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

**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**

Many thanks for undertaking review of this amendment to add the **Pandemic Appendix** to the Core Protocol for the REMAP-CAP adaptive platform trial.

As outlined in the current Core Protocol (Version 3.0) the platform is designed to adapt during a pandemic to answer time-critical questions related to the effectiveness of a range of treatments for patients with pandemic infection. The Pandemic Appendix to the Core Protocol contains information about how the key elements of the REMAP will be modified during a pandemic of severe acute respiratory infection that results in community-acquired pneumonia (CAP).

A novel Coronavirus has now emerged in China and is causing life-threatening CAP in a large number of patients. This has led to a declaration by the WHO of a Public Health Emergency of International Concern. REMAP-CAP is designated by the WHO as a Pandemic Special Study because of its capacity to generate time-critical evidence regarding effective treatments.

REMAP-CAP is recruiting currently at more than 50 ICUs in 13 countries with a further 35 to 40 sites in start-up. Although other clinical trials are likely to commence recruitment in coming weeks or months, REMAP-CAP is designed to start generating evidence on effective treatments immediately. However, approval of the Pandemic Appendix to the Core Protocol is a necessary step in allowing this to occur.

The Pandemic Appendix to the Core Protocol acts as a supplement to the Core Protocol, specifying the components of trial conduct and analysis which may need to be modified during a pandemic. The major features of the document are:

- Specification of how decisions related to activation and de-activation of the pandemic protocol changes are made
- Change to the default primary end-point, so that information is available more quickly
- Specification of how existing and potential new domains of REMAP-CAP are applied during a pandemic
- Description of an additional statistical model that will be used exclusively to analyze patients with proven or suspected pandemic infection and applied only to domains that are directly relevant to these patients
- Description of possible changes in the thresholds used to determine statistical confidence
- Outline of possible changes to eligibility criteria and definition of an ICU (as, during a pandemic, advanced life-support measures, such as invasive mechanical ventilation, may be provided outside an ICU)

- Specification of pathways that permit the DSMB to liaise directly with the appropriate authorities if the DSMB is aware of results that are of relevance to public health

The Pandemic Appendix to the Core Protocol outlines a range of possible adaptations that may occur in the event of a pandemic. The exact adaptations are specified in an operational document that will be finalized prior to the first adaptive analysis using the pandemic statistical model. The reason the Appendix only provides a range of possible adaptations relates to recognition that the exact clinical and biological features of a pandemic are known only after the emergence and preliminary description of the pandemic pathogen and its clinical effects.

We believe that, at this time, there is a critical time-imperative for review of the Pandemic Appendix to the Core Protocol. As such, we would be grateful if you could consider pathways that might allow appropriate review to be conducted in a manner that is as expeditious as possible. In conjunction with this, investigators and study staff are available to meet with you or speak by phone, as well as respond rapidly regarding any questions, areas of concern, or areas of clarification. We would also request that, in making any requests for modification of the document, that it is taken into account that this is an international clinical trial for which approval from multiple ethical review bodies is occurring simultaneously. If changes are considered necessary, we are hopeful that this can be accommodated through modification of the trial's Region-Specific Appendices.

If you have any questions or require any clarification regarding any aspect of this trial, please do not hesitate to contact myself using the details listed below.

Sincerely,

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