

Barbara Cuddon
REC Manager
Health Research Authority
Skipton House, 80 London Road, London SE1 6LH

Dear Barbara,

Re: Study Title: Randomized, Embedded, Multi-factorial, Adaptive Platform Trial for community -Acquired Pneumonia (REMAP-CAP)

REC reference: 18/lo/0660

EudraCT number: 2015-002340-14

IRAS project ID: 237150

I am pleased to enclose an amendment to **London Surrey-Borders REC**. As outlined at the time of initial approval, REMAP-CAP is an adaptive platform trial. One of the features of an adaptive platform trial is the potential to add additional research questions including both the addition of a new domain (a completely new set of alternative interventions) or addition of a new intervention to an existing domain. The protocol also has a modular structure which separates the central elements of the trial (e.g. statistical methods), from elements related to interventions specified in the trial (contained in domain-specific appendices), and from elements that relate to a country or region (contained in region-specific appendices that apply to only that region or country).

This is a substantial amendment to REMAP-CAP and the amendments may be considered in two categories. Firstly, there are amendments to Core Protocol and corresponding changes to the original domain-specific appendices and region-specific appendices. These relate largely to statistical aspects of the design and have arisen as a consequence of better understanding of operating characteristics of the platform, including insights derived from simulations of the trial which are used to understand the risk of type I (false positive) and type II (false negative) errors. We do not believe that these amendments constitute major changes to the ethical conduct of the trial.

Secondly, there are new aspects of the study that are yet to undergo ethical review, which are now submitted for such review. These comprise:

- The addition of a new domain, the Antiviral Domain
- The addition of a new intervention to the pre-existing Corticosteroid Domain
- the addition of a non-interventional, Registry Appendix

The following documents have been amended:

The Intensive Care National Audit & Research Center (ICNARC)
Napier House
24 High Holborn
London, WC1V 6AZ
Email: ukremapcap@icnarc.org

1. **Core Protocol** – minor administrative changes, incorporation of changes due to European ethical requirements, and substantive changes to the statistical model used for analysis of this trial including the way pre-defined strata are applied, evaluation of interaction between treatments in different domains, and how equivalence of interventions is evaluated.
2. **Antibiotic Domain-Specific Appendix (DSA)** – minor administrative changes and changes to reflect modification of the planned statistical analysis of this trial
3. **Macrolide Duration DSA** – minor administrative changes, changes to the definition of one study intervention to reflect clinical practice, changes so that eligibility for this domain is evaluated at a time-point that is more clinically appropriate and changes to reflect modification of the planned statistical analysis of this trial
4. **Corticosteroid DSA** – minor administrative changes, introduction of a new intervention (shock-dependent hydrocortisone, which is part of the existing spectrum of standard care) based on evidence derived from more recent clinical trials, and changes to reflect modification of the planned statistical analysis of this trial
5. **European**
6. **Region-Specific Appendix (RSA)** – minor administrative changes, and addition of information relating to the new Antiviral Domain and patient Registry
7. **Statistical Analysis Appendix** – updated to reflect the introduction of new domains, changes to the ‘unit-of-analysis’ for this trial.

The following new documents have been added:

1. **Antiviral DSA** – a new domain investigating the use of an antiviral agent for patients with severe community-acquired pneumonia (CAP) caused by influenza. All intervention options are within the spectrum of existing standard care.
2. **Registry Appendix** – outlining collection, of a dataset through routinely collected data, to be collected for all patients admitted to participating ICUs with community acquired pneumonia, including patients in REMAP-CAP as well as patients who were not randomised.

We would be grateful if the international nature of this trial and the correspondingly large number of bodies to which these documents will be submitted for ethical review is considered. The current protocol is approved in more than 10 countries in Australasia, Europe, and North America. Maintaining a single approved protocol across multiple jurisdictions can be challenging and requests for modification of amendments by ethical review bodies can contribute to this challenge. If, in this jurisdiction, it is considered necessary to make changes to common protocol documents (Core Protocol, Registry Appendix, Domain-specific appendices, Statistical Analysis Appendix) we would request the opportunity for dialogue as well as consideration for how, alternatively, the Region-Specific Appendix might be modified to meet necessary requirements for approval.

In addition to the above we also wish to add 2 new recruiting sites:

1. York Hospital, PI- Dr Joseph Carter (MD)
2. Addenbrooke's Hospital, PI - Dr Charlotte Summers (MD)

We have also submitted updated versions of the Patient information sheet and consent form, the Retrospective patient information sheet and consent form and the Personal Legal representative information sheet and consent form:

UK REMAP CAP PIS ICF V2.3 29.10.2019

UK REMAP CAP Retrospective PIS ICF V2.3 29.10.2019

UK REMAP CAP PerLRIS ICF V2.4 29.10.2019

We acknowledge the complexity of the design of this trial and that the scope of the proposed changes mean that the review of these amendments is a substantial undertaking and we thank you for the time and effort associated with this task. If you have any questions or require any clarification regarding any aspect of this trial, please do not hesitate to contact myself on the details listed below.

Sincerely,



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