



## FREQUENTLY ASKED QUESTIONS

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## ELIGIBILITY CRITERIA

### 1) What are the inclusion and exclusion criteria for REMAP-CAP?

The combination of platform inclusion/exclusion criteria as well as domain and intervention-specific inclusion/exclusion criteria in REMAP-CAP means the only way of easily evaluating eligibility is the on-line eligibility system. The system asks for various questions to be answered and the software determines which patients are eligible and for which domains.

Enter all patients into the eligibility CRF who meet the following criteria, irrespective of how long the patient has been in ICU, or other potential exclusions:

- Adult
- Admitted to ICU
- Community acquired pneumonia as part of their admission diagnosis

### 2) Why isn't there a screening log for this study?

As all potential participants are entered into the eligibility CRF, this serves as a screening log. The screening log is therefore a sub-set of all patients entered into the Eligibility CRF and includes all patients who meet study inclusion criteria.

### 3) Which patients should be entered into the eligibility CRF?

All patients with a suspected or confirmed diagnosis of community acquired pneumonia should be entered into the eligibility CRF. Patients with pneumonia that is known to be hospital-acquired are not required to be entered into the eligibility CRF.

### 4) Hospital and ICU admission times can sometimes be difficult to obtain. What happens if this information is not available at the time of eligibility?

If the exact time is unknown estimate to the nearest 15 minutes e.g. 18:00, 18:15, 18:30 or 18:45. For midnight, round to 23:59 hrs. If you are unsure, please provide a conservative estimate (e.g. if you know that it was some time between 02:30 and 04:00, enter 02:30).

If you are unsure of the time the patient presented to the first hospital's ED, but the day of presentation is known, enter 01:00 (1 am) on that day.

Once correct details are known the data points can be updated. Update hospital admission date/time on the baseline form and update ICU admission date/time by selecting edit on the patient summary page.

### 5) My patient has multiple names, which initials should I use for their initials?

Patients' initials should be entered in the format First, Middle, Last (FML). If the patient does not have a middle name, use their first and last names separated by a dash (F-L).

If the patient has multiple middle names (e.g. Geoffrey Arthur George Lucas), use the first initials of their first, second, and last names (e.g. GAL).

If the patient has multiple surnames (including hyphenated surnames) (e.g. Anne Martinez-Garcia), please use the initials of their first name, middle name (if applicable), and their first surname (e.g. A-M).

**6) If a patient presents to another hospital or ICU prior to arrival at your hospital, which hospital/ICU admission date and time should be recorded on the eligibility CRF?**

Hospital and ICU admission date and time should be recorded as the first admission to any hospital for this illness and the first ICU admission to any ICU during this illness. For a patient transferred to your hospital from another hospital or ICU, enter the date (and time if known) they were admitted to the first hospital/ICU.

**7) Can a patient be randomized into REMAP-CAP more than once? And if so, what is the time frame?**

Yes, but only more than 90 days (primary endpoint) after the previous admission. The database has checks in place to prevent duplicate randomizations prior to this time. In regions where date of birth and initials are collected if you try to randomize a patient with the same initials or DOB as a patient who has been randomized within the previous 90 days, you will be asked to check whether this patient has already been randomized. In regions where date of birth and initials are not collected, the database will ask you if the patient was randomized in the last 90 days.

In Germany, patients can never be re-randomized into the study.

**8) If a patient with CAP is entered into the database overnight and is “platform pending”, are Research Coordinators expected to review the patient the next working day?**

Yes, “platform pending” patients should be monitored closely as there is the potential for their eligibility to change. For example, a patient may not have sufficient organ support when initially screened, but may become eligible if they start to receive vasopressors or any form of ventilation (invasive and non-invasive, including high flow nasal oxygen).

**9) Are patients on high-flow oxygen eligible for REMAP-CAP?**

Yes. From July 2019, high-flow oxygen delivered via nasal prongs at a flow rate of 30L/min or more will be considered as a qualifying level of organ support. Patients receiving high-flow oxygen may therefore meet organ-support eligibility criteria for participation in the REMAP-CAP trial.

**10) A patient meets all eligibility criteria, but are planned to be discharged from ICU today or tomorrow. Can they be randomized into the trial?**

Currently there are no inclusion or exclusion criteria relating to how long patients are anticipated to remain in ICU. If a patient meets all REMAP-CAP inclusion and exclusion criteria, they can be randomized into the trial. However, if a patient is eligible but is planned to be discharged from ICU within the next 24 hours, we would consider that it is potentially not in the best interests of the patient to be randomized into the REMAP-CAP trial. Enter the patient into the eligibility system, but select “Not Appropriate” when the intervention options are displayed.

We would encourage that sites screen patients for eligibility as early as possible in their ICU admission.

- 11) An awake patient has a qualifying organ failure at time of initial completion of the eligibility CRF and goes to 'consent pending', but they are no longer on organ support when consent is obtained. Is the patient still eligible?**

Yes, so long as the patient met the qualifying organ support during the time-window they remain eligible while consent is being obtained.

## TRANSFERRING PATIENTS

- 1) Who is responsible for the transfer of a patient between study sites on the study database?**

The transferring site is responsible for initiating the patient transfer on the study database. The receiving site will confirm the transfer before the patient appears on the patient list.

Contact your Regional Project Managers if you need assistance with a transfer.

- 2) What happens when a patient with CAP is transferred to your ICU from another hospital?**

If the patient is already a REMAP-CAP patient they will be transferred on the study database. Contact the site research coordinator or your regional project manager if the transfer has not been initiated.

If the patient is not a REMAP-CAP patient and they meet the criteria for eligibility assessment (adult, in ICU, diagnosis of CAP or a direct complication of CAP) enter into the eligibility CRF.

- 3) How is data collected for patients who are transferred between sites with different chart days?**

The chart day start time will be set as the chart day for the first site. This means that the second site (who receives the patient) must continue to collect data for the chart day time of the original hospital. This is to maintain data integrity.

It is the responsibility of each hospital to complete data collection while the patient is in their hospital. If the patient is transferred from your hospital to a hospital not participating in REMAP-CAP, data completion stops at the time of discharge from your hospital.

## ANTIBIOTIC DOMAIN

- 1) Is there any guidance on antibiotic dosing and frequency?**

Yes, there is an antibiotic administration guide available via a hyperlink from the randomization page of the database. It is also available to use as a study tool within your ICU. This is guidance only, and is not a protocol requirement; clinicians can determine antibiotic dose and frequency as the Antibiotic Domain is only assessing the choice of empiric antibiotic.

- 2) My patient is only eligible for one of the antibiotics that are available at my site. Can they still be randomized into this domain?**

No. For a patient to be randomized they must be eligible for two or more interventions at your site.

**3) Do I document the antibiotics used for Selective Digestive Decontamination (SDD)?**

All systemic antibiotic agents administered to patients randomized into REMAP-CAP must be documented in the antibiotic administration CRF. However, topical antimicrobial agents that are not absorbed (including oral pastes and enteral SDD) do not need to be recorded.

**4) Antibiotics are permitted to be escalated when microbiologic testing is returned, however if a patient is clinically deteriorating can antibiotics be changed?**

Escalation of antibiotic therapy in the absence of any microbiological information is discouraged and should be documented as a protocol deviation. However, clinicians should always act in the best interests of their patient.

## MACROLIDE DURATION DOMAIN

**1) Can we participate in the Macrolide Duration Domain if we are not participating in the Antibiotic Domain?**

No. The Macrolide Duration Domain is “nested” within the Antibiotic Domain, and only patients who are randomized to receive a beta-lactam and macrolide intervention in the Antibiotic Domain will be able to participate in the Macrolide Duration Domain.

**2) What happens if consent to participate is not obtained by day 5?**

If consent is not obtained by the end of study day 5 the patient is not able to participate in the macrolide duration domain. They will receive up to 5 days of macrolide as per standard care, however their intervention allocation will not be revealed.

**3) Can we ‘reveal’ the patient’s intervention allocation before day 3?**

Yes. Reveal of allocation status (standard course or extended course of macrolide) can occur at any time before the end of study day 5, and should be entered as soon as consent is obtained and sufficient information is available to evaluate the exclusion criteria for this domain. If you reveal prior to day 3 you will be advised to continue the macrolide until they receive a dose on day 3.

**4) When should I cease Macrolide, for a patient who is allocated to standard course (3-5 days)?**

If reveal of allocation occurs before study day 3, and the patient is allocated to a standard course (3-5 days) continue macrolide therapy and discontinue at any time after the beginning of study day 3 and before the end of study day 5.

If allocation reveal occurs after day 3, and a patient is allocated to a standard course of macrolide, discontinue immediately.

**5) How is day 5 calculated for the Macrolide Duration Domain?**

Day 5 is defined as the end of chart day relating to study day 5. Consent must be entered into the database before this time for the patient to participate in the macrolide duration domain.

**6) A patient is randomized to the standard course (3-5 days) intervention. Do we stop the Macrolide at the end of study day 5, irrespective of whether the patient's lab results are back or not?**

Yes. The protocol states that patients in the standard duration arm must have their macrolide discontinued after a maximum of 5 days. It can be recommenced in patients who have a clinical indication after microbiology results are available.

## CORTICOSTEROID DOMAIN

**1) A patient has been allocated to the "no corticosteroid" intervention, but has been administered hydrocortisone. How should I record this?**

Please record the total dose of all systemic corticosteroids administered on the relevant daily data CRF and enter the reasons for administration.

For patients who are allocated to the "no corticosteroid" intervention, the administration of any systemic corticosteroid, including hydrocortisone, will be considered a protocol deviation except where it is for the treatment of new illnesses that develop in the course of a patient's ICU stay.

Similarly, the reasons for any corticosteroids administered after the end of study day 8 to patients in the fixed-duration hydrocortisone intervention, or to patients allocated to the shock-dependent hydrocortisone intervention who are not receiving vasopressors, must be recorded. These will be considered as protocol deviations, except where the administration of corticosteroid is for the treatment of new illnesses that develop in the course of a patient's ICU stay.

**2) When should we administer hydrocortisone to a patient allocated to the 'shock-dependent hydrocortisone' intervention?**

Hydrocortisone should be commenced if septic shock develops as a result of the patient's initial episode of CAP, up until study day 28. Hydrocortisone should be commenced as soon as septic shock is diagnosed, and ceased when the treating clinician believes that septic shock has resolved. Hydrocortisone should be administered whenever a patient is in septic shock as a result of their initial episode of CAP during any ICU admission, up to study day 28.

Shock is defined as the administration of any vasopressor by continuous infusion where the treating clinician believes this requirement is caused by the patient's CAP, and is not being administered for another reason such as hypovolemia or to offset the effects of mechanical ventilation or sedation. Resolution of septic shock is determined by the treating clinician; however, shock should always be regarded as having resolved if vasopressor infusion has not been administered in the preceding 24 hours.

If septic shock develops during the first or any subsequent ICU admission due to a reason other than CAP, administration of corticosteroids is at the discretion of the treating clinician.

**3) Why is daily corticosteroid administration collected until at least study day 9 for patients in the fixed-duration (7 day) course of hydrocortisone?**

The fixed-course hydrocortisone intervention requires a seven-day course of hydrocortisone to be administered. Because study day 1 is not a full 24 hours and only includes the period from randomization to the end of the chart day, this seven-day course is likely to be completed on study day 8.

Data collection on study day 9 is required to ensure that the hydrocortisone is ceased as per protocol.

**4) A patient in the fixed duration hydrocortisone intervention is discharged to the ward before the end of study day 8. Their hydrocortisone was not administered on the ward, is this a protocol deviation?**

It is the responsibility of the ICU team to ensure that the full course of hydrocortisone is prescribed; however, it is not the responsibility of the ICU team to ensure that the course of hydrocortisone is administered after ICU discharge.

It is not a protocol deviation if the course of hydrocortisone is not completed after ICU discharge.

## ANTIVIRAL DOMAIN

**1) At randomization, the patient was suspected to have influenza and was randomized to receive Oseltamivir. Microbiological testing has since confirmed that they are influenza negative. Should we continue to give Oseltamivir?**

In patients who are allocated to receive Oseltamivir but are later found to be influenza-negative, treatment with Oseltamivir may be ceased if the treating clinician believes that it is clinically appropriate to do so.

## DATA COLLECTION

**1) The same ABG data is required in both the Eligibility and Baseline forms. Do we have to enter it twice?**

No, if the ABG is entered on the Eligibility CRF then it will auto-populate on the Baseline form. However, if it was not entered on Eligibility it does need to be entered on the Baseline form.

**2) If height and weight are unknown can these fields be left blank?**

No, these are both required fields. Please refer to the data completion guidelines for information regarding how to collect these fields.

**3) Chronic Kidney Disease is not listed as past medical history. Can ‘normal renal function’ be selected on the baseline form?**

No, the data definition for this field uses the most recent serum creatinine in the year prior to hospital admission. Select ‘Not recorded’ if there is no information prior to this hospital admission.

**4) What antibiotics should be recorded?**

Enter all antibiotic courses administered between arrival at the randomizing hospital and study day 14 ICU (censored at end of study day 14 or hospital discharge). This includes antibiotics that were commenced prior to ICU admission.

**5) Do I have to complete all daily data forms that appear?**

Daily data only needs to be collected until ICU discharge or Study Day 28, whichever occurs first. If the patient is readmitted to ICU daily data needs to recommence.

For patients randomized to the fixed-duration hydrocortisone intervention of the Corticosteroid Domain, daily data on corticosteroid administration is required until at least the end of study day 9 or hospital discharge, whichever occurs first.

**6) My patient is receiving high-flow oxygen. How should I document their ventilation information on the Baseline CRF?**

For patients receiving high-flow oxygen at the time of randomization, please enter a corresponding Positive-End Expiratory Pressure (PEEP) of zero (0) in the baseline CRF.

**7) When does data need to be entered?**

Data should be entered as soon as possible; however, Day-90 follow-up CRFs cannot be entered before day 91.

Survival status at Day-90 and the results of influenza testing (microbiological testing CRF) are required for Response Adaptive Randomization and therefore must be submitted as soon as possible.

## **FOLLOW-UPS**

**1) If a patient is discharged from hospital alive but we discover they have died before Day 90 can we enter the data before Day 90?**

Yes, day 90 data for patients who die between hospital discharge and Day 90 can be entered at any time. The database validations restrict data entry for patients that are alive at day 90, this data must be entered between day 91 and Day 104.

**2) The patient is not capable of answering the questions. What should I do?**

It is important that you try to perform all follow-up questionnaires with each participant. If it is not possible for the participant to complete the questionnaires they can be completed by a proxy, however this must be documented on the CRF. If no proxy is available and the participant is unable to complete



the follow-up, please indicate this on the CRF and document the reasons why follow up cannot be completed.

**3) The patient has a pre-existing brain injury, how do I answer the questions?**

The survey tools should be read verbatim and should reflect current functionality (today for EQ5D and past 30 days for the WHODAS) even though this may have been the patient's baseline functionality.

For the WHODAS respondents should rate the difficulty experienced by taking into consideration how they usually do the activity. If assistive devices or personal assistance are usually available, respondents should keep this in mind. For example, if a respondent with a spinal cord injury has a personal assistant who helps daily with bathing and therefore experiences no difficulty with washing his or her whole body because of the help available, the item would be rated "1" for "None".

**4) What should I do if the patient does not speak the same language as me.**

DO NOT use a proxy as an interpreter. It is important that you use an independent interpreter wherever possible. If no-one at your site can interpret for you, contact your project manager to organize alternative options.

When using an interpreter, first check to see if the follow-up instrument is available in the language and use this version (refer to the CRF Data Completion Guidelines for the list of available languages). If the instrument is not available in the required language ask the interpreter to translate the questions verbatim. Tell the interpreter to use a first-person perspective when interpreting. Inform the patient about the interpreter's confidentiality.

## CONSENT CRF

**1) A participant or their proxy have refused consent in the first instance. How do I document this on the Consent CRF?**

On the consent CRF, add an "agreement/declined event". Select who the discussion was with (patient, proxy, or other), enter the date of the discussion, and then for each domain select the outcome of this discussion as Declined/Revoked.

## SERIOUS ADVERSE EVENTS (SAE)

**2) What is considered an SAE?**

SAEs are defined in accordance with the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) (July 2000) as any untoward medical occurrence which may or may not have a causal relationship with the study treatment that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Results in a congenital anomaly/birth defect
- Results in an important medical event which may require intervention to prevent one of the previously listed outcomes

In addition, for an event to be reported as a SAE in REMAP-CAP the event must also meet all the following criteria:

For an event to be reported as a SAE in REMAP-CAP the event must either be:

- An SAE that is **directly attributable** to a study intervention or participation (irrespective of whether the event is a trial primary or secondary endpoint for this participant).
- An SAE that **might reasonably (possibly or probably) have occurred** as consequence of a study intervention or study participation and the event is not captured as a trial primary or secondary endpoint for this participant.

In Germany, all SAEs must be reported, regardless of their association with study participation.