely with the study data, regardless of whether a causal relationship with the investigational drug or the study procedures can be assumed. All events that are not documented as part of the endpoint capture must be documented using the AE form of the eCRF.

Medical or surgical procedures are not documented as AEs, but rather the disease that led to the necessary intervention. Daily variations in the clinical picture as well as the usual progression of severe CAP are not listed as AEs. Diseases that already exist before inclusion in the study are not considered an AE, but an accompanying disease (documented in medical history). The clinically relevant worsening of a pre-existing condition that is not associated with severe CAP is considered an adverse event. A measure to treat a pre-existing condition that was planned prior to inclusion in the study is not considered an adverse event.

For AEs, a description (medical term), start, end, causality, measures for handling the investigational drug and the event as well as the outcome are documented. Each AE must be checked for the criteria of an SAE and, if necessary, the SAE reporting procedure must be followed (see Section 10.11.).