

Dr Farah Al-Beidh
Clinical Trial Manager
Imperial College London / ICNARC
Tel: 020 7831 6878
Mobile: 07714051401
Fax: 020 7831 6879
Email: ukremap-cap@icnarc.org

05/03/21

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

REC reference: 18/Io/0660

EudraCT number: 2015-002340-14

IRAS project ID: 237150

Substantial amendment 25 (AM025) Expedited Approval

I am submitting substantial amendment AM025 for the REMAP-CAP study.

This involves the increase of patient recruitment numbers from the original 1000 to 6000.

The addition of new interventions to the Anticoagulation domain

The addition of the ACE2/RAS domain.

Anticoagulation Domain

New Anticoagulation Domain interventions:

Conventional low dose thromboprophylaxis

Intermediate thromboprophylaxis

Continuation of therapeutic dose anticoagulation (only for those started on therapeutic dose on the ward)

As outlined in the background section of this amended Domain-Specific Appendix (DSA), a multi-platform randomized controlled trial (mpRCT) including REMAP-CAP and the ATTACC and ACTIV-IV trials has recently reported on the effectiveness of routine therapeutic anticoagulation, compared with local standard venous thromboprophylaxis, for patients admitted to hospital with COVID-19 infection. In critically ill patients routine therapeutic dose anticoagulation was not effective (reaching a statistical trigger for futility) and with a moderate probability that it results in harm. In non-critically ill patients, routine therapeutic anticoagulation was effective and may well become standard of care. In REMAP-CAP (and the mpRCT), non-critically ill patients correspond to the Moderate illness severity state and critically ill patients correspond to the Severe illness severity state.

The results from the mpRCT have led to the current amendment. Although both Moderate State and Severe State patients could be enrolled in the previous version of this domain, this amendment restricts eligibility only to patients in the Severe State. Patients in the Moderate State are no longer included because many of the investigators in the mpRCT, including REMAP-CAP, believe that the relevant clinical question has been answered in this patient group (i.e. routine therapeutic anticoagulation is clinically indicated).

This amendment, applying to patients in the Severe State, serves to resolve residual questions that are of high relevance to clinical practice. There are two questions:

1. In patients who were not critically ill and have been receiving routine therapeutic anticoagulation, who then progress to being critically ill, what is the optimal approach to subsequent anticoagulation therapy during critical illness. This includes whether there should be continuation of therapeutic anticoagulation, noting this was the treatment strategy that demonstrated superiority in the mpRCT (i.e. started when not critically ill and continued if the patient became critically ill) but was also demonstrated to be ineffective and possibly harmful when commenced in patients who were critically ill.
2. For patients who have not been receiving routine therapeutic anticoagulation and are critically ill what is the optimal approach to anticoagulation within the spectrum of local standard thromboprophylaxis, noting that therapeutic dose anticoagulation has been identified as not effective, and possibly harmful, and is not an available option within the randomization schedule in this patient group.

Much of the residual uncertainty arises as a consequence of variation in practice within the completed components of the mpRCT with respect to intensity of anticoagulation in patients assigned to the standard of care control group. Within the previous version of this domain, patients assigned to local standard venous thromboprophylaxis could receive what is referred to as conventional low dose thromboprophylaxis or intermediate dose thromboprophylaxis. Both doses are used in routine practice, however there is uncertainty regarding their relative treatment effect.

We believe that evaluating different doses of thromboprophylaxis within the spectrum of standard care to be an important question for critically ill patients with COVID-19, and believe that the results will be both clinically impactful and practice changing.

ACE2 RAS domain

We are adding a new domain where patients will be randomised to receive one of up to three renin-angiotensin system (RAS) blockade strategies, depending on availability and acceptability, or control. This includes an Angiotensin converting enzyme inhibitor (ACEi) or Angiotensin II receptor blocker (ARB).

I have also made the below changes to the MHRA CTA.

We are adding 9 IMP product to the MHRA CTA. These IMPs will be used from normal hospital stock.

The addition of 5 ACEi Drugs:

Ramipril, Lisanopril, Perindopril, Enalapril, Captopril

The addition of 4 ARB Drugs:

Losartan, Valsartan, Candesartan, Irbesartan

Within the current ACE2 RAS domain specific appendix there is also has an additional DMX-200 intervention, a chemokine receptor-2 (CCR2) inhibitor that can be used in combination with an ARB. However, DMX-200 is a novel drug that will be supplied as a clinical trial IMP with clinical trial labelling but as of yet, this drug is not available for shipment to the UK. This intervention will be added to the MHRA as part of a future substantial amendment.

Many Thanks

Farah

Farah Al-Beidh PhD

UK REMAP-CAP Trial Manager

Imperial College London / ICNARC

Tel: 020 7831 6878

Mobile: 07714051401

Fax: 020 7831 6879

Email: ukremap-cap@icnarc.org

Coordinating Centers

EUROPE

University Medical Center Utrecht
Heidelberglaan 100
3584 CX

THE NETHERLANDS

Phone +31 (0) 6 277 444 77
Email prepare_icu@umcmrecht.nl

NEW ZEALAND

The Medical Research Institute of
New Zealand
Private Bag 7902, Newtown,
Wellington 6242,
NEW ZEALAND
Phone +64 4 805 0147
Email anne.turner@mrnz.ac.nz

AUSTRALIA

The Australian and New Zealand
Intensive Care Research Centre,
Monash University
Level 3, 533 St Kilda Road
Melbourne, Victoria, 3004
AUSTRALIA
Phone +61 3 9903 0247
Email anzirc@med.monash.edu