SECTION 1: REMAP-CAP VITAMIN C DOMAIN INTERVENTIONS

This domain aims to determine the effectiveness of vitamin C in the treatment for patients who meet platform entry criteria for REMAP-CAP. In this domain, patients are randomised to receive:

- No vitamin C (no placebo)
- Vitamin C (50mg/kg IV every 6 hours for 16 doses)

The allocated intervention should be commenced immediately following allocation reveal at the time of randomisation or after obtaining consent, if required.

SECTION 2: NO VITAMIN C INTERVENTION

**Intervention**
In this intervention, patients are not to receive any IV vitamin C during this hospitalisation, except where administered as part of Total Parenteral Nutrition (TPN).

**Duration of intervention**
The withholding of IV vitamin C (unless in TPN) for this episode or its complications is to continue until the end of study day 28 or hospital discharge, whichever occurs first. Administration of IV vitamin C (unless in TPN) after discharge from ICU will be considered a protocol deviation.

SECTION 3: VITAMIN C INTERVENTION

**Intervention**
In this intervention, patients are to receive a course of IV vitamin C. Each dose is 50 mg/kg, diluted in a 50 or 100ml bag of NS or D5W, or according to local pharmacy advice, given every 6 hours for a course of 16 doses. The maximum dose will be capped at 7.5g (equivalent to 50 mg/kg for a 150kg person).

Infusion rate should not exceed 100 mg/min. If the patient is discharged to the ward before the course is completed, continued administration to complete the course is at the discretion of the treating clinicians. Patients are not to receive any other IV vitamin C, except in TPN or the equivalent very low dose (e.g. 100 mg/day) as part of an IV multivitamin.

**Duration of intervention**
Administration is to commence immediately after allocation is revealed at the time of randomisation. IV vitamin C should be discontinued after the 16th dose or at hospital discharge, whichever occurs first.

For patients enrolled on the ward who are transferred to an ICU, it will be considered a protocol deviation if the treatment course is discontinued. In patients discharged from ICU before completion of the course, continuation of administration to complete the course is at the discretion of the treating clinician.

Administration of any form of vitamin C, unless as part of enteral or parenteral nutrition, should not occur after the course of IV vitamin C is completed. Omission of ≥2 consecutive doses or >4 total doses while in ICU will be considered to be a protocol deviation.

Vitamin C should be discontinued if there is development of an SAE. Study drug can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

SECTION 4: CONCOMITANT CARE

There are no other restrictions on concomitant care.
Factitious hyperglycaemia
Vitamin C is associated with factitious hyperglycaemia when measured on standard hospital glucometers. If treated with insulin or oral hypoglycaemic agents, the patient could experience iatrogenic hypoglycaemia. This risk is highest during the vitamin C intervention period, defined as the period from the commencement of the first dose to 36 hours after the last dose.

Therefore, for patients in the vitamin C intervention period, before and during treatment for hyperglycaemia with insulin or an oral hypoglycaemic agent, we recommend glucose measurement with one of the following accurate methods:

- Hospital core lab instrument
- Point of care arterial blood gas machine with glucose measurements validated in the setting of high vitamin C concentrations, or
- Nova Biomedical StatStrip glucometer

In addition, in patients receiving insulin or oral hypoglycaemic agents, from 36 hours to 7 days after the last dose of vitamin C we suggest glucose monitoring as above. A standard glucometer is also acceptable if the difference between its value and that measured by a validated method listed above is low (e.g. ≤2 mmol/L on two occasions more than 4 hours apart).

If a participant is discharged home less than 7 days after the last dose of vitamin C, we suggest the same approach using the participant’s glucometer, or if not available, a standard hospital glucometer.