ecraid

UMC Utrecht

Region-Specific Appendix:

EUROPE

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

REMAP-CAP European Region-Specific Appendix Version 4.0 dated 06 November 2024

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1. ABBREVIATIONS

ASR	Annual Safety Report
CA	Competent Authority
CAP	Community Acquired Pneumonia
CTR	Clinical Trials Regulation (Regulation (EU) No 536/2014)
DCC	Data Coordinating Center
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSUR	Development Safety Update Report
DSWG	Domain-Specific Working Group
eCRF	Electronic Case Report Form
EC	Ethics Committee
Ecraid	European Clinical Research Alliance on Infectious Diseases
Eu	European
EU	European Union
Eu RCC	European Regional Coordinating Center
Eu RMC	European Regional Management Committee
ICH-GCP	International Conference on Harmonization-Good Clinical Practice
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
IIG	International Interest Group
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITSC	International Trial Steering Committee
LAR	Legal Authorized Representative
PANDA	Patient, Pathogen and Disease Appendix
PAtC	Pandemic Appendix to the Core Protocol
PREPARE	Platform for European Preparedness Against (Re-)emerging Epidemics
QA	Quality Assurance
RAR	Response Adaptive Randomization
RCC	Regional Coordinating Center
RECOVER	Rapid European SARS-CoV-2 Emergency research Response
REMAP-CAP	Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

RMC	Regional Management Committee
SAA	Statistical Analysis Appendix
RSA	Region-Specific Appendix
RSI	Reference Safety Information
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
UK	United Kingdom
UMC Utrecht	University Medical Center Utrecht

2. MODULAR PROTOCOL STRUCTURE

The structure of the REMAP-CAP 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 and/or interventions (see glossary, section 1.2 Core Protocol V4.0 for definitions of these terms) or commencement of the trial in new geographical regions.

The trial protocol has multiple modules. In brief, these consist of a

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 studied. 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.

Patient, Pathogen and Disease Appendix (PANDA) – specifies conditions, within the larger population of respiratory tract infection, where specific Strata are defined. The document does not include information about interventions, but includes information about the relevant categories of patients hospitalized with respiratory tract infection and eligible for enrolment in the Platform. The PANDA may be amended in the context of a future pandemic.

Pandemic Appendix to the Core Protocol (PAtC) – described modifications made to previous versions of the Core Protocol during the COVID-19 pandemic. As of Core Protocol Version 4.0, there is no longer a stand-alone PAtC.

Statistical Analysis Appendix – an operational document which provides information about statistical analyses and RAR. Each domain will also have a corresponding Statistical Analysis Plan, that is finalized before the analysis of (part of) the domain. Trial simulations are described in a separate operational document.

Domain-Specific Appendices (DSA) – detailed information about all trial interventions studied within each domain. These appendices are anticipated to change over time, with removal, change and addition of interventions within an existing domain or removal and addition of entire domains.

Region-Specific Appendices (RSA) – list information that is specific to each region conducting REMAP-CAP. This includes information related to regional management, governance, and ethical and

regulatory aspects not covered elsewhere. Additional country-specific information may be annexed to the RSA, if applicable (see section 12 of this RSA).

Registry Appendix – provides an observational dataset of patients who are admitted to an Intensive Care Unit (ICU) for community acquired pneumonia (CAP). It includes patients who are allocated to an intervention 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 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.

Biological Sampling Appendix – describes the strategy for biological sampling at participating sites. The intention of these samples is to create a repository of biological samples that may be used to investigate a range of prespecified and post-hoc questions related to respiratory tract infections. Domain-specific sampling, if required, may additionally be specified in the relevant DSAs.

Any new (version of the) Core protocol and/or Appendices mentioned above are considered a substantial amendment and will be submitted to the relevant Ethics Committees (EC) and Competent Authorities (CA) for approval and will only be implemented after required approvals are obtained.

The current version of all protocol elements and Appendices to the Protocol can be found on the trial website (https://www.remapcap.org/).

Information tailored to the European Region is published on https://www.remapcap.eu/.

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

Version 3.1: Approved by the Eu RMC on 13 March 2020

Version 3.2: Approved by the Eu RMC on 03 April 2020

Version 3.3: Approved by the Eu RMC on 08 April 2020

Version 3.4: Approved by the Eu RMC on 20 April 2020

Version 3.5: Approved by the Eu RMC on 03 May 2020

Version 3.6: Approved by the Eu RMC on 17 Dec 2020

Version 4.0: Approved by the Eu RMC on 31 Jul 2024

3. EUROPEAN REGION

The European (Eu) region comprises the 27 European Union (EU) member states, the UK and other countries in the Eu region as listed below. The region does not include any site that is located in a country that is governed by another REMAP-CAP region.

The countries to which this appendix applies are:

• Austria • Albania • Belgium • Bosnia and Herzegovina • Bulgaria • Croatia • Cyprus • Czech Republic • Denmark	• Lithuania • Luxembourg • Malta • Montenegro • Netherlands • Norway • Poland • Portugal • Romania

• Estonia • Finland • France • Germany • Greece • Hungary • Ireland • Israel • Italy • Latvia	• Serbia • Slovakia • Slovenia • Spain • Sweden • Switzerland • Turkey • Ukraine • United Kingdom

4. EUROPEAN TRIAL ADMINISTRATION STRUCTURE

The Eu Region trial administration consists of the European Regional Coordinating Center (Eu RCC) and European Regional Management Committee (Eu RMC).

4.1. Regional Coordinating Center

The Sponsor and Regional Coordinating Center (RCC) of REMAP-CAP for the European Region is the University Medical Center Utrecht (UMC Utrecht). Since November 2022, the *European Clinical Research Alliance on Infectious Diseases* (Ecraid) manages clinical trial operations as the Sponsor's delegate. In the UK, *Imperial College London* and *Intensive Care National Audit and Research Center* (ICNARC) together act as Sponsor delegates (UK RCC), see figure 1. Specific sponsor tasks may be delegated to other parties, this is described in contractual agreements and will be described in this document as appropriate.

This document outlines the responsibilities of the Eu RCC, including the UK RCC. The Eu RCC is responsible for the trial conduct in countries in the region as described above, and any country that joins the EU as member state or associated country in the future.

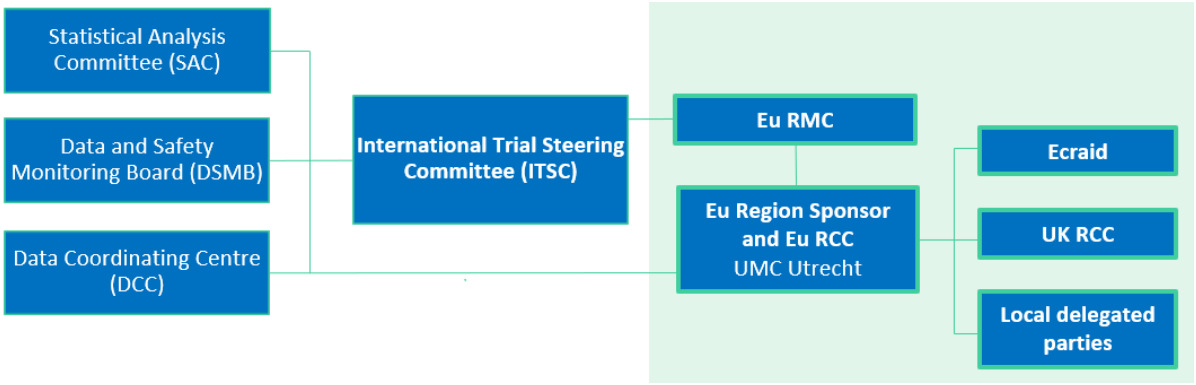

Figure 1: Eu Region Trial Governance

4.1.1. Responsibilities

The Eu RCC is responsible for scientific conduct and integrity, project management and operational oversight in the European region to ensure the trial is conducted in accordance with ICH-GCP to guard subject rights, safety and wellbeing as well as data integrity. This responsibility is operationalized through management of clinical trial operations by Ecraid, by scientific decision-making through the Eu RMC, and by delegating specific responsibilities.

This is effectuated with the following responsibilities for the Eu Region:

Table 1: Responsibilities for the Eu Region

	Eu RCC	**Eu RMC**
Scientific	• Liaise with the ITSC, the DSMB (where needed), the DCC, and other RCCs and the working groups and teams under these committees, in relation to protocol development, oversight of choice of interventions, data analysis, manuscript writing, site management, funding, the strategic direction of the trial and any other scientific issues that may arise • Authorization of the Eu RSA (amendments)	• Liaise with the Eu RCC and the ITSC on scientific and operational aspects of the trial. • Liaise with, and provide adequate information to, the sponsor (UMCU) • Liaise with ITSC, DSWGs, IIGs, and other RCCs with regard to analysis and interpretation of results, and collaboration on publications and presentations • Determine the strategic direction of the platform in the Eu Region • Consideration of the feasibility and suitability of interventions (and domains) as approved by the ITSC and all other aspects of the trial, including

		prioritization of new domains, new interventions within a domain or both. • Development and approval of the Eu RSA (amendments) and trial materials for the region
Regulatory	• Management of regulatory affairs • Management of trial set up and modifications, including EC/CA applications, and compulsory regulatory reporting • Assessing and reporting of (suspected) serious breaches	
Safety	• Safety management for the Eu Region • Safety event notification to relevant stakeholders, including DSMB, regulators and sites per Eu Region requirements	
Clinical Operations and Monitoring	• Recruitment and selection of sites • Training of site staff • Initiation, monitoring and close-out site visits • Coordination of data entry and monitoring of data queries • Contract Research Organisation and monitor management • Liaise with other RCCs to develop standardized trial documents, tools and materials • Project management (including investigational medicinal product (IMP) management, Trial Master File maintenance, central data review)	• General trial management issues • site recruitment and management • Make decisions regarding co-enrolment with other trials that are being or will be conducted in Eu Region
Finances and contracts	• Management of trial budget for the Eu Region and central costs; and liaising with funding bodies • Preparation and arrangement of investigator payments • Management of contracts and contract amendments between Eu Region Sponsor and sites / third parties	• Obtaining funding and coordination of cost sharing for operations of the platform in the Eu Region • Liaison with regional funding bodies
Database	• eCRF and/or database design for any region-specific data collection or region-specific data handling	• Development and approval of data management systems for the region

Other	• Communications to all stakeholders, including the lay public and patient representatives, about the trial and its results • Organizing meetings and events	• ensuring collaboration, harmonization, and optimization of the REMAP-CAP trial network in Europe • Stakeholder engagement • Reviewing requests for data sharing and referring to ITSC as appropriate

4.2. European Regional Management Committee

4.2.1. Responsibilities

The focus of the Eu RMC is on the scientific content and operational management of REMAP-CAP and the trial budget in the European region. For details see table 1 in section 4.1.1.

4.2.2. Members

Eu RMC membership

For membership of the Eu RMC, we agree to the following ground rules for the composition of the Eu RMC:

- At least two individuals from the scientific team and two from the operational team representing the Sponsor. Additional representation is possible if agreed by the Eu RMC.
- One individual representing each significant grant holder for REMAP-CAP in the Eu Region.
- A DCC representative
- For each country with 5 sites or more, a scientific and (where needed, at discretion of the Eu RMC) operational representative
- Cross-representation from ITSC and other RCCs is stimulated. A representative from new regions will be proposed and additional representation (>1 individual) is assessed on a case-by-case basis.

Eu RMC members changing role, can remain an Eu RMC member if they a) continue to play an important role in REMAP-CAP and b) have expertise that is not available from other members of the Eu RMC and c) continuation is supported by a majority of Eu RMC members.

Internal REMAP-CAP collaborators may be invited to join the meetings as observers. External collaborators may be invited to join the meetings as observers, but never without consensus within the Eu RMC. Eu RMC members who no longer have their role in REMAP-CAP will end their term.

The Eu RMC is chaired by one of the Sponsor representatives, preferably the Principal Investigator for the Eu.

Executive Director and Chair	Dr. Lennie Derde, Principal Investigator Eu region, Medical Monitor Eu Region
Deputy Executive director	Prof. Marc Bonten, Vice-Principal Investigator Eu Region
Members	Prof. Djillali Annane, Coordinating Investigator France Prof. Derek Angus, Representative US Region Ms. Aisha Anjum, Project Manager UK Dr. Scott Berry, Statistical Representative Ms. Janis Best-Lane, Project Manager UK Prof. Frank Brunkhorst, Coordinating Investigator Germany Prof. Maurizio Cecconi, Coordinating Investigator Italy Prof. Stephan Ehrmann, Co-Investigator France Prof. Anthony Gordon, Coordinating Investigator UK, Medical Monitor UK Dr. Leanne Marie Hays, PPIE lead, Ireland Ms. Niamh Mahon, Project Manager, Ireland Dr. Colin McArthur, representative New Zealand region Mr. Paul Mouncey, DCC representative and co-investigator UK Prof. Alistair Nichol, Coordinating Investigator Ireland Ms. Svenja Peters, Sr Project Manager Eu Region Prof. Kathy Rowan, Co-coordinating Investigator UK Prof. Julian de la Torre Cisneros, Coordinating Investigator Spain Ms. Eveline Verheijen, Sr Project Manager Eu Region Prof. Steve Webb, representative Australian Region Prof. Sebastian Weis, Co-Investigator Germany

4.3. Contact Details

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5. SPONSOR AUTHORISATION

The Eu RMC have developed and approved this document. The Sponsor authorizes it as the official Eu Regional appendix for the trial titled REMAP-CAP. Signed on behalf of the Sponsor and the Eu RMC.

Eu RMC Chair PI Eu Region	Signature / date
Dr. Lennie Derde	 Lennie Derde (Nov 7, 2024 10:58 GMT+1)

6. TRIAL REGISTRATION

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

The REMAP-CAP EUCT number is 2023-507889-89.

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

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

7. FUNDING OF REGION

7.1. Sources of funding

The REMAP-CAP trial was initiated as part of the Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE) project. PREPARE was funded by the EU FP7-HEALTH-2013-INNOVATION-1 (grant number 602525) from 01-Feb-2014 until 01-Feb-2021. As of 11-Jun-2020, REMAP-CAP received additional funding through the EU Horizon 2020 research and innovation program (grant agreement number 101003589) as part of the RECOVER (Rapid European SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) Emergency research Response) consortium. Since 01-Mar-2021, REMAP-CAP is part of the ECRAID-Base consortium, which has received funding from the EU Horizon 2020 research and innovation program (grant agreement number 965313). The duration is 60 months (ends 28 February 2026). New sources of funding are sought as appropriate for extensions in number of sites, countries and patients; for new domains and for continuation in time, including continued pandemic preparedness.

7.2. Site costs

Per-patient, screen failure 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 for the European region is the University Medical Center Utrecht (the Netherlands).

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 and in this document.

7.5. Insurance

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

8. TRIAL BACKGROUND AND RATIONALE

In the European region, there are no anticipated issues related to the background and rationale provided in the Core Protocol. However, some domains or interventions may not be available in all countries or participating sites within the region.

9. TRIAL DESIGN

9.1. Trial setting

As described in the Core Protocol, the PANDA and the Domain Specific Appendices.

9.2. Interventions

The Eu RCC will offer the interventions that are available in Europe to participating sites depending on availability and feasibility of the intervention in the respective site and/or country.

The addition of (new) interventions within existing domains, the creation of new domains, and the inclusion of new populations is driven by priorities and contingencies developed by the ITSC and existing or new clinical need. For any new interventions, domains or populations, these will be submitted for regulatory and ethical approval as substantial modification or amendments before commencing.

If external evidence, platform conclusion(s) or safety signals occur in REMAP-CAP, that necessitate changes to interventions or domains (e.g. closing a domain), the Eu RCC is immediately informed by the ITSC. The Eu RCC will notify the Eu RMC, participating sites and regulatory bodies about these changes according to local requirements.

Amendment definition and handling of cessation of interventions are described in the Core Protocol. REMAP-CAP domains available in the European region are listed on the European trial website (https://www.remapcap.eu/domains/).

9.2.1. Registry

Site participation in the Registry is optional within the European region. 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 trial population specified for the Registry.

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

In the Eu Region, 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, details of which are described in the UK Registry Appendix.

9.3. Endpoints

Data will be collected as set out in the Core Protocol, and all other protocol parts.

9.4. Co-enrollment

Co-enrollment is possible and encouraged, as described in the Core Protocol. Co-enrollment requests specific for the Eu Region are assessed and approved by the Eu RMC. A tracker of co-enrolling studies or trials is kept by the Sponsor.

9.5. Criteria for termination of the trial

It is anticipated that the trial continues to include participants and test additional domains, interventions and/or populations until one of the following occurs:

- Hospitalization with respiratory tract infection 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 in any of the trial's patient populations
- Funding is not available.

Trial activities, including patient recruitment, may be paused in a single, in some or all countries of the European Region depending on available funding, and may resume when the funding situation changes. Any such (interim) recruitment stop will be submitted to the relevant authorities. Current estimated end date for funding in Europe is 28Feb2026 under the ECRAID-Base consortium funding. New sources of funding would change this estimate.

10.TRIAL CONDUCT

10.1. Recruitment and embedding

As described in the Core Protocol. Randomization of trial participants is a trial-specific task and may only be performed by a trained and delegated investigator or by trained and delegated clinical staff.

10.2. Pregnancy testing and breastfeeding

For some countries in the EU, pregnancy testing is mandatory for female participants of childbearing age. This is necessary because in such countries, pregnancy is a platform-level exclusion criterion, it does not exclude the patient from the registry. The country-specific annex to this RSA contains this information, where applicable.

In specific domains, known or suspected pregnancy is an exclusion criterion for that domain. If applicable, this is indicated in the respective Domain Specific Appendix.

Breastfeeding can also be a platform- or domain-level exclusion criterium. For countries to which this requirement applies the country-specific annex to this RSA will list the relevant information.

10.3. Inclusion of children

Core protocol versions after Core protocol version 3.0 do not contain age restrictions for participants. DSAs define the categories to constrain eligibility of the patient population, one of which are patient characteristics, including age. Age is stratified as three categories, adult, adolescent or pediatric, at the time of platform enrolment. Countries in the Eu Region do not recruit adolescent or pediatric patients, unless this is specified in the country-specific annex to this RSA.

10.4. Treatment allocation

Central randomization for the Eu Region will occur online by SPIRAL Web Solutions Ltd. Future randomization may be carried out by a database provider other than SPIRAL Web Solutions, this is not considered a substantial amendment as long as the randomization procedure remains unchanged and the global DCC accepts the new database provider as adhering to the REMAP-CAP standard they defined.

Medical decisions must be made during the randomization process (e.g. best interest of the patient confirmation). Therefore, randomization should be done by a trained and delegated investigator or by trained and delegated clinical staff. At sites where trained trial nurses randomize participants, a documented procedure should be in place to describe appropriate medical supervision.

An investigator confirmation of patient eligibility must be available in the source data of each subject.

10.5. Concomitant care and co-interventions

As described in the Core Protocol and DSAs.

10.6. Distribution of trial drugs

The processes and management of distribution of any drug provided by the trial are outlined in the IMP management plan and, as required, specified in the contracts with involved Pharmaceutical Companies and trial sites.

10.6.1. Type of trial drugs and labelling

To determine the optimal treatment for patients hospitalized with respiratory tract infections different, types of trial interventions are evaluated. REMAP-CAP includes fully licensed medications

being used within its marketing authorization (on-label), licensed medications used in an indication or dosage outside of its existing marketing authorization (off-label), and unlicensed medications without a marketing authorization. For countries that follow the Clinical Trials Regulation, labelling for on-label and off-label used trial drugs is not required. By not labelling IMP, subject safety and the reliability and robustness of data generated in REMAP-CAP is not compromised. This is because the IMP already have an established safety profile, the IMP does not go home with the patient but remains in a clinical setting, and is administered by trained healthcare professionals. If additional labelling would be applied, patient safety is likely not improved and deviating from current hospital processes significantly increases complexity. It results in unnecessary loss of products (randomization to IMP is not according to a fixed randomization ratio and labelled products cannot be used for regular patients anymore) and heavy demand on the time of healthcare professionals. Especially during a pandemic setting, time of healthcare professionals is scarce. The entailed additional workload and cost increase of these effects would impose severe constraints.

Unlicensed IMP requires a full label as mentioned in CTR Article 66.

Countries that do not fall under CTR will follow their national guidelines.

More details about labelling per country is specified in the country-specific annexes where applicable.

Drug accountability / traceability and appropriate documentation remains in place and allows for reliable and robust recording of IMP related data.

10.6.2. Trial drug administration after patient transfer

Randomized participants might be transferred from one clinical location to another before allocated fixed-course interventions have been completed. This transfer can occur between departments (e.g. ICU and ward) within the same hospital or from hospital to another.

If the participant is transferred to a clinical location that is not participating in REMAP-CAP, all further treatment is at the discretion of the treating clinician. Continuation or discontinuation of any allocated trial treatments is a clinical decision in the context of routine treatment, rather than an intervention administered under trial protocols. Trial-specific treatment is considered terminated at the time of transfer and the continued treatment at the other location falls outside of the direct responsibility of the investigator. Drug accountability and active monitoring of patient well-being for trial purposes ends. It is not a protocol deviation if treatment is not completed after transfer.

If the participant is transferred to a clinical location that is participating in REMAP-CAP, trial interventions should be continued as per protocol if the receiving location is also participating in the allocated intervention(s).

10.7. Unblinding of allocation status

Although the default is the provision of open-label treatments, the blinding of treatment status is not precluded within REMAP-CAP. Whether interventions are open-label or blinded will be specified in DSAs. Where interventions are conducted on an open-label basis, members of the Sponsor and RCC will remain blinded until a Platform Conclusion is reported by the DSMB. Only (medical) monitors are unblinded to the intervention.

Unblinding of any blinded treatment by site research staff or the treating clinician should occur only when it is deemed that knowledge of the actual treatment is essential for treatment of the participant. A procedure for emergency unblinding will be provided in the DSA 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. Any unblinding and reason for unblinding will be documented. Unblinding should not necessarily be a reason for trial drug discontinuation.

10.8. Data collection

Data collection will be as outlined in the Core Protocol. All data entered in the eCRF needs to be traceable in site source documents. In line with the Core protocol, the eCRF can be used as source document (direct entry) in some cases, where there are no existing source documents. For these data elements, the eCRF is the source. Details on source documents and their location (including direct entry) must be noted on the Source Document Location Log.

10.8.1. Data collection after day 90

The collection of data up to and including day 90 is mandatory, which includes all primary and secondary endpoint data. The collection of data for additional outcomes from time-points after day 90 is voluntary in the European region, but sites in countries with regulatory approval for day 180 data collection are encouraged to collect these data. Approved versions of EQ-5D (EQ-5D-5L or EQ-5D-Y), PedsQL-SF15 and WHODAS 2.0 questionnaires will be used to measure Quality of Life and Disability status at day 180.

10.9. Data management

Data collected for the REMAP-CAP trial in the Eu Region is entered into a secure, password protected, web-based eCRF designed by SPIRAL Web Solutions Ltd., in New Zealand, using a server located in Australia.

Each subject is allocated a unique trial number that is used as the common identifier in the database. Data management and transfer will comply with General Data Protection Regulation (GDPR) requirements of the country in which a site is located. The Project Managers of the Eu RCC will monitor data entry and data management.

Global data coordination tasks are performed by the Data Coordination Center (DCC) at ICNARC.

10.10. Trial group linkage / participation

The participation of established trial networks is recognized as a method to facilitate high quality trial conduct.

The Ecraid foundation will facilitate the identification of suitable sites to participate in the trial for countries throughout the European region, and will be the employer for the Eu Region project managers of the trial where feasible, to contribute to adequate and consistent training and familiarity with all trial procedures.

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.

In France, the Clinical Research in Intensive Care and Sepsis Trial Group For Global Evaluation and Research in Sepsis (CRICS-TRIGGERSEP) supports the identification and participation of suitable sites.

In Ireland, the Irish Critical Care Clinical Trials Network, University College Dublin Research Centre, St. Vincent's Hospital will support the identification and participation of suitable sites.

In Italy, Humanitas Research Hospital in Milan will facilitate the identification and participation of suitable sites.

In Spain, Hospital Universitario Reina Sofia in Cordoba 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 and collaborators in REMAP-CAP. When only few sites in a country are eligible to participate in the trial, identification and participation of suitable sites will be through Ecraid directly.

10.11. Site start up and initiation

The Eu RCC, in collaboration with local Sponsor representatives, arranges all required submission, approval and essential documents in line with local regulatory requirements. Only Eu RCC Project Managers have access to the REMAP-CAP Clinical Trial Information System (CTIS) account that facilitates submissions for European Union member states.

A remote or on-site initiation visit will be conducted before site activation. Details are listed in the European Appendix to the Global Monitoring Plan.

10.12. Quality assurance and quality control

The global approach is described in the Core Protocol Section 8.10.

10.12.1. Quality assurance

Quality assurance (QA) is the systematic and independent examination of trial-related activities and documents. These audits determine whether the evaluated activities were appropriately conducted, and that the data were generated, recorded, analyzed, and accurately reported according to protocol, standard operating procedures (SOPs), and good clinical practices (GCPs).

In the Eu Region, UMCU is accountable for quality assurance. The QA activities to be conducted are included in an QA audit plan.

10.12.2. Monitoring

Monitoring is a quality control function that routinely, and on an ongoing basis, assesses the various aspects of trial conduct at the participating sites.

The trial uses a monitoring plan with a risk-based approach. At least 1 routine monitoring visit will be conducted during the recruitment period; and a close out visit. Additional monitoring visits will be

planned as described in the European Appendix to the Global Monitoring Plan. Email and telephone communication will supplement site visits.

10.13. Safety

10.13.1. Data Safety and Monitoring Board

The purpose of the global DSMB is to act in an independent, advisory capacity to the ITSC, other Committees and Working Groups specified in the Core Protocol, and the Sponsors to provide guidance to help ensure:

- The protection of human subjects participating in the trial
- Adherence to the trial protocol and data collection procedures
- The proper conduct and interpretation of adaptive analyses, and
- The ongoing scientific validity, integrity, and clinical and scientific relevance of the trial.

The DSMB meets regularly. Their role and responsibilities are further outlined in the DSMB charter.

10.13.2. Safety reporting

Safety reporting will occur in line with ICH-GCP definitions and as outlined in the Core protocol (section 8.12), protocol appendices and Eu region safety management plan.

Safety monitoring in the Eu Region follows the global trial risk-based approach to safety monitoring, with monitoring activities and safety reporting being based on risks to participants and to the scientific validity of the trial.

Any SAE considered by the site investigator to be possibly, probably or definitely related to a trial intervention or trial participation, and that occur between randomization and hospital discharge, censored at day 90, should be reported (see 10.13.2.1).

In addition, domain-specific SAEs can be pre-specified in DSAs, and are referred to as Adverse Events of Special Interest (AESI), e.g. for interventions without established safety profiles. These SAEs must be reported for all participants enrolled in that domain, regardless of relatedness or suspected relationship to participation in the domain.

AE and SAEs which are not considered by the site investigator to be attributable to a trial intervention, or are not pre-specified in a DSA, should not be reported.

10.13.2.1. *Serious Adverse Events (SAE)*

All reportable SAEs 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 source data verification. However, any SAE that is considered by the site-investigator to be attributable to a trial intervention or trial participation (see 10.13.2) should be reported as detailed below.

For sites in the European Region, all SAEs must be reported immediately (within 24 hours of becoming aware) to the Sponsor (UMC Utrecht) by completing the SAE form in the eCRF. The Sponsor will automatically receive a notification of the report. If for any reason the eCRF is not available, an SAE reporting form (available in the Investigator Site File) needs to be sent via email (EU.remapcap@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 site investigator has to follow the SAE until resolution and monitor subject SAE recovery until hospital discharge. In the event an SAE occurred in the ICU and a subject is discharged from the ICU to the Ward; subject monitoring can be a daily medical chart check by a site investigator until hospital discharge.

The Sponsor records SAEs in an overview list (line listing) that will be submitted every year to the relevant authorities as part of the Development Safety Update Report (DSUR), see section 10.13.4.

eCRF SPIRAL Web Solutions Ltd: Web address https://remapcap.spinnakersoftware.com

10.13.2.2. *Suspected unexpected serious adverse reactions (SUSARs)*

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (Please refer to Core protocol section 8.12);

2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;

3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:

    a) Summary of Product Characteristics (SmPC) for an authorised medicinal product;

    b) Investigator's Brochure for an unauthorised medicinal product.

The Sponsor will report all SUSARs to the EMA Eudravigilance database.

Reporting will occur within 15 days after the sponsor has first knowledge of the adverse reaction. For fatal or life-threatening events the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

The expedited reporting of SUSARs through the EMA Eudravigilance database is not sufficient as notification to the competent authority or EC. The sponsor or local representative will report all SUSARs to the appropriate authorities in European Region, according to the requirements of the relevant Member States.

Sponsor will also share relevant information with the applicable investigational sites, the ITSC for further dissemination to the DSMB, and other RCCs.

10.13.3. Monitoring of renal and hepatic function

For all domains where off-label use of medication occurs, or experimental use of medication, follow up of renal or hepatic function or both may be necessary where these drugs are cleared via these organ systems. If specific rules exist for (the frequency of) monitoring renal or hepatic function or both in countries or sites of the Eu Region, outside of what is described in the DSA, these will be included under the relevant country-specific annex to this RSA.

Treating physicians are generally advised to check interactions of medications given to patients receiving off-label or experimental medication. Widely available interaction-checkers like https://reference.medscape.com/drug-interactionchecker can be used for this.

10.13.4. Annual Safety Report

The Sponsor prepares and submits a single annual safety report (ASR) on all investigational medicinal products (IMPs) used in the clinical trial in accordance with CTR Article 43(2). REMAP-CAP is a single clinical trial on IMPs with a marketing authorization in at least one of the EU/EEA member states and the SmPC is used as Reference Safety Information (RSI).

The format and content of the ASR is in accordance with the ICH E2F guideline on Development Safety Update Report (DSUR) and presents a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period, including the line listing of SAEs.

The ASR includes a list of subjects who died during the reporting period. Patients who are enrolled in this trial are at high risk of death (e.g. progression of underlying diseases). Vital status of patients is collected until day 180, but the cause of death is only collected if death is the outcome of a reportable SAE.

10.14. Serious Breaches

A serious breach is any deviation of the approved protocol versions or the clinical trial regulation or the conditions and principles of GCP that is likely to affect the safety, rights of trial participants and/or data reliability and robustness to a significant degree in this clinical trial.

The Sponsor is responsible for the assessment of potential serious breaches and the reporting of serious breaches to the relevant regulatory authorities within the timelines specified by the regulatory authorities. The Sponsor may delegate the reporting responsibility to third-parties. Any such delegation is documented in a contractual agreement.

10.15. Contraceptive advice

If any trial interventions require specific contraceptive advice in the trial population, the details will be provided in the relevant Domain Specific Appendix and the relevant Summary of Product Characteristics.

11. ETHICAL CONSIDERATIONS

11.1. Ethical and regulatory issues

The trial will be conducted in accordance with EU and national legislation relevant in each participating country in the European Region. Research ethics and regulatory authorities' approvals will be obtained prior to the start of the trial at each institution from the responsible local or central EC and relevant CA. It is the site principal investigator's responsibility to ensure that all conditions for approval of the trial 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 local EC as required by that committee and all relevant regulatory authorities.

11.2. Informed Consent

The Core protocol describes the broad approach for consenting that is used within REMAP-CAP.

Patients who will be eligible for this trial are hospitalized, and many eligible patients will be critically ill and receiving sedative medications for comfort, safety and to facilitate standard life saving ICU procedures. In patients who are not necessarily receiving sedative medications, the presence of critical illness, itself, leads commonly to an altered mental state that will affect the patient's mental capacity. The presence of these factors will mean that many patients who are eligible for the trial will not be able/capacitated to provide prospective consent for participation. Consent can only be obtained if the person providing consent is capacitated, or of sound mind, to do so. Careful consideration by site staff of patient capacity to provide informed consent is needed. Documentation of this evaluation in the patient medical chart is important, especially if a subject is not able to write/complete all fields of the informed consent form.

Also in an emergency setting such as an ICU admission or a pandemic, all efforts should be made to obtain prospective consent from the patient. If this is not possible (for example because a patient is incapacitated), consent will be required from a legal authorized representative (LAR) as permitted by local law. It is the responsibility of the investigator or delegated person to check the validity of the LAR in the relevant location, prior to a LAR signing Informed Consent Forms on behalf of a patient. After LAR consent, consent must still be obtained from the participant. When an enrolled participant regains capacity, their participation should be explained and opportunity must be provided to the participant to provide or refuse their consent for treatment and data collection.

When an investigator, or delegate, determines prospective consent is (temporarily) not possible and treatment start is urgent and enrolment is beneficial for the patient, delayed consent may be an option if approved in the relevant country, i.e. a patient may be enrolled without prior consent by patient or LAR. Consent must be obtained as soon as possible (preferably within 24 hrs) from the participant or, if not possible, from their representative, after initiation of the trial interventions.

Where possible, written consent should be obtained from the patient or LAR as applicable. When an investigator, or delegate, determines written consent is not possible, verbal consent may be an option, if approved in the relevant country. Verbal consent can be provided in person or via the phone and has to be documented. For valid verbal informed consent, presence of an impartial witness is required, who has to sign the informed consent form. Written consent must subsequently be obtained wherever possible.

For participants that remain incapacitated at hospital discharge, sites are expected to check at least at day 90 and day 180 if the subject has regained capacity to provide consent, if still alive.

The participant can withdraw participation in the trial at any time. However, data collected before this time will continue to be available and utilized in the analysis of the trial unless consent to use this data has been withdrawn before data is included in a data export for analysis and included in a manuscript, in which case patient data can be deleted from the eCRF.

If a participant dies before consent was obtained from either the patient or the legal representative, the data collected during the trial can be used if this is permitted by local regulations. All efforts should be made within reasonable limits to obtain consent for use of the patient data from the legal representative of the deceased.

Additional country-specific information related to the consenting process is included in the relevant country-specific annex to this RSA, if applicable.

12.MODIFICATIONS SPECIFIC TO A COUNTRY IN THE EUROPEAN REGION

Any country-specific issues that are different in a country in the European region and vary from what is specified elsewhere in this RSA or the Core Protocol or both, are listed in a country-specific annex to this RSA. Country-specific annexes can be created, modified and submitted for regulatory approval without amending the Eu RSA. Country-specific requirements related to DSAs for countries under CTR are listed in a *Domain Specific Deviations Annex: EUROPE* for the applicable domain.

REMAP-CAP_Protocol_EU RSA_V4.0_20241106

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