Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
REMAP-CAP

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

(●) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

( ) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

( ) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Is this a commercially sponsored Phase 1 or Phase 1/2a trial involving healthy volunteers?

( ) Yes (●) No

2b. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2c. Please answer the following question:

Is this trial subject to advice from the Expert Advisory Group on Clinical Trials and the Commission on Human Medicine prior to authorisation from MHRA? ○ Yes ◉ No

2d. Please answer the following question:

Is this a trial of a gene therapy medicinal product? ○ Yes ◉ No

2e. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ○ Yes ◉ No

b) Will you be taking new human tissue samples (or other human biological samples)? ○ Yes ◉ No

c) Will you be using existing human tissue samples (or other human biological samples)? ○ Yes ◉ No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

- ☑ England
- ☐ Scotland
- ☑ Wales
- ☑ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- ◉ England
- ○ Scotland
- ○ Wales
- ○ Northern Ireland
- ○ This study does not involve the NHS

4. Which applications do you require?

IMPORTANT: If your project is taking place in the NHS and is led from England select 'IRAS Form'. If your project is led from Northern Ireland, Scotland or Wales select 'NHS/HSC Research and Development Offices' and/or relevant Research Ethics Committee applications, as appropriate.

- ☑ IRAS Form
- ☑ Medicines and Healthcare products Regulatory Agency (MHRA) – Medicines
- ☐ Confidentiality Advisory Group (CAG)
- ☐ Her Majesty's Prison and Probation Service (HMPPS)

For NHS/HSC R&D Offices in Northern Ireland, Scotland and Wales the CI must create NHS/HSC Site Specific Information forms, for each site, in addition to the study wide forms, and transfer them to the PIs or local collaborators.

For participating NHS organisations in England different arrangements apply for the provision of site specific information. Refer to IRAS Help for more information.

5. Will any research sites in this study be NHS organisations?

◉ Yes ○ No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or a Diagnostic Evidence Co-operative in all study sites?

Please see information button for further details.

○ Yes ◉ No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

◉ Yes ○ No

The NIHR Clinical Research Network provides researchers with the practical support they need to make clinical studies happen in the NHS e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

◉ Yes ○ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

○ Yes ◉ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

Integrated Research Application System
Application Form for Clinical trial of an investigational medicinal product

IRAS Form (project information)

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
REMAP-CAP

Please complete these details after you have booked the REC application for review.

REC Name:
London-Surrey Borders

REC Reference Number:
18/LO/0660

Submission date:
23/03/2018

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

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

A3-2. National coordinating investigator (for a multicentre trial) **or principal investigator** (for a single centre trial)

- (●) National coordinating investigator
- ( ) Principal investigator

Given name	Anthony
Family name	Gordon
Qualification (MD...)	MD, FRCA, FFICM
ORCID ID	0000 0002 0419 547X
Institution name	Imperial College London
Institution department name	Surgery & Cancer
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Fax	02078316879

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
	Dr	Farah	Al-Beidh
Address	ICNARC		
	Napier House		
	24 High Holborn		
Post Code	WC1V 6AZ		
E-mail	farah.al-beidh@icnarc.org		
Telephone	02033110211		
Fax	02078316879		

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	
Sponsor's/protocol number:	
Protocol Version:	2.0
Protocol Date:	12/12/2017
Funder's reference number:	602525
Project website:	https://www.prepare-europe.eu/About-us/Workpackages/Workpackage-5

Registry reference number(s):
The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):	
ClinicalTrials.gov Identifier (NCT number):	NCT02735707
European Clinical Trials Database (EudraCT) number:	2015-002340-14

Additional reference number(s):

Ref.Number Description	Reference Number
Universal Trial number	U1111-1189-1653

A5-2. Is this application linked to a previous study or another current application?

○ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

REMAP-CAP is a randomised controlled trial for patients admitted to the intensive care unit (ICU) with severe Community-Acquired Pneumonia (CAP). All patients with severe CAP who are treated in an ICU will receive a combination of multiple different treatments. For many of these treatments, different options are available and used variably in current standard practice. An example of one of these treatments is antibiotics to treat infection. There are a number of different antibiotics that are widely used for patients with CAP, which are known safe and effective but it is not currently known which one is best. This trial studies a number of different treatment categories under one platform with an aim to determine the best package of treatment for patients.

In addition to testing different treatment categories, the trial will also be 'adaptive'. In REMAP-CAP data will be reviewed regularly and dependent upon the results, the trial will allocate more patients to the treatments that seem to be the most beneficial. Each research site will also be able to choose which interventions to make available at that site, from among those available within the trial.

REMAP-CAP will take place in 20 hospitals within the UK and aims to enrol 800 patients. The primary objective is to identify the most clinically effective treatments for adult ICU patients with severe CAP. The eligibility criteria for patients are applied at two levels. The first level is the patient eligibility to the overall trial. Once the patient meets these criteria, they can then be reviewed for eligibility to specific treatment categories. Patients will be followed up to 6 months after enrolment. This important and high quality trial will allow us to determine the best range of treatments for treating community acquired pneumonia on a global scale.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

Purpose and design:

REMAP-CAP is an international, multicentre, randomised adaptive platform clinical trial to evaluate, for patients with severe CAP who are admitted to an ICU, what are the relative effects of a range of interventions. The primary outcome is the all cause mortality (censored at 90 days from the date of enrolment). There is genuine uncertainty as to the most effective way to treat patients with CAP across a number of therapy areas ('domains').

In addition to being a platform, REMAP-CAP uses an adaptive design, relying on pre-specified criteria for adaptation, that:

1. Avoids indeterminate results; concludes an answer to a question when sufficient data has been accrued (rather than when a pre-specific sample size is reached)
2. Evaluates the effect of treatment options in pre-defined subgroups of patients (strata);
3. Utilises already accrued data to increase the likelihood that patients within the trial are randomised to treatments that are more likely to be beneficial
4. Evaluates multiple questions simultaneously
5. Is intended to be perpetual (or at least open-ended), substituting new questions in series as initial questions are answered
6. Can evaluate the interaction between interventions in different domains.

Bayesian statistical methods will be used to establish the superiority, inferiority, or equivalence of interventions within a domain. Interventions determined to be superior will be incorporated into standard care within the ongoing study. Interventions determined to be inferior will be discontinued. While a limited number of initial treatments and treatment domains have been specified at initiation (antibiotics; macrolide durations; and corticosteroids), it is planned that REMAP-CAP will continue to evaluate other treatments in the future. Furthermore, in the event of a future epidemic of a novel or re-emerging respiratory pathogen (which typically presents as severe CAP), this REMAP would be adapted to evaluate the most relevant treatment options. Each new treatment that is proposed to be evaluated will be submitted for prospective ethical review.

REMAP-CAP was designed by experts in critical care and adaptive trials, with each domain being led by international experts in the field. The UK Chief Investigator is Professor Anthony Gordon, who has vast experience of delivering clinical trials in a critical care setting.

Recruitment and consent:
This trial is designed to help patients with severe community acquired pneumonia.

Eligible patients will be:
1. adult patients admitted to an ICU for severe CAP within 48hours of hospital admission with:
a) symptom or signs or both that are consistent with lower respiratory tract infection
b) radiological evidence of a new onset consolidation
2. Requiring organ support with one or more of:
a) non-invasive or invasive ventilator support
b) receiving an infusion of vasopressors, inotropes or both
Each domain will have additional domain specific exclusion criteria, but patients who fulfil the overall REMAP-CAP eligibility criteria will be assessed for enrolment into all domains that are active at a site.

The main ethical issue arises from the fact that the treatment for severe CAP in an ICU is a medical emergency. Evidence from previous studies suggests that earlier treatment improves outcomes. Therefore, to ensure there is no delay to treatment, it is imperative that patients are randomised as soon as they become eligible on ICU. Any delay to treatment could also affect the scientific validity of the trial, making the results less generalisable to usual practice. Due to their critical illness, most eligible patients for the study will have a reduced level of consciousness and will be unable to give consent at that time. Hence treatment with the study drugs will need to be started in most cases without prospective consent in place. The specific nature of usual supportive care measures (which includes administration of antibiotics and other routinely administered interventions is critical care) are seldom discussed with their families and are presented to patients and their families as a package deal when time persists (in contrast to surgical procedures, which are more likely to be discussed in detail). No analysis of data will occur until retrospective consent is obtained.

As this is an emergency situation it is not possible to identify eligible patients in advance of them losing the capacity to provide consent. In addition, relatives are likely to be distressed by the patient´s illness and admission to critical care at the point the patient is eligible for the trial – and are unlikely to have capacity to make a decision in the short time-frame available. The minimisation of further distress has been a priority when deciding on the proposed consent process. The process has been based on qualitative work with family members in similar studies regarding the preferred timing and way of approach for consent. This process has also been used in a number of other similar critical care research studies.

After randomisation, the clinical team will identify the next-of-kin (family / relative / friend) recorded in the patients clinical notes and they will be approached by a member of the clinical research team and asked if they would be happy to provide personal legal consent. The trial will be explained to them, they will be given an information sheet about the trial and they will be asked to give an opinion on the patient´s participation in the trial. If a Personal legal representative cannot be contacted in an adequate timeframe a Professional legal representation will be approached. This will be a doctor in the hospital who is not part of the research team (i.e. not on the research delegation log). They will be informed about the trial and asked to give an opinion on the patient´s participation in the trial. Once patients regain capacity in the hospital, they will be approached by a member of the clinical research team, the trial explained to them, including their participation and that the study was discussed with their Personal or Professional legal representative while they lacked capacity. They will then be given the patient information sheet and asked to consent for the continuation of the study.

All patients in critical care units are monitored closely and clinical/research staff in this setting are very experienced in assessing mental capacity.

Risks, burdens and benefits:
As all the study drugs are routinely used in the management of severe CAP there is minimal extra risk from participation in this study. In addition, the response adaptive randomisation will make it more likely that patients will be randomised to the interventions that are more likely to be beneficial.
Patients in all groups will be closely monitored for adverse events that may be related to trial interventions, which will

be reported to the Sponsor, and where relevant, to oversight committees and the regulatory authority.

Confidentiality: Minimal patient identifiable data will be required to enable the trial team to link data to routine data sources.

Use of tissues in future research:None

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply*:

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☐ Questionnaire, interview or observation study
- ☑ Randomised controlled trial
- ☐ Other (please specify)

A8. Type of medicinal trial:

- ☐ Clinical trial of an unlicensed investigational medicinal product
- ☐ Clinical trial of a licensed medicinal product in new conditions of use (different from those in the SmPC, i.e. new target population, new dosage schemes, new administration route, etc.)
- ☑ Clinical trial of a licensed medicinal product used according to the SmPC
- ☐ Other (please specify)

A9. Phase of medicinal trial: *(Tick one category only)*

Human pharmacology (Phase I)	○ Yes	◉ No
Therapeutic exploratory trial (Phase II)	○ Yes	◉ No
Therapeutic confirmatory trial (Phase III)	○ Yes	◉ No
Therapeutic use trial (Phase IV)	◉ Yes	○ No

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

The primary objective of the REMAP is to identify the effect of a range of interventions to improve outcome of adult patients with severe community acquired pneumonia, who are admitted to ICU. This is defined by all cause mortality at 90 days from the date of enrolment into the trial.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

The secondary objectives are to determine the effect of the interventions on:
ICU Mortality
ICU length of stay
Hospital length of stay
Ventilator free day censored at 28 days
Organ failure free days censored at 28 days
Survival at 6 months
Health Related quality of life at 6 months including EQ5D5L and WHODAS.
Secondary Antibiotic Domain-specific endpoints(censored at day 90):
1. Multi-resistant organisms (MRO) colonization/infection: Isolation of multi-drug resistant (MDR) bacteria from clinical or screening specimens
2. C. difficile illness based on detection from feces using current standard of care diagnostics used at site
3. Serious adverse event (SAE) as defined in CORE protocol
Secondary Macrolide Domain-specific endpoints (censored at day 90):
1. Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital.
2. Serious Adverse Events (SAE) as defined in CORE protocol

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

Community acquired pneumonia (CAP) is an important health problem and a common cause of death from infection globally, with lower respiratory tract infections implicated in 3.1 million deaths in 2012 and ranked as 4th most common cause of death (mostly in low and middle income countries). Among patients who are admitted to hospital with CAP around 10-20% are admitted to ICU and of these 20-50% will have a fatal outcome.

Patients with severe pneumonia routinely receive multiple treatments at the same time while in ICU, for example antibiotics to treat infection. For each category of treatment, there are different options that are widely used. All of these are known or believed to be safe and effective but it is not currently known which options are best. This trial aims to determine the best treatment for each category of treatment.

In a conventional trial, patients are allocated a single treatment from a short list of alternatives. In this trial, many alternative treatments are being tested, and although treatments will be allocated randomly, as the trial progresses, patients will be randomised to the treatments that statistical models have shown are the most likely to be effective. Once a treatment is identified as being optimal it would then be routinely provided to all eligible patients in the trial.

A range of guidelines have been published that are relevant to the care of the critically ill, however there is a stark contrast between the substantial public health impact of severe CAP and the quality of evidence that guides therapy. As a consequence of the limited evidence-base, there are a number of inconsistencies and in some cases contradictions among the international guidelines.

Many factors contribute to a substantial need for better evidence to determine the optimal treatment for patient with severe CAP. Severe CAP is common and fatality is high and there is a lot of variation in current standard care. Because of all of these factors there is a strong rationale for the need for a better quality of evidence about the impact of the various treatments in existing practise, the impact of different combinations of treatment options and the evaluation of new interventions to improve patient and hospital outcomes.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

This is a randomised, embedded, multifactorial adaptive platform trial for community acquired pneumonia. This trial aims to identify the effect of a range of interventions on adult ICU patients with severe CAP in order to improve patient and hospital outcomes.

The eligibility criteria for the trial are applied at two levels. One level is that there are inclusion and exclusion criteria that determine eligibility for randomisation into the REMAP-CAP trial as a whole. The second level is that, once eligible for inclusion into the trial, there are additional exclusion criteria for eligibility into the specific domains within the trial. A patient is therefore only eligible for inclusion into a domain once all REMAP-CAP inclusion criteria are met, none of the

REMAP-CAP exclusion criteria are present and none of the domain specific exclusion criteria are present. However, patients who are not eligible for one or more domains can still be enrolled in other domains for which they are eligible.

This type of trial allows for broad enrolment but still retains the ability to examine the differences in treatment effects between the various subgroups of patients. It also allows us to evaluate a wide range of treatment options that are used within standard care by embedding it within routine healthcare delivery. The use of Response Adaptive Randomisation within this trial means that the allocation ratios change over time based on accruing outcomes data thereby maximising the number of patients randomised to the interventions which have been shown to be more likely to have better outcomes for patients.

Patients will be deemed eligible for randomisation to REMAP-CAP if they meet the following eligibility criteria
Inclusion criteria
1. Adult patients admitted to an ICU for severe CAP within 48 hours of hospital admission with:
a) symptoms or signs or both that are consistent with lower respiratory tract infection (for example, acute onset of dyspnea, cough, pleuritic chest pain); AND
b) radiological evidence of new onset consolidation (in patients with pre-existing radiological changes, evidence of new infiltrate)
2. Requiring organ support with one or more of:
a) Non-invasive or invasive ventilatory support;
b) Receiving infusion of vasopressor or inotropes or both

Exclusion criteria
1. Healthcare-associated pneumonia:
a) Prior to this illness, the patients has been an inpatient in any healthcare facility within the last 30 days
b) The patient is a resident of a nursing home or long term care facility
2. Death is deemed imminent or inevitable during this hospital admission AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment
3. Previous participation in this REMAP within the last 90 days

Patients will be deemed eligible for each treatment domain if they don´t meet any of the following exclusion criteria

Antibiotic Domain
1. Received more than 48 hours of intravenous antibiotic treatment for this index illness
2. More than 24 hours has elapsed since becoming eligible for this domain
3. Known hypersensitivity to all of the study drugs in the site randomization schedule
4. A specific antibiotic choice is indicated
5. The treating clinician believes that participation in the domain would not be in the best interests of the patient

Macrolide Duration Domain (if randomised to a beta-lactam plus macrolide intervention within the Antibiotic Domain)
1. The treating clinician believes that participation in the domain would not be in the best interests of the patient

Corticosteroid Domain
1. An indication to prescribe systemic corticosteroids for a reason other than community-acquired pneumonia (CAP) (or severe sepsis) such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven Pneumocystis jiroveci pneumonia
2. Have received an immunomodulatory dose of systemic corticosteroid therapy for more than 24 hours prior to the time of enrolment. An immunomodulatory dose is defined as >20mg of hydrocortisone, >5mg prednisone, >4mg methylprednisolone or >0.8mg dexamethasone per 24 hours.
3. The treating clinician believes that participation in the domain would not be in the best interests of the patient

Sample size
Due to the trial design, there is no formal sample size calculation, funding is currently in place to allow recruitment of up to 1200 patients (target 800) in the UK from 20 adult general critical care units, participating in the Case Mix Programme (national clinical audit of critical care).

Primary Outcome
The primary outcome will be all cause mortality up till day 90.
Secondary Outcomes
Secondary endpoints will include ICU, in-hospital, and post-hospital outcomes and domain-specific endpoints.

Currently available domains:

Antibiotic Domain
If the patient is deemed eligible they will be randomised to receive one of possible five antibiotics / combinations.
•Ceftriaxone + Macrolide (various options; azithromycin preferred)

•Moxifloxacin or Levofloxacin
•Piperacillin-tazobactam + Macrolide
•Ceftaroline + Macrolide
•Amoxicillin-clavulanate + Macrolide

Macrolide Duration Domain
Patients randomised to the beta-lactam plus macrolide intervention in the antibiotic domain would be randomised to receive either:
•Short course macrolide (3days) or extended course macrolide for 14 days or until hospital discharge, whichever occurs first

Corticosteroid Domain
A patient will be randomised to either:
•Intravenous hydrocortisone, 50 mg every six hours for up to seven days
•No hydrocortisone (i.e. no treatment)

It is intended that REMAP-CAP will be perpetual. The international steering committee will take responsibility for determining what new questions will be introduced to the trial whether it be new interventions to current domains or new domains.

Because of the emergency nature of the treatment there will be delayed consent. It is important for the selected antibiotics and associated therapies are initiated as quickly as possible. This is why these interventions will be assigned to patients when they are randomised as soon as they are admitted to the ICU.
Most eligible patients for this study will have a reduced level of consciousness due to their illness or due to sedative medication used as part of their treatment and may be unable to give consent at the time of eligibility. Therefore consent will be initially obtained from personal or professional legal representatives and the patient's consent obtained retrospectively once they have recovered and are able to give informed consent themselves.

Antibiotic intervention
Patients will be randomly assigned to receive one of the following study interventions. While it is expected that all sites will participate in the ceftriaxone intervention, each site has the option to opt-in to one or more of the remaining 4 interventions based on local practice and the availability at site:
• Ceftriaxone ≥1 gram IV 24h
• Moxifloxacin 400mg IV 24h or Levofloxacin 750mg IV 24h
• Piperacillin-tazobactam ≥4.5 grams IV 8h
• Ceftaroline 600 mg IV 12h
• Amoxicillin-clavulanate ≥1200mg IV 8h

All patients receiving ceftriaxone, piperacillin-tazobactam, ceftaroline, or amoxicillin-clavulanate will also receive a macrolide. Patients allocated to the moxifloxacin or levofloxacin intervention will not receive a macrolide or any beta-lactam or monobactam agent.

The choice of macrolide will depend on the availability and acceptability of the agents at each site in the following order of preference;
1. IV azithromycin, with switch to enteral azithromycin when appropriate
2. IV clarithromycin, with switch to enteral azithromycin when appropriate
3. Enteral azithromycin
4. Enteral clarithromycin or roxithromycin
5. IV or enteral erythromycin.
Sites in which only erythromycin is available are not able to participate in the Macrolide Duration Domain

The objective of the macrolide domain is to determine the effectiveness of short course versus extended course of macrolide treatment. The interventions to be compared are:
• Short course macrolide discontinued after 3 days unless there is confirmed or strongly suspected microbiological cause for prolonged administration
• Extended course macrolide for 14 days or hospital discharge, whichever occurs first

Patients will be followed up daily whilst on ICU and routine clinical data recorded.

Patients will be followed up to ascertain survival status at 90 days and at 6 months and their quality of life and disability will be assessed at 6 months .

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users,

and/or their carers, or members of the public?

- [ ] Design of the research
- [x] Management of the research
- [ ] Undertaking the research
- [x] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
This trial was developed outside the United Kingdom in a jurisdiction where patient involvement in trial design is not routine.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- [ ] Blood
- [ ] Cancer
- [ ] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [ ] Generic Health Relevance
- [x] Infection
- [ ] Inflammatory and Immune System
- [ ] Injuries and Accidents
- [ ] Mental Health
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal
- [ ] Neurological
- [ ] Oral and Gastrointestinal
- [ ] Paediatrics
- [ ] Renal and Urogenital
- [ ] Reproductive Health and Childbirth
- [x] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Male and female participants
Lower age limit: 18	Years
Upper age limit:	No upper age limit

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

1. Adult patient admitted to an ICU for severe CAP within 48 hours of hospital admission with:
a) symptoms or signs or both that are consistent with lower respiratory tract infection (for example, acute onset of dyspnea, cough, pleuritic chest pain); AND
b)radiological evidence of new onset consolidation (in-patients with pre-existing radiological changes, evidence of new infiltrate)
2. Requiring organ support with one or more of:
a) Non-invasive or invasive ventilatory support;
b) Receiving infusion of vasopressor or inotropes or both

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

Exclusion criteria
1. Healthcare-associated pneumonia:
a) Prior to this illness, has been an in-patient in any healthcare facility within the last 30 days
b) Resident of a nursing home or long term care facility
2. Death is deemed imminent or inevitable during this hospital admission AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment
3. Previous participation in this REMAP within the last 90 days

Patients will be deemed eligible for each treatment domain if they don´t meet any of the following domain specific exclusion criteria

Antibiotic Domain
1. Received more than 48 hours of intravenous antibiotic treatment for this index illness
2. More than 24 hours has elapsed since becoming eligible for this domain
3. Known hypersensitivity to all of the study drugs in the site randomization schedule
4. A specific antibiotic choice is indicated
5. The treating clinician believes that participation in the domain would not be in the best interests of the patient

Macrolide Duration Domain (if randomised to a beta-lactam plus macrolide intervention within the Antibiotic Domain)
1. The treating clinician believes that participation in the domain would not be in the best interests of the patient

Corticosteroid Domain
1. An indication to prescribe systemic corticosteroids for a reason other than community-acquired pneumonia (CAP) (or severe sepsis) such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven Pneumocystis jiroveci pneumonia
2. Have received an immunomodulatory dose of systemic corticosteroid therapy for more than 24 hours prior to the time of enrolment. An immunomodulatory dose is defined as >20mg of hydrocortisone, >5mg prednisone, >4mg methylprednisolone or >0.8mg dexamethasone per 24 hours.
3. The treating clinician believes that participation in the domain would not be in the best interests of the patient

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Informed consent to participate in the study	1		30 minutes	Doctor and/or REMAP-CAP research nurse
Health related quality of life questionnaire including EQ5D and WHODAS	1		15 minutes	6 month follow up telephone questionnaire's undertaken by REMAP-CAP CTU research team.

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Antibiotic intervention- administration of specific antibiotic the patient is allocated.	1	1	20mins-24hours	administered by member of the research team or clinical team that the hospital has deemed qualified to perform the procedure. Administration of the specific antibiotic intervention may be via bolus dose or infusion but this will be determined by the treating clinician on a daily basis and will be prescribed for as long as deemed necessary
Macrolide duration intervention	1	1	3-14 days	patients would either be randomised into the short course (3 days) or extended course (14 days) of macrolide. administered by member of the research team or clinical team that the hospital has deemed qualified to perform the procedure.
Corticosteroid intervention	1	1	4-28 doses	if randomised into the arm that will be given the intervention; IV hydrocortisone given 6 hourly for up to 7 days if needed.administered by member of the research team or clinical team that the hospital has deemed qualified to perform the procedure.

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

○ Yes ◉ No

A21. How long do you expect each participant to be in the study in total?

6 months - final follow up telephone call at 6 months

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

In estimating the risks associated with participation in a clinical trial, the appropriate comparator is the risk associated with usual care assuming non-participation. All patients in routine clinical practice will need to have

antibiotics and, if applicable, macrolides and corticosteroids starting. As such, all patients regardless if they were enrolled onto the study would be exposed to potential side-effects associated with any of the interventions. The treatments being investigated in this study are the same as the treatments used in daily practice. The only difference is that the study will randomly determine which treatment is received instead of the treating clinician. As there is clinical equipoise regarding which specific interventions to treat patients with (and therefore the trial) there is minimal increase in risk to the patient. All of the interventions would normally be available to the patient in standard care and all drugs will be administered on an open label basis.

The potential risks and burdens associated with participation in this trial are due to the strategy randomised for the individual patients rather than the antibiotics, macrolides or corticosteroids that the patient will take, as these would be drugs that would normally be prescribed to the patients in their normal standard of care.

Antibiotic intervention:
The antibiotics used as part of this study may have the following side effects: diarrhoea; abdominal pain; nausea; vomiting; heartburn; unpleasant taste; itching, or a rash. These side-effects are similar for most different antibiotics. As the main difference to standard practice is that which antibiotic to treat with will be decided by a protocol rather than by individual clinician preference there will be little additional risks to participants.

Macrolide duration intervention:
The dosing and administration for the macrolide intervention is not specified in the protocol but guidelines are provided. As macrolides can be administered either through IV or enterally (if the treating clinician has determined the patient has improved clinically) there should not be an extra burden on the patient regarding leaving cannulas in place till the end of the intervention if the patient has been randomised to the extended duration macrolide. The intervention is also only continued while the patient is in hospital so there will not be an additional burden when the patient is discharged home.

Corticosteroid intervention:
If the patient is eligible for the corticosteroid domain,they will be randomised either to receive hydrocortisone IV, 50mg every 6hrs for up to 7 days while they are in ICU or no hydrocortisone.
Hydrocortisone is an anti-inflammatory medication, which may help reduce inflammation in the lungs and elsewhere in the body. Hydrocortisone, though, may have the following side effects: fluid retention, nausea, increased risk of infection, high blood pressure, high blood sugar and a general feeling of discomfort (malaise). These risks are the same as those experienced by patients who are prescribed it during normal standard of care.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

○ Yes ◉ No

A24. What is the potential for benefit to research participants?

There may be no real apparent benefit to the research participants, but there is a substantial unmet need for better evidence to determine the optimal treatment for patients with severe CAP. This REMAP-CAP trial utilises a novel trial design where patients can be randomised to receive several different therapies simultaneously. Data accumulated is then analysed on a regular basis to inform adaptation of the randomisation system. This works by weighting the randomisation proportions towards the intervention(s) more likely to offer benefit, therefore, more patients should receive interventions more likely to be effective more quickly. Each site will also be able to choose which interventions to make available at that site, from among those available within the trial.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

Not applicable. The interventions will be provided to the patients for the period that they are in the intensive care unit/hospital.

A26. What are the potential risks for the researchers themselves? *(if any)*

none

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Potential participants will be identified by the medical and nursing team on the intensive care unit. They will assess if the patient meets the inclusion criteria and that none of the exclusion criteria are present from the patient's medical history and clinical notes.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

○ Yes ◉ No

Please give details below:
The clinical information of potential patients will be reviewed by the local NHS staff to assess eligibility. These staff are part of the direct care team.

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

○ Yes ◉ No

A29. How and by whom will potential participants first be approached?

Patients will be screened at adult, general, critical care units in NHS hospitals by members of the local clinical team (members of the patients direct healthcare team).

Patients admitted with community acquired pneumonia will most often need treatment started in a life-threatening emergency and will be unable to provide informed consent at this time due to reduced mental capacity. In life-threatening situations, any delay in commencing treatment could be detrimental to the patient (and also to the scientific validity of the trial – see 'Recruitment and consent' in section A6-2). This makes any attempt to obtain prior informed consent inappropriate.
Therefore, once a patient is identified as being eligible for the study (i.e. satisfies inclusion and exclusion criteria), they will be enrolled and randomised to receive the assigned treatment(s) immediately. This method of consent is known as 'deferred' or 'retrospective' consent and is recognised in European Law and the Mental Capacity Act (in England and Wales). The study team acknowledges that the use of the terms 'deferred' and 'retrospective' are misnomers as a patient will have already received an intervention as part of the study before any information about the study is shared with families and/or patients. Rather, the process should be understood, first, as the provision of information about what has already happened, and then as an invitation to consent for future procedures (where appropriate) and permission for the use of any data already collected.

Patients in critical care units are monitored closely and clinical/research staff working in this setting have extensive experience of assessing capacity in their patients. Once a patient has regained capacity, they will be approached by an authorised member of the site research team for informed deferred consent. This will be done as soon as practically possible (usually within 24 - 48 hours of the patient regaining capacity). A Participant Information Sheet (PIS) will be provided to the patient by an authorised staff member. The PIS will provide information about the purpose of the study, what participation means for the patient, confidentiality and data security, and the future availability of the trial results. A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is given for access to medical records (including routine data sources) for data collection. The Consent Form will cover consent for use of data already collected for the trial, as well as ongoing data collection and follow-up.

Patients will be given time to read the PIS and have an opportunity to ask any questions they may have about participation in REMAP-CAP. After verifying that the PIS and Consent Form are understood, the person seeking consent

will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes and the original kept in the Investigator Site File. If the patient is unable to physically sign the Consent Form (e.g. due to weakness, reduced dexterity), an independent witness can sign on their behalf.

Patients will only be approached by authorised staff members who have received training in REMAP-CAP processes and procedures and in Good Clinical Practice (GCP). The recruitment process will be done in such a way to mitigate any potential undue influence or coercion. No therapeutic promises will be made.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

REMAP-CAP will use a model of informed deferred consent, as used in a number of recent trials in the UK including Fluids in Shock (ISRCTN15244462), AIRWAYS-2 (ISRCTN08256118), PARAMEDIC 2 (SRCTN73485024), VANISH trial (ISRCTN 20769191), 65 trial (ISRCTN10580502) amongst others and has been shown to be acceptable to patients and their family members.

We will seek advice and consent about a patient's participation in the collection of research specific data from a personal legal representative or a professional legal representative while the patient lacks capacity.

We believe that this is the only appropriate model for consent in the face of the time pressure of needing to allocate treatment early in the process of critical care referral and stabilisation. Moreover, the process of obtaining consent while active intensive treatment is ongoing and the patient is in a critical state sometimes appears coercive and adds undue stress to an already stressful situation. Due to the severity of illness and its impact on mental capacity of the target population (critically ill patients), it will not be possible to involve REMAP-CAP trial participants early on in the consenting process. Instead, consent will be obtained prior to hospital discharge when their condition allows (e.g. they regain capacity). If the patient does not regain capacity prior to hospital discharge, the decision for use of information in the study will lie with the patients Personal Legal Representative. If the patient dies, or the Personal Legal representative does not wish to be involved in the consultation, a Professional Legal Representative will be appointed.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

◉ Yes ○ No

A31. How long will you allow potential participants to decide whether or not to take part?

Treating severe CAP is a medical emergency and delays in administering the appropriate drugs including study drugs may affect patient outcome. Therefore in most cases, the patient will be treated urgently as part of the trial before it is possible to identify and seek consent. The treating doctor will ensure that the patient meets all of the inclusion criteria and none of the exclusion criteria before enrolment.

At the first available opportunity, once the clinical condition has stabilised, consent will be sought. Many patients will be unable to consent themselves and so a personal legal representative will be sought. They will be given information about the study, including why it was necessary to initiate urgent treatment with the study drugs. They will given adequate time (min 24 hours) to make a fully informed decision, with the aim of obtaining consent prior to hospital discharge. If a patient or representative will come to a decision within less than 24 hrs after being provided with the information, this is accepted.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

- (●) Yes
- ( ) No
- ( ) Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

Co-enrolment of participants in other research studies, including interventional trials, is strongly encouraged. The principle is that co-enrolment should always occur and is only not permitted when there is a clear threat to the validity of either study or it would materially influence the risk to, or be too burdensome to the participants. Decisions regarding co-enrolment with other trials will be made on a trial-by-trial basis. Where REMAP-CAP is also being conducted the decision regarding co-enrolment will lie with the International Trial Steering Committee. Where a potentially co-enrolling trial is being conducted only in one region (for example the UK) in which the REMAP is being conducted the decision regarding co-enrolment will be the responsibility of the ITSC, but the ITSC may rely on input and advice of the UK Trial management committee. Decisions regarding co-enrolment with other trials will be distributed to participating sites as an operational document and will not require or involve amendment of the protocol.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

Hospital translators and interpreters will be used as needed.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

All participating hospitals in Wales will have access to a Welsh translator.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

Due to the short intervention period it is highly unlikely information will come available which would be relevant to the patients' continued participation. If new information becomes available during the trial, the patient information sheet will be updated.

We are aware of the relevant studies in progress from clinical trial databases and none are currently recruiting (or to our knowledge planned) that are addressing these specific question.

The international REMAP-CAP Clinical Trial website will also be updated if applicable

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?*(Tick as appropriate)*

- [x] Access to medical records by those outside the direct healthcare team
- [ ] Access to social care records by those outside the direct social care team
- [x] Electronic transfer by magnetic or optical media, email or computer networks
- [x] Sharing of personal data with other organisations

- [ ] Export of personal data outside the EEA
- [x] Use of personal addresses, postcodes, faxes, emails or telephone numbers
- [ ] Publication of direct quotations from respondents
- [ ] Publication of data that might allow identification of individuals
- [ ] Use of audio/visual recording devices
- [x] Storage of personal data on any of the following:
  - [x] Manual files (includes paper or film)
  - [x] NHS computers
  - [ ] Social Care Service computers
  - [ ] Home or other personal computers
  - [ ] University computers
  - [x] Private company computers
  - [ ] Laptop computers

Further details:
Medical records will only be accessed by the direct healthcare team and members of the local clinical research team who will all be registered medical and nursing staff employed by the NHS Trust. Those outside the direct healthcare team who will require access include auditors, representatives of the sponsor, and regulatory authorities and this would be stated in the patient information sheet and will only access records when consent is in place.

Data collection will be in three clear sections.
1) Identifiable data, including name and telephone number, will need to be sent to and stored at ICNARC CTU securely to enable patients to be contacted to complete follow-up questionnaires over the telephone at six months post-randomisation. This will only be collected for patients deemed alive by the hospital prior to the six month telephone call, in order not to cause additional distress by contacting patients who have passed away in this high-risk cohort. NHS number will also be collected

2) Clinical data relevant for the trial will be sent to and stored at the Julius Center for Health Science and Primary Care University Medical Center Utrecht (Sponsor) securely to enable study analysis, as described in the protocol.

3) Routinely collected data relevant for assessing the trial outcomes (e.g. readmission to critical care and hospital) will be used where possible. Patients will be linked to the Case Mix Programme, the national clinical audit for critical care, through admission number and NHS number obtained through data collection method 1). In addition, access to data held by NHS Digital will be requested, which will include mortality and readmission data through hospital estimate Only pseudonymised data would be shared with other organisations.

A37. Please describe the physical security arrangements for storage of personal data during the study?

The only access to patient identifiable data, needed for telephone follow-up and linking to the Case Mix Progamme, national clinical audit will be by ICNARC.

At ICNARC, all personal data collected will be stored on a secure web-based data entry system housed at Red Technology. This is a specialist eCommerce hosting provider and all data centre buildings include proximity access control and digital CCTV to control physical access to equipment. These data are transferred to servers at ICNARC via a site-to-site IPsec VPN between ICNARC and Red Technology (VPN access is unidirectional from ICNARC to Red Technology).

Data are processed and stored on a server located in a secure, locked, air-conditioned room at ICNARC. Access to this room is restricted to authorised staff only. Access to both the web-based data entry system (by NHS and ICNARC staff) and ICNARC servers (by ICNARC staff) is restricted to authorised personnel only (permissions are attached to user names which requires a secure password).

Data are not encrypted on the servers in the ICNARC office due to the logical and physical office security in place, however, data are encrypted at the point they are stored on backup tapes. Physical office security includes a Grade 3 Red Care intruder detection system that has been supplied, installed and is maintained by ADT Fire and Security Plc. All visitors are notified to building security by ICNARC staff in advance.

Data destruction will be carried out in compliance with the Clinical Trials Regulations and we work with suitably qualified contractors for both electronic and paper record destruction. For example, data stored at ICNARC are removed via a sector by sector wipe of the hard drive prior to physical destruction of the hard drive. Darik's Boot and Nuke is used to perform multiple passes of Mersenne Twister using DoD Short. This automatically and completely deletes the contents of any hard disk that it detects, making it an appropriate utility for bulk or emergency data destruction.

Clinical data collected by the Sponsor in Utrecht will be via Research Online 2 (RO2), which is an Electronic Data Capture (EDC) system developed by the Julius Center Utrecht. RO2 meets all requirements according to ICH-GCP standards for electronic data entry with respect to safeguarding data integrity and data security regulations. Users will have role based access to the system after logging in using a general account for randomisation. Since it is an general account, the physician performing the randomisation will need to enter his/her name in the eCRF for audit trail purposes. Data collection after randomisation will be performed by a dedicated nurse/physician by using their personal username and password. The system has an complete electronic audit trail that will log all data entry steps with timestamps and user information . The role based access to the system will avoid unauthorised data access and prevents that users perform actions that they are not allowed to do.

RO2 data traffic over the internet is encrypted using secured data communication protocols. The Data Management department of the Julius Center works according to a Quality Management System using Standard Operating Procedures for all crucial RO2 related
processes.

RO2 is developed in Mendix. This state of the art development platform enables very flexible and fast development of new functionality to the system. Therefore new functionalities and new modules are likely to be released with short intervals. A full DTAP (Development, Test, Acceptance, Production) approach is used in order to develop, test and deploy new releases of the RO2 software in a controlled way to production.

RO2 databases and web servers in the Netherlands are hosted in data centers that meets the highest available standards for security. The RO2 servers are actively monitored to prevent failure (including memory, storage, CPU usage and network connections). Backups of all data are made on a daily basis for the test, acceptance and production environment. Backups are stored in secured locations that are geographically dispersed. Backups will be stored one year.

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

To minimise the use of personal identifiers, participants will be allocated a unique trial number and this will be used by the REMAP-CAP trial team and in communications with the local research teams at participating sites.

The only access to patient identifiable data, needed for telephone follow-up and linking to the Case Mix Progamme, national clinical audit will be by ICNARC. ICNARC is registered under the Data Protection Act (Registration number: Z6289325). Confidentiality forms the basics of ICNARC's Information Security Policy. All staff employed by ICNARC sign a contract, which incorporates a confidentiality clause and the consequences of breaching confidentiality are covered in our Disciplinary Procedure.

External researchers, temporary staff and contractors are all required to sign a formal confidentiality agreement with ICNARC. Data security and confidentiality are a fixed agenda item at monthly staff meetings for all staff at ICNARC.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Participant data will be held on the two pre-specified secure web-based data entry systems. Access to the secure web-based data entry systems in the hospitals will be restricted (by username and password) to trained staff in the hospital, authorised by the site Principal Investigator(s).

Patients' identification data, including full name, NHS number and telephone number will be required at ICNARC. It is necessary to collect this identifiable information as ICNARC will be contacting the patients to complete the follow-up questionnaires by telephone. ICNARC will act to preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified to a third party. Data will be stored in a secure manner and ICNARC are registered in accordance with the Data Protection Act 1998. Access to participant's personal data will be limited to authorised staff members at the ICNARC CTU. These details will be linked to additional data on critical care stay, survival and readmissions to critical care and hospital held by ICANRC Case Mix Programme and NHS Digital. Patients will provide informed consent covering this.

The site Principal Investigators will take responsibility for ensuring that study data stored on paper at the site is restricted to authorised personnel only (as per the delegation log).

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

The study sponsor and trial coordinating centre is UMC Utrecht based in the Netherlands. They will be responsible for data management, oversight and monitoring of data collection and statistical analysis.

The principal means of data collection and data processing will be via a password protected website. All computerised forms will be electronically signed by the authorised staff and all changes made following the electronic signing will have an electronic audit trail with a signature and a date. Only pseudonymised data will be uploaded to the database.

The ICNARC CTU will collect data only for the purposes of linkage to routine data sources and for conducting patient follow-up. No analysis will be carried out

Folders will be provided for the local research coordinator to file any paper documents used for any form of data collection. A comprehensive guide to the data collection with the definitions and rationale will be provided together with a paper version of the data collection forms. Paper documents will be stored in secure locked cabinets, in locked rooms with access limited to authorised persons.
A comprehensive guide to accessing the data entry forms on the website and entering all follow up data is also provided in the guidelines for case report form completion. All of the documents will also be available in PDF format for printing from the study website as required. These aim to assist the local research coordinator to ensure high quality data collection and data entry.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title	Forename/Initials	Surname
	Prof	Marc	Bonten
Post	REMAP-CAP EU Executive director		
Qualifications	MD,PhD		
Work Address	University Medical Center Utrecht		
	Heidelberglaan 100 (Room number: G.04.5.25), 3584 CX Utrecht, The Netherlands		
	Internal mail no G.04.6.14, P.O. Box 85500, 3508 GA UTRECHT		
Post Code	3584 CX Utrecht, Netherlands		
Work Email	M.J.M.Bonten@umcutrecht.nl		
Work Telephone	+31 88 75 573 94		
Fax	+31 30 25 237 41		

A43. How long will personal data be stored or accessed after the study has ended?

- ○ Less than 3 months
- ○ 3 – 6 months
- ○ 6 – 12 months
- ○ 12 months – 3 years
- ◉ Over 3 years

If longer than 12 months, please justify:
University Medical Centre Utrecht Policy is to store data for 15 years

A44. For how long will you store research data generated by the study?

Years: 15
Months: 0

A45. Please give details of the long term arrangements for storage of research data after the study has ended.*Say where data will be stored, who will have access and the arrangements to ensure security.*

All archived material will be stored in archive boxes that are clearly labelled with the trial name and reference number, sponsor, investigator and date to be archived.
The archive boxes will be stored in a secure environmentally controlled location. The archived material will be stored in a legible condition and all documents on thermal fax paper will be photocopied onto standard paper.Once the study has ended, and all research sites have been closed out. All research data will be stored securely in archiving facilities. The main TMF will be archived with the sponsor at UMC Utrecht. Details of the archiving location will be recorded by the CI and the sponsor.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

○ Yes ◉ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

◉ Yes ○ No

Please give details, or justify if not registering the research.
The Trial has a universal Trial number, and is already registered at Clinical Trials.gov and with EudraCT

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study?*Tick as appropriate:*

- ☑ Peer reviewed scientific journals
- ☑ Internal report
- ☑ Conference presentation
- ☑ Publication on website
- ☐ Other publication
- ☑ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ No plans to report or disseminate the results
- ☐ Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

It will not be possible to identify any person who has taken part in REMAP-CAP in any reports or articles. All analysis will be performed on anonymised data.

A53. Will you inform participants of the results?

◉ Yes ○ No

Please give details of how you will inform participants or justify if not doing so.
The results of the trial will be made publicly available via institutional websites and also through charity / patient groups(e.g.ICU Steps, Intensive Care Foundation).

Participants will not routinely be given results as this is a trial that is unlikely to offer individual patients or their doctors any information that will be of relevance to their ongoing or future clinical care.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed?*Tick as appropriate:*

- ☑ Independent external review
- ☐ Review within a company
- ☐ Review within a multi−centre research group
- ☑ Review within the Chief Investigator's institution or host organisation
- ☑ Review within the research team
- ☐ Review by educational supervisor
- ☐ Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

This research project has undergone internal review with the multiple co-investigators across the various regions. In addition, the protocol has undergone external peer review as part of the EU funding process.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed?*Tick as appropriate:*

- [x] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician
- [ ] Review by a statistician within the Chief Investigator's institution
- [x] Review by a statistician within the research team or multi−centre group
- [ ] Review by educational supervisor
- [ ] Other review by individual with relevant statistical expertise
- [ ] No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Dr	Scott	Berry
Department			
Institution	Berry Consultants LLC		
Work Address	3345 Bee Caves Rd		
	Suite 201		
	Austin Texas		
Post Code	78746		
Telephone			
Fax			
Mobile			
E-mail	scott@berryconsultants.com		

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

The primary outcome for all domains will be the occurrence of death at 90 days post enrolment.

A58. What are the secondary outcome measures?*(if any)*

The secondary objectives are to determine, for adult patients with severe CAP who are admitted to an ICU, the effect of interventions on ICU mortality, ICU length of stay (LOS), hospital LOS, ventilator free days (VFDs) censored at 28 days, organ failure free days (OFFDs) censored at 28 days, survival at 6 months, health related quality of life (HRQoL) assessed after 6 months using the EQ5D and disability assessed after 6 months using the World Health Organization Disability Assessment Schedule(WHODAS).

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size:	800
Total international sample size (including UK):	6800
Total in European Economic Area:	4000

Further details:

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

The design of the trial, at initiation, and in conjunction with the planning of the introduction of new interventions within a domain, or of new domains, will be informed by the conduct of extensive simulations using standard Monte Carlo methods. Simulations will be updated whenever a new intervention is added within a domain or whenever a new domain is added to the REMAP. However simulations will not be updated when an intervention is removed from a domain because of the declaration of a Platform Conclusion that the intervention is inferior. These simulations will evaluate the impact of a range of plausible scenarios on the statistical properties of the trial. Existing simulations indicate that when a single intervention in a domain with two interventions, is beneficial, with a constant benefit for all participants, the power to be determined superior to the complement intervention as a function of its odds-ratio benefit is greater than 90% when there is at least a 25% odds ratio decrease in he probability of mortality for the funded sample size of 6800 participants. The timings of these conclusions of superiority have a median time of less than 2000 participants. The probability that an intervention will be deemed superior to a complementary intervention when in truth the two are equal (a type 1 error) is typically less than 2.5%.

A61. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, please give details of the intended method of randomisation:
Randomisation will be conducted through a password-protected, secure website using a central, computer-based randomisation program. Randomisation will be at the patient level and occur after data necessary to implement the inclusion and exclusion criteria have been entered into the secure randomisation website.

Response Adapted Randomisation (RAR) will occur centrally as part of the computerised randomisation process. Sites will receive the allocation status and will not be informed of the randomization proportions. Each region will maintain its own computer-based randomisation program that is accessed by sites in that region but the RAR proportions will be determined centrally and provided monthly to the administrator of each region's randomization program who will update the RAR proportions.

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

Inferences in this trial are based on a Bayesian statistical model, which estimates the probability of all cause mortality at 90 days (primary endpoint),of the combinations of interventions (posterior probability distribution), taking into account the evidence accumulated during the trial (based on outcome data of the participants)and an assumed prior knowledge (prior distribution).This differs from conventional (frequentist) trials where inferences are based on a likelihood of observed outcomes against a null hypothesis.

The statistical model takes into account the variation in outcomes by country, age, pre-specified strata, temporal changes, treatment effects, interactions between treatment and strata ad interactions between interventions across different domains.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Prof	Kathy	Rowan
Post	UK Methodology Lead		
Qualifications	PhD		
Employer	ICNARC		
Work Address	Napier House		
	24 High Holborn		
	london		
Post Code	WC1V 6AZ		
Telephone	02078316879		
Fax			
Mobile			
Work Email	kathy.rowan@icnarc.org		

	Title	Forename/Initials	Surname
	Mr	Paul	Mouncey
Post	UK Project Manager		
Qualifications			
Employer	ICNARC		
Work Address	Napier House		
	24 High Holborn		
	London		
Post Code	WC1V 6AZ		
Telephone	02072699277		
Fax			
Mobile			
Work Email	Paul.Mouncey@icnarc.org		

	Title	Forename/Initials	Surname
	Dr	Farah	Al-Beidh
Post	UK Trial Manager		
Qualifications	PhD		
Employer	Imperial College London		
Work Address	5th floor lab block, Charing Cross Hospital		
	Fulham Palace Road		
	london		
Post Code	W6 8RF		
Telephone	07714051401		
Fax			
Mobile			
Work Email	ukremap-cap@icnarc.org		

	Title	Forename/Initials	Surname
	Prof	Marc	Bonten
Post	International chief investigator and European Executive Director and Chair European RMC		
Qualifications	MD PhD		
Employer	University Medical Centre Utrecht		
Work Address	eidelberglaan 100 (Room number: G.04.5.25), 3584 CX Utrecht, The Netherlands		
	Internal mail no G.04.6.14, P.O. Box 85500, 3508 GA UTRECHT		

Post Code	3584 CX Utrecht, Netherlands
Telephone	+31 88 75 573 94
Fax	+31 30 25 237 41
Mobile	
Work Email	M.J.M.Bonten@umcutrecht.nl

Title	Forename/Initials	Surname
Prof	Derek	Angus

Post	International Trial steering committee member
Qualifications	MD, MPH, FRCP
Employer	University of Pittsburgh School of Medicine,
Work Address	Department of Critical Care Medicine Pittsburgh, PA United States of America
Post Code	
Telephone	
Fax	
Mobile	
Work Email	angusdc@upmc.edu

Title	Forename/Initials	Surname
Ms	Wilma	van Bentum-Puijk

Post	European Project Manager
Qualifications	
Employer	University Medical Center Utrecht
Work Address	Heidelberglaan 100 (Room number: Str. 3.116), 3584 CX Utrecht, The Netherlands Internal mail no Str.6.131, P.O. Box 85500, 3508 GA UTRECHT
Post Code	3584 CX Utrecht, Netherlands
Telephone	+31887555196
Fax	+31887568099
Mobile	
Work Email	w.w.puijk-2@umcutrecht.nl

Title	Forename/Initials	Surname
Dr	Scott	Berry

Post	Lead Trial statistician
Qualifications	
Employer	Berry Consultants, LLC
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Post Code	78746
Telephone	
Fax	
Mobile	
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	Title	Forename/Initials	Surname
	Dr	Lennie	Derde
Post	International Trial steering committee member		
Qualifications			
Employer	University Medical Center Utrecht		
Work Address	Heidelberglaan 100, 3584 CX Utrecht, The Netherlands		
Post Code	3584 CX Utrecht, Netherlands		
Telephone			
Fax			
Mobile			
Work Email	L.P.G.Derde@umcutrecht.nl		

	Title	Forename/Initials	Surname
	Dr	Colin	McArthur
Post	ANZ Deputy Director		
Qualifications	MBChB, FANZCA, FCICM		
Employer	Auckland City Hospital		
Work Address	Auckland		
	New Zealand		
Post Code			
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Fax			
Mobile			
Work Email	colinm@adhb.govt.nz		

	Title	Forename/Initials	Surname
	Prof	Alistair	Nichol
Post	International Trial steering committee member		
Qualifications	MD, PhD		
Employer	University College Dublin		
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	Dublin		
	Ireland		
Post Code			
Telephone			
Fax			
Mobile			
Work Email	alistair.nichol@ucd.ie		

	Title	Forename/Initials	Surname
	Associate Prof	Gernot	Rohde
Post	International Trial steering committee member		
Qualifications	MD, PhD		
Employer	Maastricht University Medical Center		
Work Address	Department of Respiratory Medicine		
	Maastricht Netherlands		
	Netherlands		

Post Code	
Telephone	
Fax	
Mobile	
Work Email	Gernot.Rohde@kgu.de

Title	Forename/Initials	Surname
Prof	Steve	Webb

Post	Australia Chief Investigator, ANZ Executive Director
Qualifications	MBBS, MPH, PhD, FRACP, FCICM, FAHMS
Employer	Royal Perth Hospital
Work Address	Intensive Care Unit Royal Perth Hospital Perth, Western Australia
Post Code	
Telephone	
Fax	
Mobile	
Work Email	steve@stevewebb.com.au

Title	Forename/Initials	Surname
Miss	Genevieve	O'Neill

Post	Australian Project Manager
Qualifications	
Employer	MONASH university
Work Address	Australian and New Zealand Intensive Care Research Centre Department of Epidemiology and Preventative medicine Monash University, level 3, 553 St Kilda Road, Melbourne
Post Code	3004
Telephone	399030247
Fax	
Mobile	
Work Email	genevieve.oneill@monash.edu

Title	Forename/Initials	Surname
Prof	Anthony	Gordon

Post	UK Chief Investigator
Qualifications	MD, FRCA, FFICM
Employer	Imperial College London
Work Address	11th floor Intensive Care Unit Charing Cross Hospital Fulham Palace Road
Post Code	w6 8rf
Telephone	02033130657
Fax	
Mobile	
Work Email	anthony.gordon@imperial.ac.uk

	Title	Forename/Initials	Surname
	Prof	David	Harrison
Post	UK Lead Trial statistician		
Qualifications			
Employer	ICNARC		
Work Address	Napier House 24 High Holborn		
Post Code	WC1V 6AZ		
Telephone			
Fax			
Mobile			
Work Email	david.harrison@icnarc.org		

A64. Details of research sponsor(s)

A64-1. Sponsor

SP1

Status:
- ○ NHS or HSC care organisation
- ◉ Academic
- ○ Pharmaceutical industry
- ○ Medical device industry
- ○ Local Authority
- ○ Other social care provider (including voluntary sector or private organisation)
- ○ Other

Commercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	University Medical Centre Utrecht
Given name	Wilma
Family name	van Bentum-Puijk
Address	Heidelberglaan 100 (Room number: Str. 3.116), 3584 CX Utrecht, The Netherlands
Town/city	Utrecht
Post code	3584 CX
Country	NETHERLANDS
Telephone	0887555196
Fax	0887568099
E-mail	W.W.Puijk-2@umcutrecht.nl

Legal representative in the European Economic Area for the purpose of this trial
A legal representative must be appointed for a clinical trial of an investigational medicinal product if the sponsor is not established within the European Economic Area (EEA) (see article 19 of Directive 2001/20/EC). If this applies, please enclose evidence that the legal representative is established within the EEA and has accepted the role of legal representative.

Legal representative

Contact person

Name of organisation	University Medical Centre Utrecht
Given name	Albert
Family name	Vermaas
Address	Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
Town/city	Utrecht
Post code	3584 CX
Country	NETHERLANDS
Telephone	
Fax	
E-mail	A.M.Vermaas@umcutrecht.nl

A65. Has external funding for the research been secured?

- [x] Funding secured from one or more funders
- [ ] External funding application to one or more funders in progress
- [ ] No application for external funding will be made

What type of research project is this?

- ○ Standalone project
- ◉ Project that is part of a programme grant
- ○ Project that is part of a Centre grant
- ○ Project that is part of a fellowship/ personal award/ research training award
- ○ Other

Other – please state:

Please give details of funding applications.

Organisation	University Medical Center Utrecht
Address	Heidelberglaan 100
Post Code	3584 CX Utrecht
Telephone	
Fax	
Mobile	
Email	

Funding Application Status: ◉ Secured ○ In progress

Amount: 6,238,017

Duration

Years: 4

Months:

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

FP7-HEALTH-2013-INNOVATION-1

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

(●) Yes ( ) No

Name: Imperial College London

Type of organisation:

( ) NHS (●) Academic ( ) Commercial ( ) Other

Please give further details of sub-contractor and main areas of delegated responsibility: UK Trial Management (site selection and delivery)

Name: Intensive Care National Audit & Research Centre

Type of organisation:

( ) NHS ( ) Academic ( ) Commercial (●) Other

Please give further details of sub-contractor and main areas of delegated responsibility: UK Trial Management (site selection, delivery and patient follow-up)

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

( ) Yes (●) No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

	Title	Forename/Initials	Surname
	Mrs	Gisela / M	Pereira Barreto
Organisation	Imperial College London Healthcare Trust		
Address	Room 221, 2nd floor medical school building, st Marys campus		
	london		
	Praed street		
Post Code	W2 1NY		
Work Email	g.pereira-barreto@imperial.ac.uk		
Telephone	02075941862		
Fax			

Mobile

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A68-2. Select Local Clinical Research Network for NHS Organisation identified in A68-1:

North West London

For more information, please refer to the question specific guidance.

A69-1. How long do you expect the study to last in the UK?

Planned start date: 01/06/2018
Planned end date: 31/07/2021
Total duration:
Years: 3 Months: 1 Days: 31

A69-2. How long do you expect the study to last in all countries?

Planned start date: 01/06/2018
Planned end date: 31/07/2021
Total duration:
Years: 2 Months: 5 Days: 22

A70. Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial (1)

The study will end when the required numbers of patients have been recruited, the final follow up visit data for the last patient has collected and the database has been locked.

The design features of this trial create a 'perpetual' trial whose main objective is to continuously update best patient treatment for the life time of the REMAP, but current EU funding is provided until 2021.

A71-1. Is this study?

- ○ Single centre
- ◉ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- ☑ England
- ☐ Scotland
- ☑ Wales
- ☑ Northern Ireland
- ☐ Other countries in European Economic Area

Total UK sites in study 20

Does this trial involve countries outside the EU?

◉ Yes ○ No

☐ USA

☐ Other international (please specify)

Australia and New Zealand

A72. Which organisations in the UK will host the research? *Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

☑ NHS organisations in England	17
☑ NHS organisations in Wales	2
☐ NHS organisations in Scotland	
☑ HSC organisations in Northern Ireland	1
☐ GP practices in England	
☐ GP practices in Wales	
☐ GP practices in Scotland	
☐ GP practices in Northern Ireland	
☐ Joint health and social care agencies (eg community mental health teams)	
☐ Local authorities	
☐ Phase 1 trial units	
☐ Prison establishments	
☐ Probation areas	
☐ Independent (private or voluntary sector) organisations	
☐ Educational establishments	
☐ Independent research units	
☐ Other (give details)	
Total UK sites in study:	20

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

○ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

The trial will be conducted in accordance with the current approved protocol, Good Clinical Practice (GCP), relevant regulations and SOPs.
Data entry and data management will be coordinated by the UK Trial managers including:
• Start-up meeting for all research coordinators and investigators will be held prior to study commencement to ensure consistency in procedures;
• A detailed dictionary will define the data to be collected on the CRF;
• The data management centre will perform timely validation of data, queries and corrections if errors are found during quality control checks;
• Data monitoring will occur as described below.

A site initiation teleconference or visit will be conducted before site activation. Sites will be monitored on-site by a monitor from the ICNARC CTU. Routine monitoring visits will be conducted the frequency of which will be determined by each sites rate of recruitment. Email and telephone communication will supplement site visits.
A monitoring report will be prepared following each visit and reviewed by the UK Trial manager additionally the sponsor

will also receive a copy of the report. 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 for these monitoring visits during the course of the study and at the completion of the study as needed.

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

An independent Data Safety and Monitoring Board (DSMB) will be set up to review data for safety and efficacy at regular intervals as specified in the DSMB charter.
A single DSMB will take responsibility for the trial in all regions in which this trial is conducted. The DSMB compiled for this study will consist of 5-7 members; the chair has been selected to have expertise in clinical trial methodology, and to have experience with adaptive clinical trial design. Additional medical, statistical, and other experts will be selected to ensure all necessary expertise to oversee a trial of this complexity and scope. The DSMB will conduct its activities in accordance with a separate Charter; the Charter must be approved by the DSMB, and International Trial Steering Committee prior to the initiation of the trial. The DSMB will be unblinded to ensure the highest quality oversight of the trial, in accordance with current recommendations of regulatory authorities.

The DSMB will review the received frequent updates of the trial's adaptive analyses from the Statistical Analysis Committee. The role of the DSMB will be to ensure that the pre-specified trial algorithm is being implemented as designed, that the design remains appropriate from a scientific and ethical point of view, to confirm when a Statistical Trigger has been reached, and to either reach or recommend that a Platform Conclusion has been reached.

Trial enrolment and conduct will be continuous.

The DSMB will not make design decisions. If the DSMB believes the trial's algorithms are no longer acceptable from an ethical, safety, or scientific point of view it will make recommendations to the ITSC which has ultimate decision-making authority regarding the trial design.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

This trial is designed as a platform, allowing for continued research in patients with CAP admitted to an ICU. The platform allows for the study to be perpetual, with multiple different domains that can be evaluated at any one time, and over time. Frequent adaptive analyses are performed to determine whether the interventions under evaluation are still eligible for further testing or randomisation should be stopped due to demonstrated inferiority, superiority or equivalence.

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:
• Funding or other necessary support is no longer available
• 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

Should the whole study be stopped, the end of trial is the date of the last scheduled follow up for any participant.

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:* in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland**

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (NHS sponsors only)

☑ Other insurance or indemnity arrangements will apply (give details below)

Subject Insurance is provided by the sponsor, UMC Utrecht.

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (protocol authors with NHS contracts only)

☑ Other insurance or indemnity arrangements will apply (give details below)

Subject Insurance is provided by the sponsor, UMC Utrecht.

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

☐ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ◉ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

○ Yes ◉ No ○ Not sure

Part B Section 1: Investigational Medicinal Products

Information on each IMP.

Information on each 'bulk product' before trial-specific operations (blinding, trial specific packaging and labelling) should be provided in this section for each investigational medicinal product (IMP) being tested including each comparator, if applicable.
If the trial is performed with several products please create a separate set of the following questions for each product. If the product is a combination product please give separate information for each active substance.
Click on the first row and enter details of the product in the following screens. When you have completed the details, click on the navigate button or the "See All" link and return to this section to enter details of the next product. When you have completed details of all products please move to question 13 using the navigation screen.

Investigational medicinal products

PR1 ceftriaxone

PR2 moxifloxacin

PR3 levofloxacin

PR4 piperacilin-tazobactam

PR5 ceftaroline

PR6 amoxicillin-clavulanate

PR7 azithromycin

PR8 clarithromycin

PR10 hydrocortisone

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR1**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
ceftriaxone
EV Product Code
Name of the MA holder:
RANBAXY (UK)
MA number (if MA granted by a Member State):
PL 14894 / 0342
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?

UNITED KINGDOM

Is this the Member State concerned with this application?

◉ Yes ○ No ○ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?

○ Yes ◉ No ○ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?

◉ Yes ○ No ○ Not Answered

If 'Yes', give active substance in D.3.8 or D.3.9

The products to be administered as IMPs are defined as belonging to an ATC group

◉ Yes ○ No ○ Not Answered

If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1

Other :

○ Yes ◉ No ○ Not Answered

14-3. IMPD submitted:

Full IMPD

○ Yes ◉ No ○ Not Answered

Simplified IMPD

○ Yes ◉ No ○ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◉ Yes ○ No ○ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

○ Yes ◉ No ○ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

○ Yes ◉ No ○ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

○ Yes ◉ No ○ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◯ No ◉ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◯ No ◉ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	ceftriaxone
Product code where applicable	ceftriaxone
ATC codes, if officially registered	J01DD04
Pharmaceutical form (use standard terms)	Powder for solution for injection or infusion
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment of a subject according to the protocol	1-2g daily of ceftriaxone, once a day infusion for as many days as is clinically necessary

Dose allowed

First dose for first-in-human clinical trial	ceftriaxone has a well established safety profile in patients with pneumonia. As in normal clinical care patients will be prescribed 1-2mg / day for as long as is clinically necessary
Specify per day or total:	◉ per day ◯ total ◯ Not Answered
Specify total dose (number and unit)	1-2 g gram(s)
Route of administration (relevant to the first dose):	Intravenous Use

Maximum dose allowed	4g/day
Specify per day or total	◉ per day ◯ total ◯ Not Answered
Specify total dose (number and unit)	4 g gram(s)
Route of administration (relevant to the maximum dose):	Intravenous Use

Routes of administration for this IMP

Intravascular Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	ceftriaxone sodium
CAS number:	73384-59-5
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C18-H18-N8-O7-S3
Chemical/biological description of the Active Substance	
Strength	
Concentration unit:	g gram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	1

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	(●) Yes ( ) No ( ) Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	( ) Yes (●) No ( ) Not Answered
Is this a:	
Advanced Therapy IMP (ATIMP) [1]	( ) Yes (●) No ( ) Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	( ) Yes (●) No ( ) Not Answered
Radiopharmaceutical medicinal product?	( ) Yes (●) No ( ) Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	( ) Yes (●) No ( ) Not Answered
Plasma derived medicinal product?	( ) Yes (●) No ( ) Not Answered
Extractive medicinal product?	( ) Yes (●) No ( ) Not Answered
Recombinant medicinal product?	( ) Yes (●) No ( ) Not Answered
Medicinal product containing genetically modified organisms?	( ) Yes (●) No ( ) Not Answered
Herbal medicinal product?	( ) Yes (●) No ( ) Not Answered
Homeopathic medicinal product?	( ) Yes (●) No ( ) Not Answered
Another type of medicinal product?	( ) Yes (●) No ( ) Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Ceftriaxone inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

Is it an IMP to be used in a first-in-human clinical trial? ○ Yes ◉ No ○ Not Answered

(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable

(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended

(4) As defined in Article 2(1)(b) of Regulation 1394/2007/EC

(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR2**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
moxifloxacin
EV Product Code
Name of the MA holder:
Bayer
MA number (if MA granted by a Member State):
PL 00010/0291
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UNITED KINGDOM
Is this the Member State concerned with this application?
◉ Yes ○ No ○ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
○ Yes ◉ No ○ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◉ Yes ○ No ○ Not Answered

If 'Yes', give active substance in D.3.8 or D.3.9

The products to be administered as IMPs are defined as belonging to an ATC group
◉ Yes ○ No ○ Not Answered

If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1

Other :
○ Yes ◉ No ○ Not Answered

14-3. IMPD submitted:

Full IMPD
○ Yes ◉ No ○ Not Answered

Simplified IMPD

◯ Yes ◉ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◉ Yes ◯ No ◯ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◯ No ◉ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◯ No ◉ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	moxifloxacin
Product code where applicable	
ATC codes, if officially registered	J01MA14
Pharmaceutical form (use standard terms)	Solution For Infusion
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment of a subject according to the protocol	400mg daily of moxifloxacin, for as many days as is clinically necessary

Dose allowed

First dose for first-in-human clinical trial	400mg daily of moxifloxacin, for as many days as is clinically necessary
Specify per day or total:	◉ per day ○ total ○ Not Answered
Specify total dose (number and unit)	400 mg milligram(s)
Route of administration (relevant to the first dose):	Intravenous Use

Maximum dose allowed	400mg
Specify per day or total	◉ per day ○ total ○ Not Answered
Specify total dose (number and unit)	400 mg milligram(s)
Route of administration (relevant to the maximum dose):	Intravenous Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	moxifloxacin hydrochloride
CAS number:	354812-41-2
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C21H24FN3O4
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg/ml milligram(s)/millilitre
Concentration type:	equal
Concentration number (only use both fields for range):	1.6

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin? ◉ Yes ○ No ○ Not Answered

Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	○ Yes ◉ No ○ Not Answered
Is this a:	
Advanced Therapy IMP (ATIMP) [1]	○ Yes ◉ No ○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes ◉ No ○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes ◉ No ○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes ◉ No ○ Not Answered
Plasma derived medicinal product?	○ Yes ◉ No ○ Not Answered
Extractive medicinal product?	○ Yes ◉ No ○ Not Answered
Recombinant medicinal product?	○ Yes ◉ No ○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes ◉ No ○ Not Answered
Herbal medicinal product?	○ Yes ◉ No ○ Not Answered
Homeopathic medicinal product?	○ Yes ◉ No ○ Not Answered
Another type of medicinal product?	○ Yes ◉ No ○ Not Answered
Specify the mode of action for the active substance in this medicinal product *The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action.* Moxifloxacin inhibits bacterial type II topoisomerases (DNA gyrase and topoisomerase IV) that are required for bacterial DNA replication, transcription and repair	
Is it an IMP to be used in a first-in-human clinical trial?	○ Yes ◉ No ○ Not Answered

[1,2,3,4,5] Complete sections D.4, D.5, D.6. and D.7, as applicable

[2,3] As defined in Annex 1 part IV of Directive 2001/83/EC as amended

[4] As defined in Article 2(1)(b) of Regulation 1394/2007/EC

[6] Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR3**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
levofloxacin
EV Product Code
Name of the MA holder:
Amneal Pharma Europe Ltd
MA number (if MA granted by a Member State):
PL 42357/0192
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
IRELAND
Is this the Member State concerned with this application?
◉ Yes ○ No ○ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
○ Yes ◉ No ○ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◉ Yes ○ No ○ Not Answered

If 'Yes', give active substance in D.3.8 or D.3.9

The products to be administered as IMPs are defined as belonging to an ATC group
◉ Yes ○ No ○ Not Answered

If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1

Other :
○ Yes ◉ No ○ Not Answered

14-3. IMPD submitted:

Full IMPD
○ Yes ◉ No ○ Not Answered

Simplified IMPD

◯ Yes ◉ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◉ Yes ◯ No ◯ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◯ No ◉ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◯ No ◉ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	levofloxacin
Product code where applicable	
ATC codes, if officially registered	J01MA12
Pharmaceutical form (use standard terms)	Solution For Infusion
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment of a subject according to the protocol	500 mg once or twice daily for as many days as is clinically necessary (typically 5-10 days)

Dose allowed

First dose for first-in-human clinical trial	500 mg once or twice daily
Specify per day or total:	(●) per day ( ) total ( ) Not Answered
Specify total dose (number and unit)	1000 mg milligram(s)
Route of administration (relevant to the first dose):	Intravenous Use

Maximum dose allowed	1000 mg /day
Specify per day or total	(●) per day ( ) total ( ) Not Answered
Specify total dose (number and unit)	1000 mg milligram(s)
Route of administration (relevant to the maximum dose):	Intravenous Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	levofloxacin hemihydrate
CAS number:	100986-85-4
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C18H20FN3O4
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg/ml milligram(s)/millilitre
Concentration type:	equal
Concentration number (only use both fields for range):	5

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	(●) Yes ( ) No ( ) Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	( ) Yes (●) No ( ) Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) [1]	○ Yes ◉ No ○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes ◉ No ○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes ◉ No ○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes ◉ No ○ Not Answered
Plasma derived medicinal product?	○ Yes ◉ No ○ Not Answered
Extractive medicinal product?	○ Yes ◉ No ○ Not Answered
Recombinant medicinal product?	○ Yes ◉ No ○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes ◉ No ○ Not Answered
Herbal medicinal product?	○ Yes ◉ No ○ Not Answered
Homeopathic medicinal product?	○ Yes ◉ No ○ Not Answered
Another type of medicinal product?	○ Yes ◉ No ○ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

Is it an IMP to be used in a first-in-human clinical trial?	○ Yes ◉ No ○ Not Answered

[1,2,3,4,5] Complete sections D.4, D.5, D.6. and D.7, as applicable
[2,3] As defined in Annex 1 part IV of Directive 2001/83/EC as amended
[4] As defined in Article 2(1)(b) of Regulation 1394/2007/EC
[6] Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR4**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
piperacilin-tazobactam
EV Product Code
Name of the MA holder:
Hospira UK Limited
MA number (if MA granted by a Member State):
PL 04515/0374
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UNITED KINGDOM
Is this the Member State concerned with this application?
◉ Yes ○ No ○ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
○ Yes ◉ No ○ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◉ Yes ○ No ○ Not Answered

If 'Yes', give active substance in D.3.8 or D.3.9

The products to be administered as IMPs are defined as belonging to an ATC group
◉ Yes ○ No ○ Not Answered

If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1

Other :
○ Yes ◉ No ○ Not Answered

14-3. IMPD submitted:

Full IMPD
○ Yes ◉ No ○ Not Answered

Simplified IMPD

◯ Yes ◉ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◉ Yes ◯ No ◯ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◯ No ◉ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◯ No ◉ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	piperacilin-tazobactam
Product code where applicable	
ATC codes, if officially registered	J01C R05
Pharmaceutical form (use standard terms)	Powder for solution for injection or infusion
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment of a subject according to the protocol	4g piperacillin / 0.5g tazobactam given every 6-8 hours Piperacillin/tazobactam 4 g / 0.5 g is administered by intravenous infusion (over 30 minutes) for as many days as is clinically necessary (typically 5-10 days)

Dose allowed

First dose for first-in-human clinical trial	Piperacillin/tazobactam 16g / 2g
Specify per day or total:	◉ per day ○ total ○ Not Answered
Specify total dose (number and unit)	16 / 2.0 g gram(s)
Route of administration (relevant to the first dose):	Intravenous Use

Maximum dose allowed	Piperacillin/tazobactam 16 g / 2.0 g
Specify per day or total	◉ per day ○ total ○ Not Answered
Specify total dose (number and unit)	16 / 2.0 g gram(s)
Route of administration (relevant to the maximum dose):	Intravascular Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Piperacillin
CAS number:	61477-96-1
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C23H27N5O7S
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	g gram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	4

Active Substance 2

Name of active substance (INN or proposed INN if available):	tazobactam
CAS number:	89786-04-9
Current sponsor code:	
Other descriptive name:	

Full Molecular formula	C10H12N4O5S
Chemical/biological description of the Active Substance	
Strength	
Concentration unit:	g gram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	0.5

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	(●) Yes ( ) No ( ) Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	( ) Yes (●) No ( ) Not Answered
Is this a:	
Advanced Therapy IMP (ATIMP) [1]	( ) Yes (●) No ( ) Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	( ) Yes (●) No ( ) Not Answered
Radiopharmaceutical medicinal product?	( ) Yes (●) No ( ) Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	( ) Yes (●) No ( ) Not Answered
Plasma derived medicinal product?	( ) Yes (●) No ( ) Not Answered
Extractive medicinal product?	( ) Yes (●) No ( ) Not Answered
Recombinant medicinal product?	( ) Yes (●) No ( ) Not Answered
Medicinal product containing genetically modified organisms?	( ) Yes (●) No ( ) Not Answered
Herbal medicinal product?	( ) Yes (●) No ( ) Not Answered
Homeopathic medicinal product?	( ) Yes (●) No ( ) Not Answered
Another type of medicinal product?	( ) Yes (●) No ( ) Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Piperacillin, a broad spectrum, semisynthetic penicillin exerts bactericidal activity by inhibition of both septum and cell-wall synthesis.
Tazobactam, a beta-lactam structurally related to penicillins, is an inhibitor of many beta-lactamases which commonly cause resistance to penicillins and cephalosporins but it does not inhibit AmpC enzymes or metallo beta-lactamases. Tazobactam extends the antibiotic spectrum to those bacteria that have acquired resistance to piperacillin

Is it an IMP to be used in a first-in-human clinical trial? ( ) Yes (●) No ( ) Not Answered

[1,2,3,4,5] Complete sections D.4, D.5, D.6. and D.7, as applicable
[2,3] As defined in Annex 1 part IV of Directive 2001/83/EC as amended
[4] As defined in Article 2(1)(b) of Regulation 1394/2007/EC

(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR5**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
ceftaroline
EV Product Code
Name of the MA holder:
Pfizer Ireland Pharmaceuticals
MA number (if MA granted by a Member State):
EU/1/12/785/001
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered
Which country granted the MA?
IRELAND
Is this the Member State concerned with this application?
◉ Yes ○ No ○ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
○ Yes ◉ No ○ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◉ Yes ○ No ○ Not Answered
If 'Yes', give active substance in D.3.8 or D.3.9

The products to be administered as IMPs are defined as belonging to an ATC group
◉ Yes ○ No ○ Not Answered
If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1

Other :
○ Yes ◉ No ○ Not Answered

14-3. IMPD submitted:

Full IMPD
○ Yes ◉ No ○ Not Answered

Simplified IMPD

◯ Yes ◉ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◉ Yes ◯ No ◯ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◯ No ◉ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◯ No ◉ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	ceftaroline
Product code where applicable	
ATC codes, if officially registered	J01DI02
Pharmaceutical form (use standard terms)	Powder For Concentrate For Solution For Infusion
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment of a subject according to the protocol	600mg, every 12 hours for as long as is required

Dose allowed

First dose for first-in-human clinical trial	600mg, every 12 hours
Specify per day or total:	(●) per day ( ) total ( ) Not Answered
Specify total dose (number and unit)	1200 mg milligram(s)
Route of administration (relevant to the first dose):	Intravenous Use

Maximum dose allowed	1200mg
Specify per day or total	(●) per day ( ) total ( ) Not Answered
Specify total dose (number and unit)	1200 mg milligram(s)
Route of administration (relevant to the maximum dose):	Intravenous Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	ceftaroline fosamil acetic acid solvate monohydrate
CAS number:	400827-46-5
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C24H25N8O10PS4
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg/ml milligram(s)/millilitre
Concentration type:	equal
Concentration number (only use both fields for range):	30

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	(●) Yes ( ) No ( ) Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	( ) Yes (●) No ( ) Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) [1]	○ Yes ◉ No ○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes ◉ No ○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes ◉ No ○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes ◉ No ○ Not Answered
Plasma derived medicinal product?	○ Yes ◉ No ○ Not Answered
Extractive medicinal product?	○ Yes ◉ No ○ Not Answered
Recombinant medicinal product?	○ Yes ◉ No ○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes ◉ No ○ Not Answered
Herbal medicinal product?	○ Yes ◉ No ○ Not Answered
Homeopathic medicinal product?	○ Yes ◉ No ○ Not Answered
Another type of medicinal product?	○ Yes ◉ No ○ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. In vitro studies have shown that ceftaroline is bactericidal and able to inhibit bacterial cell wall synthesis in methicillin-resistant Staphylococcus aureus (MRSA) and penicillin non-susceptible Streptococcus pneumoniae (PNSP) due to its affinity for the altered penicillin-binding proteins (PBPs) found in these organisms

Is it an IMP to be used in a first-in-human clinical trial?	○ Yes ◉ No ○ Not Answered

[1,2,3,4,5] Complete sections D.4, D.5, D.6. and D.7, as applicable
[2,3] As defined in Annex 1 part IV of Directive 2001/83/EC as amended
[4] As defined in Article 2(1)(b) of Regulation 1394/2007/EC
[6] Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR6**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
amoxicillin-clavulanate
EV Product Code
Name of the MA holder:
Sandoz Ltd
MA number (if MA granted by a Member State):
PL 04416/0634
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UNITED KINGDOM
Is this the Member State concerned with this application?
◉ Yes ○ No ○ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
○ Yes ◉ No ○ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◉ Yes ○ No ○ Not Answered

If 'Yes', give active substance in D.3.8 or D.3.9

The products to be administered as IMPs are defined as belonging to an ATC group
◉ Yes ○ No ○ Not Answered

If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1

Other :
○ Yes ◉ No ○ Not Answered

14-3. IMPD submitted:

Full IMPD
○ Yes ◉ No ○ Not Answered

Simplified IMPD

◯ Yes ◉ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◉ Yes ◯ No ◯ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◯ No ◉ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◯ No ◉ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	amoxicillin-clavulanate
Product code where applicable	
ATC codes, if officially registered	J01CR02
Pharmaceutical form (use standard terms)	Powder for solution for injection or infusion
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment of a subject according to the protocol	1000 mg/ 200 mg every 6-8 hours for as many days as is clinically necessary (typically 5-10 days)

Dose allowed

First dose for first-in-human clinical trial	1000 mg/ 200 mg every 6-8 hours
Specify per day or total:	(●) per day ( ) total ( ) Not Answered
Specify total dose (number and unit)	4000 / 800 mg milligram(s)
Route of administration (relevant to the first dose):	Intravenous Use

Maximum dose allowed	total daily dose of 3000 mg amoxicillin and 600 mg clavulanic acid
Specify per day or total	(●) per day ( ) total ( ) Not Answered
Specify total dose (number and unit)	4000/800 mg milligram(s)
Route of administration (relevant to the maximum dose):	Intravenous Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	sodium amoxicillin
CAS number:	26787-78-0
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C16H19N3O5S
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg milligram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	1000

Active Substance 2

Name of active substance (INN or proposed INN if available):	potassium clavulanate
CAS number:	61177-45-5
Current sponsor code:	

Other descriptive name:

Full Molecular formula C8H8NO5.K

Chemical/biological description of the Active Substance

Strength

Concentration unit: mg milligram(s)

Concentration type: equal

Concentration number (only use both fields for range): 200

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	◉ Yes ○ No ○ Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	○ Yes ◉ No ○ Not Answered
Is this a:	
Advanced Therapy IMP (ATIMP) [1]	○ Yes ◉ No ○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes ◉ No ○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes ◉ No ○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes ◉ No ○ Not Answered
Plasma derived medicinal product?	○ Yes ◉ No ○ Not Answered
Extractive medicinal product?	○ Yes ◉ No ○ Not Answered
Recombinant medicinal product?	○ Yes ◉ No ○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes ◉ No ○ Not Answered
Herbal medicinal product?	○ Yes ◉ No ○ Not Answered
Homeopathic medicinal product?	○ Yes ◉ No ○ Not Answered
Another type of medicinal product?	○ Yes ◉ No ○ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Amoxicillin is a semisynthetic penicillin that inhibits one or more enzymes in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death. Clavulanic acid inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin.

Is it an IMP to be used in a first-in-human clinical trial? ○ Yes ◉ No ○ Not Answered

[1,2,3,4,5] Complete sections D.4, D.5, D.6. and D.7, as applicable
[2,3] As defined in Annex 1 part IV of Directive 2001/83/EC as amended
[4] As defined in Article 2(1)(b) of Regulation 1394/2007/EC

(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR7**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
azithromycin
EV Product Code
Name of the MA holder:
Aspire Pharma Ltd
MA number (if MA granted by a Member State):
PL 35533/0026
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UNITED KINGDOM
Is this the Member State concerned with this application?
◉ Yes ○ No ○ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
○ Yes ◉ No ○ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◉ Yes ○ No ○ Not Answered

If 'Yes', give active substance in D.3.8 or D.3.9

The products to be administered as IMPs are defined as belonging to an ATC group
◉ Yes ○ No ○ Not Answered

If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1

Other :
○ Yes ◉ No ○ Not Answered

14-3. IMPD submitted:

Full IMPD
○ Yes ◉ No ○ Not Answered

Simplified IMPD

◯ Yes ◉ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◉ Yes ◯ No ◯ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◯ No ◉ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◯ No ◉ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	azithromycin
Product code where applicable	
ATC codes, if officially registered	J01FA10
Pharmaceutical form (use standard terms)	Powder For Solution For Infusion
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment of a subject according to the protocol	500 mg administered as a single intravenous daily dose for up to 14 days

Dose allowed

First dose for first-in-human clinical trial	500 mg administered as a single intravenous daily
Specify per day or total:	◯ per day ◯ total ◯ Not Answered
Specify total dose (number and unit)	500 mg milligram(s)
Route of administration (relevant to the first dose):	Intravenous Use

Maximum dose allowed	500 mg administered as a single intravenous daily
Specify per day or total	◉ per day ◯ total ◯ Not Answered
Specify total dose (number and unit)	500 mg milligram(s)
Route of administration (relevant to the maximum dose):	Intravenous Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	azithromycin dihydrate
CAS number:	83905-01-5
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C38H72N2O12
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg/ml milligram(s)/millilitre
Concentration type:	equal
Concentration number (only use both fields for range):	100

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	◉ Yes ◯ No ◯ Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	◯ Yes ◉ No ◯ Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) [1]	○ Yes ◉ No ○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes ◉ No ○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes ◉ No ○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes ◉ No ○ Not Answered
Plasma derived medicinal product?	○ Yes ◉ No ○ Not Answered
Extractive medicinal product?	○ Yes ◉ No ○ Not Answered
Recombinant medicinal product?	○ Yes ◉ No ○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes ◉ No ○ Not Answered
Herbal medicinal product?	○ Yes ◉ No ○ Not Answered
Homeopathic medicinal product?	○ Yes ◉ No ○ Not Answered
Another type of medicinal product?	○ Yes ◉ No ○ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50s sub-unit and inhibition of peptide translocation.

Is it an IMP to be used in a first-in-human clinical trial?	○ Yes ◉ No ○ Not Answered

[1,2,3,4,5] Complete sections D.4, D.5, D.6. and D.7, as applicable
[2,3] As defined in Annex 1 part IV of Directive 2001/83/EC as amended
[4] As defined in Article 2(1)(b) of Regulation 1394/2007/EC
[6] Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR8**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
clarithromycin
EV Product Code
Name of the MA holder:
Mercury Pharmaceuticals Ltd.,
MA number (if MA granted by a Member State):
PL 12762/0404
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered
Which country granted the MA?
UNITED KINGDOM
Is this the Member State concerned with this application?
◉ Yes ○ No ○ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
○ Yes ◉ No ○ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◉ Yes ○ No ○ Not Answered
If 'Yes', give active substance in D.3.8 or D.3.9

The products to be administered as IMPs are defined as belonging to an ATC group
◉ Yes ○ No ○ Not Answered
If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1

Other :
○ Yes ◉ No ○ Not Answered

14-3. IMPD submitted:

Full IMPD
○ Yes ◉ No ○ Not Answered

Simplified IMPD

◯ Yes ◉ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◉ Yes ◯ No ◯ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◯ No ◉ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◯ No ◉ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	clarithromycin
Product code where applicable	
ATC codes, if officially registered	J01FA09
Pharmaceutical form (use standard terms)	Powder for solution for injection or infusion
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment of a subject according to the protocol	1.0 gram daily of Clarithromycin powder for concentrate for solution for infusion for upto 14 days

Dose allowed

First dose for first-in-human clinical trial	1.0 gram daily of Clarithromycin powder for concentrate for solution for infusion.
Specify per day or total:	(●) per day ( ) total ( ) Not Answered
Specify total dose (number and unit)	1 g gram(s)
Route of administration (relevant to the first dose):	Intravenous Use

Maximum dose allowed	1.0 gram daily of Clarithromycin powder for concentrate for solution for infusion.
Specify per day or total	(●) per day ( ) total ( ) Not Answered
Specify total dose (number and unit)	1 g gram(s)
Route of administration (relevant to the maximum dose):	Intravenous Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	clarithromycin
CAS number:	81103-11-9
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C38H69NO13
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg/ml milligram(s)/millilitre
Concentration type:	equal
Concentration number (only use both fields for range):	2

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	◉ Yes ○ No ○ Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	○ Yes ◉ No ○ Not Answered
Is this a:	
Advanced Therapy IMP (ATIMP) [1]	○ Yes ◉ No ○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes ◉ No ○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes ◉ No ○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes ◉ No ○ Not Answered
Plasma derived medicinal product?	○ Yes ◉ No ○ Not Answered
Extractive medicinal product?	○ Yes ◉ No ○ Not Answered
Recombinant medicinal product?	○ Yes ◉ No ○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes ◉ No ○ Not Answered
Herbal medicinal product?	○ Yes ◉ No ○ Not Answered
Homeopathic medicinal product?	○ Yes ◉ No ○ Not Answered
Another type of medicinal product?	○ Yes ◉ No ○ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. The mechanism of action of clarithromycin is based on the inhibition of the protein biosynthesis by its binding to the 50S subunit of the bacterial ribosome.

The 14(R)-hydroxy metabolite of clarithromycin, a product of the metabolisation of the parent substance which is found in humans, also has an antibacterial effect.

Is it an IMP to be used in a first-in-human clinical trial?	○ Yes ◉ No ○ Not Answered

[1,2,3,4,5] Complete sections D.4, D.5, D.6. and D.7, as applicable
[2,3] As defined in Annex 1 part IV of Directive 2001/83/EC as amended
[4] As defined in Article 2(1)(b) of Regulation 1394/2007/EC
[6] Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR10**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
hydrocortisone
EV Product Code
Name of the MA holder:
Pfizer
MA number (if MA granted by a Member State):
PL 00057/1050
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UNITED KINGDOM
Is this the Member State concerned with this application?
◉ Yes ○ No ○ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
○ Yes ◉ No ○ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◉ Yes ○ No ○ Not Answered

If 'Yes', give active substance in D.3.8 or D.3.9

The products to be administered as IMPs are defined as belonging to an ATC group
◉ Yes ○ No ○ Not Answered

If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1

Other :
○ Yes ◉ No ○ Not Answered

14-3. IMPD submitted:

Full IMPD
○ Yes ◉ No ○ Not Answered

Simplified IMPD

◯ Yes ◉ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◉ Yes ◯ No ◯ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◯ No ◉ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◯ No ◉ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	hydrocortisone
Product code where applicable	
ATC codes, if officially registered	H02AB09
Pharmaceutical form (use standard terms)	Powder for solution for injection or infusion
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment of a subject according to the protocol	Intravenous Hydrocortisone, 50 milligrams (mg) every 6 hours for up-to 7 days

Dose allowed

First dose for first-in-human clinical trial	Intravenous Hydrocortisone, 50 milligrams (mg) every 6 hours for up-to 7 days
Specify per day or total:	(●) per day ( ) total ( ) Not Answered
Specify total dose (number and unit)	200 mg milligram(s)
Route of administration (relevant to the first dose):	Intravenous Use

Maximum dose allowed	200mg
Specify per day or total	(●) per day ( ) total ( ) Not Answered
Specify total dose (number and unit)	200 mg milligram(s)
Route of administration (relevant to the maximum dose):	Intravenous Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	hydrocortisone sodium succinate
CAS number:	125-04-2
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C25H34NaO8
Chemical/biological description of the Active Substance	
Strength	
Concentration unit:	mg milligram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	133.7

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin? (●) Yes ( ) No ( ) Not Answered

Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	◯ Yes ◉ No ◯ Not Answered
Is this a:	
Advanced Therapy IMP (ATIMP) [1]	◯ Yes ◉ No ◯ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	◯ Yes ◉ No ◯ Not Answered
Radiopharmaceutical medicinal product?	◯ Yes ◉ No ◯ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	◯ Yes ◉ No ◯ Not Answered
Plasma derived medicinal product?	◯ Yes ◉ No ◯ Not Answered
Extractive medicinal product?	◯ Yes ◉ No ◯ Not Answered
Recombinant medicinal product?	◯ Yes ◉ No ◯ Not Answered
Medicinal product containing genetically modified organisms?	◯ Yes ◉ No ◯ Not Answered
Herbal medicinal product?	◯ Yes ◉ No ◯ Not Answered
Homeopathic medicinal product?	◯ Yes ◉ No ◯ Not Answered
Another type of medicinal product?	◯ Yes ◉ No ◯ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action.
Corticosteroids exhibit anti-inflammatory, antipruritic, and vasoconstrictive properties. At the cellular level, corticosteroids induce peptides called lipocortins. Lipocortins antagonize phospholipase A2, an enzyme which causes the breakdown of leukocyte lysosomal membranes to release arachidonic acid. This action decreases the subsequent formation and release of endogenous inflammatory mediators including prostaglandins, kinins, histamine, liposomal enzymes and the complement system

Is it an IMP to be used in a first-in-human clinical trial?	◯ Yes ◉ No ◯ Not Answered

[1,2,3,4,5] Complete sections D.4, D.5, D.6. and D.7, as applicable
[2,3] As defined in Annex 1 part IV of Directive 2001/83/EC as amended
[4] As defined in Article 2(1)(b) of Regulation 1394/2007/EC
[6] Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

Information on Placebo

13. Is there a placebo:

◯ Yes ◉ No

Index of Sites where the qualified person certifies batch release

14. IMPs and placebos for which no responsible site needs to be identified:

This section is used to identify IMPs and placebos which:

- Have an MA in the EU **and**
- Are sourced from the EU market **and**
- Are used in the trial without modification (eg not overencapsulated) **and**
- The packaging and labeling is carried out for local use only as per article 9.2 of the Directive 2005/28/EC (GCP Directive).

If all the conditions above are met, then select below the IMPs and placebos to which this applies.

Finished IMP
PR1

Finished IMP
PR2

Finished IMP
PR3

Finished IMP
PR4

Finished IMP
PR5

Finished IMP
PR6

Finished IMP
PR7

Finished IMP
PR8

Finished IMP
PR10

This section is dedicated to finished IMPs, i.e. medicinal products randomised, packaged, labelled and certified for use in the clinical trial. In the case of multiple sites indicate the product certified by each site.

15. Identify who is responsible in the Community for the certification of the finished IMPs.
Where the product does not have a MA in the EU, but is supplied in bulk and final packaging and labelling for local use is carried out in accordance with article 9.2. of Directive 2005/28/EC (GCP Directive) then enter the site where the product was finally certified for release by the Qualified Person for use in the clinical trial.

RS1

Manufacturer

Organisation
Address

Town/city

Post code

Country

Give the manufacturing authorisation number

If no authorisation, give the reasons:

Select the relevant IMP(s) and Placebo(s) from the drop down lists.

Part B: Section 6 - Adults unable to consent for themselves

A. Clinical trials of investigational medicinal products

In this sub-section, an adult means a person aged 16 or over.

A1. What clinical condition(s) will the participants have? *The trial must relate directly to this condition.*

REMAP-CAP is a randomised controlled trial for patients admitted to the intensive care unit (ICU) with severe Community-Acquired Pneumonia (CAP).
Eligible patients will be:
1. adult patients admitted to an ICU for severe CAP within 48hours of hospital admission with:
a) symptoms or signs or both that are consistent with lower respiratory tract infection
b) radiological evidence of a new onset consolidation
2. Requiring organ support with one or more of:
a) non-invasive or invasive ventilator support
b) receiving an infusion of vasopressors, inotropes or both
Each domain will have additional domain specific exclusion criteria, but patients who fulfil the overall REMAP-CAP eligibility criteria will be assessed for enrolment into all domains that are active at a site

A2. Could the trial be carried out equally effectively if confined to adults capable of giving consent?

○ Yes ◉ No

A3. Who in the research team will decide whether or not the participants have the capacity to give consent? What training/experience will they have to enable them to reach this decision?

The ICU clinical team, who are all trained to manage critically ill patients will decide whether or not patients have the capacity to give consent. As sedation is ubiquitously used to facilitate mechanical ventilation and maintain patient comfort, we do not expect many patients to have capacity at the time of inclusion.

Patients in critical care units are monitored closely and clinical/research staff working in this setting have extensive experience of assessing capacity in their patients. Once a patient has regained capacity, they will be approached by an authorised member of the site research team for informed deferred consent. This will be done as soon as practically possible (usually within 24 - 48 hours of the patient regaining capacity).

Patients will be given time to read the PIS and have an opportunity to ask any questions they may have about participation in REMAP-CAP. After verifying that the PIS and Consent Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes and the original kept in the Investigator Site File. If the patient is unable to physically sign the Consent Form (e.g. due to weakness, reduced dexterity), an independent witness can sign on their behalf.

Patients will only be approached by authorised staff members who have received training REMAP-CAP processes and procedures and in Good Clinical Practice (GCP). The recruitment process will be done in such a way to mitigate any potential undue influence or coercion. No therapeutic promises will be made.

A4. What benefit is the administration of the investigational medicinal product expected to produce for these participants? *You may refer back to your answer to Question A24.*

There may be no real apparent benefit to the research participants, but there is a substantial unmet need for better evidence to determine the optimal treatment for patients with severe CAP. This REMAP-CAP trial utilises a novel trial design where patients can be randomised to receive several different therapies simultaneously. Data accumulated is then analysed on a regular basis to inform adaptation of the randomisation system. This works by weighting the randomisation proportions towards the intervention(s) more likely to offer benefit, therefore, more patients should receive interventions more likely to be effective more quickly. Each site will also be able to choose which interventions to make available at that site, from among those available within the trial.

A5. Will the trial involve any foreseeable risk or burden for these participants, or interfere in any way with their freedom

of action or privacy?

◯ Yes ◉ No

A6. What arrangements will be made to identify and seek informed consent from a legal representative?

The clinical team will identify the next of kin (family / friend / relative) recorded in the patient's clinical records. They will be approached by a member of the local clinical research team and asked if they would be happy to act as a personal legal representative. The clinical trial will be explained to them, they will be given an information sheet about the trial and provided with time to read the information and ask questions.They will then be asked to give an opinion on the patients participation in the research (collection of research specific data). The patients treatment will be explained to them and that routinely collected data will be recorded, as is normal practise in the NHS, if the Personal Legal representative feels that their friend / relative / family member be happy to take part in this trial they can provide consent as a Personal Legal Representative. If a Personal Legal Representative cannot be contacted, then a Professional Legal representative will be approached. This will be a doctor in the hospital who is not part of the research team (i.e not on the research delegation log). They will be informed about the trial and asked if they are willing to provide Professional legal consent on the patients behalf.

A7. Is it possible that a participant requiring urgent treatment might need to be recruited into the trial before it is possible to identify and seek consent from a legal representative?

◉ Yes ◯ No

If Yes, outline how decisions will be made on the inclusion of participants and what arrangements will be made to seek consent from the participant (if capacity has been recovered) or a legal representative as soon as practicable thereafter.

REMAP-CAP will use a model of informed deferred consent, as used in a number of recent trials in the UK including Fluids in Shock (ISRCTN15244462), AIRWAYS-2 (ISRCTN08256118), PARAMEDIC 2 (SRCTN73485024), VANISH trial (ISRCTN 20769191), 65 trial (ISRCTN10580502) amongst others.

We will seek advice and consent about a patient’s participation in the collection of research specific data from a personal legal representative or a professional legal representative while the patient lacks capacity.

We believe that this is the only appropriate model for consent in the face of the time pressure of needing to allocate treatment early in the process of critical care referral and stabilisation. Moreover, the process of obtaining consent while active intensive treatment is ongoing and the patient is in a critical state sometimes appears coercive and adds undue stress to an already stressful situation. Due to the severity of illness and its impact on mental capacity of the target population (critically ill patients), it will not be possible to involve REMAP-CAP trial participants early on in the consenting process. Instead, consent will be obtained prior to hospital discharge when their condition allows (e.g. they regain capacity). If the patient does not regain capacity prior to hospital discharge, the decision for use of information in the study will lie with the patients Personal Legal representative. If the patient dies, or the Personal Legal Representative does not wish to be involved in the consultation, a Professional Legal Representative will be appointed.

A8. What arrangements will be made to continue to consult legal representatives during the course of the research where necessary?

Any Personal Legal Representatives will be kept up to date as appropriate

A9. Will steps be taken to provide information about the trial to participants, according to their capacity of understanding, and to consider the wishes of participants capable of forming an opinion?

◉ Yes ◯ No

If Yes, give details.

Once patients regain capacity in the hospital, they will be approached by a member of the local clinical research team. The study will be explained to them, including that they were treated according to the treatment strategy randomised as part of the trial, that routine clinical information has been collected as is standard in the NHS and that the study was discussed with a Personal or Professional Legal Representative and consent obtained while they lacked capacity. they will be given a Patient information sheet and asked to consent for continuation of the study,

i.e the collection of any ongoing research specific data

A10-1. What will be the criteria for withdrawal of participants?

Patients will be able to withdraw from the study at any time without giving reasons and this will not affect their ongoing care.

A10-2. Where a participant is recruited prior to consent being obtained, and consent is later withheld or the participant dies before consent can be given, what provisions will apply to the study data collected up to this point?

If a patient is recruited and later withholds their consent or is withdrawn on the advice of a legal representative, they will be asked if they are happy for existing research specific data to be included in the final analysis. If the patient dies before consent / consultation takes place with a Personal Legal Representative, then a Professional Legal Representative will be approached.

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For further information please refer to guidance.*

Investigator identifier	Research site		Investigator Name	
IN1	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email	Anthony Gordon anthony.gordon@imperial.ac.uk
	Organisation name	IMPERIAL COLLEGE HEALTHCARE NHS TRUST	Qualification (MD...)	MD
	Address	ST. MARYS HOSPITAL PRAED STREET LONDON GREATER LONDON	Country	UNITED KINGDOM
	Post Code	W2 1NY		
	Country	ENGLAND		
IN2	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email	David Rogerson david.rogerson1@nhs.net
	Organisation name	DERBY TEACHING HOSPITALS NHS FOUNDATION TRUST	Qualification (MD...)	MD
	Address	ROYAL DERBY HOSPITAL UTTOXETER ROAD DERBY DERBYSHIRE	Country	UNITED KINGDOM
	Post Code	DE22 3NE		
	Country	ENGLAND		
IN3	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email	Ascanio Tridente Ascanio.tridente@sthk.nhs.uk
	Organisation name	ST HELENS AND KNOWSLEY HOSPITAL SERVICES NHS TRUST	Qualification (MD...)	MD
	Address	WHISTON HOSPITAL WARRINGTON ROAD	Country	UNITED KINGDOM

	PRESCOT MERSEYSIDE
Post Code	L35 5DR
Country	ENGLAND

IN4

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Forename	Matt
Middle name	
Family name	Thomas
Email	matt.thomas@nbt.nhs.net
Qualification (MD...)	MD
Country	UNITED KINGDOM

Organisation name	NORTH BRISTOL NHS TRUST
Address	SOUTHMEAD HOSPITAL SOUTHMEAD ROAD WESTBURY-ON-TRYM BRISTOL AVON
Post Code	BS10 5NB
Country	ENGLAND

IN5

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Forename	Ceri
Middle name	
Family name	Battle
Email	ceri.battle@wales.nhs.uk
Qualification (MD...)	MD
Country	UNITED KINGDOM

Organisation name	Morriston Hospital
Address	Intensive Care Heol Maes Eglwys, Morriston, Swansea
Post Code	SA6 6NL
Country	WALES

IN6

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Forename	Tom
Middle name	
Family name	Lawton
Email	tom.lawton@bthft.nhs.uk
Qualification (MD...)	MD
Country	UNITED KINGDOM

Organisation name	BRADFORD TEACHING HOSPITALS NHS FOUNDATION TRUST
Address	BRADFORD ROYAL INFIRMARY DUCKWORTH LANE BRADFORD WEST YORKSHIRE
Post Code	BD9 6RJ

Country	ENGLAND

IN7

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	UNIVERSITY HOSPITALS COVENTRY AND WARWICKSHIRE NHS TRUST
Address	WALSGRAVE GENERAL HOSPITAL CLIFFORD BRIDGE ROAD COVENTRY WEST MIDLANDS
Post Code	CV2 2DX
Country	ENGLAND

Forename	Christopher
Middle name	
Family name	Bassford
Email	christopher.bassford@uhcw.nhs.uk
Qualification (MD...)	MD
Country	UNITED KINGDOM

IN8

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	ROYAL CORNWALL HOSPITALS NHS TRUST
Address	ROYAL CORNWALL HOSPITAL TRELISKE TRURO CORNWALL
Post Code	TR1 3LJ
Country	ENGLAND

Forename	Jonathan
Middle name	
Family name	Paddle
Email	jonathon.paddle@nhs.net
Qualification (MD...)	MD
Country	UNITED KINGDOM

IN10

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	BLACKPOOL TEACHING HOSPITALS NHS FOUNDATION TRUST
Address	VICTORIA HOSPITAL WHINNEY HEYS ROAD BLACKPOOL LANCASHIRE
Post Code	FY3 8NR
Country	ENGLAND

Forename	Jason
Middle name	
Family name	Cupitt
Email	Dr.cupitt@bfwhospitals.nhs.uk
Qualification (MD...)	MD
Country	UNITED KINGDOM

IN11

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	CENTRAL MANCHESTER UNIVERSITY HOSPITALS NHS FOUNDATION TRUST
Address	TRUST HEADQUARTERS, COBBETT HOUSE MANCHESTER ROYAL INFIRMARY OXFORD ROAD MANCHESTER GREATER MANCHESTER
Post Code	M13 9WL
Country	ENGLAND

Forename	Daniel
Middle name	
Family name	Conway
Email	Daniel.Conway@cmft.nhs.uk
Qualification (MD...)	MD
Country	UNITED KINGDOM

IN14

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	LEEDS TEACHING HOSPITALS NHS TRUST
Address	ST. JAMES'S UNIVERSITY HOSPITAL BECKETT STREET LEEDS WEST YORKSHIRE
Post Code	LS9 7TF
Country	ENGLAND

Forename	Simon
Middle name	
Family name	Whiteley
Email	simon.whiteley@nhs.net
Qualification (MD...)	MD
Country	UNITED KINGDOM

IN15

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	TAUNTON AND SOMERSET NHS FOUNDATION TRUST
Address	MUSGROVE PARK HOSPITAL TAUNTON SOMERSET
Post Code	TA1 5DA
Country	ENGLAND

Forename	Richard
Middle name	
Family name	Innes
Email	Richard.Innes@tst.nhs.u
Qualification (MD...)	MD
Country	UNITED KINGDOM

IN16

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Organisation name

Address

Post Code

Country ENGLAND

Forename

Middle name

Family name

Email

Qualification (MD...)

Country

IN17

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Organisation name

Address

Post Code

Country ENGLAND

Forename

Middle name

Family name

Email

Qualification (MD...)

Country

IN18

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Organisation name

Address

Post Code

Country ENGLAND

Forename

Middle name

Family name

Email

Qualification (MD...)

Country

IN19

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Forename
Middle name
Family name
Email
Organisation name
Qualification (MD...)
Address
Country
Post Code
Country ENGLAND

IN20

- ( ) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Forename
Middle name
Family name
Email
Qualification (MD...)
Country

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to fulfil the responsibilities of the chief investigator for this study as set out in the UK Policy Framework for Health and Social Care Research.

3. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

4. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

5. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

6. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

7. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

8. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

9. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

10. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.

11. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

12. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

13. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- ◯ Chief Investigator
- ◯ Sponsor
- ◯ Study co-ordinator
- ◯ Student
- ◯ Other – please give details
- ◯ None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Dr Anthony Gordon on 23/03/2018 13:34.

Job Title/Post:	Professor
Organisation:	Imperial College London
Email:	anthony.gordon@imperial.ac.uk

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The responsibilities of sponsors set out in the UK Policy Framework for Health and Social Care Research will be fulfilled in relation to this research.

7. The statutory responsibilities of sponsors set out in the Medicines for Human Use (Clinical Trials) Regulations 2004 will be undertaken in relation to this trial.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*

8. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

9. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by MSc Wilma Van Bentum-Puijk on 23/03/2018 13:35.

Job Title/Post:	Project Manager
Organisation:	UMC Utrecht
Email:	W.W.Puijk-2@umcutrecht.nl