SECTION 1: REMAP-CAP ACE2 RAS DOMAIN INTERVENTIONS

This domain aims to determine the effectiveness of different renin-angiotensin system (RAS) modifying strategies for patients with suspected or confirmed COVID-19. In this domain, patients are randomised to receive:

- No RAS inhibitor (no placebo)
- Angiotensin converting enzyme inhibitor (ACEi)
- Angiotensin-II receptor blocker (ARB)
- ARB in combination with DMX-200, a chemokine receptor-2 (CCR2) inhibitor (ARB + DMX-200)

Your site may be participating in any combination of these interventions in this domain, depending on local practice. It is required that all sites will participate in the no RAS inhibitor intervention. The allocated intervention should be commenced immediately following allocation reveal at the time of randomisation or after obtaining consent, if required.

SECTION 2: NO RAS INHIBITOR INTERVENTION

Intervention
Patients allocated to the no RAS inhibitor intervention are not to receive any RAS inhibitor (ACEi or ARB). There is no administration of placebo.

Discontinuation of intervention
Withholding of RAS inhibitors is to continue to the end of study day 10 or hospital discharge, whichever occurs first. Initiation of an ACEi or ARB before the end of study day 10 will be considered a protocol deviation. After study day 10, administration of ARB/ACEi is at the discretion of the treating clinician.

For patients allocated to the no RAS inhibitor intervention who develop hypertension necessitating treatment during the study period, the preference is for non-ABR/ACEi agents to be used where clinically appropriate. Initiation of an ACEi/ARB is permitted but is considered a protocol deviation.

SECTION 3: ANGIOTENSIN CONVERTING ENZYME INHIBITOR INTERVENTION

Intervention
Patients allocated to the ACEi intervention are to be prescribed a course of oral ACEi for 10 days post-randomisation.

Choice of agent and Dosing
Each participating site must pre-specify which ACEi agent they will administer, depending on local preference and availability. A hierarchy of acceptable ACEi agents is specified in Table 3 of the ACE2 RAS DSA.

Dosing and titration of the selected ACEi agent determined by the treating clinician based on blood pressure and electrolytes. Example dosing algorithms for each ACEi agent are listed in Table 3 of the ACE2 RAS DSA.

Duration of intervention
Administration is to commence immediately after allocation is revealed. This course will be continued until the end of study day 10 or hospital discharge, whichever occurs first.

The following reasons should prompt discontinuation of an ACEi, with recommencement when clinically appropriate:

- **Hyperkalaemia**: serum potassium >5.5 mmol/L, although absolute and relative change in serum potassium should be interpreted in conjunction with urine output and change in serum creatinine
- **Significant renal impairment**: eGFR < 15 ml/min/1.73m², new initiation of renal replacement therapy/dialysis, or deteriorating renal function such as >50% increase in creatinine in 48 hours
- **Significant exposure to other nephrotoxic agents**, including IV contrast medium (noting that exposure to other nephrotoxic agents should only occur if no acceptable alternative exists)
- **Clinically relevant hypotension**, including need for significant escalation in therapies such as the initiation of vasopressor when not previously required

Occurrence of angioedema should result in permanent cessation of ACEi agents. Temporary or permanent cessation of the study intervention for any of the reasons listed above is not a protocol deviation.
**SECTION 4: ANGIOTENSIN-II RECEPTOR BLOCKER INTERVENTION**

**Intervention**
Patients allocated to the *ARB intervention* are to be prescribed a course of oral ARB for 10 days post-randomisation.

**Choice of agent and Dosing**
Each participating site must pre-specify which ARB agent they will administer, depending on local preference and availability. A hierarchy of acceptable ARB agents is specified in Table 4 of the ACE2 RAS DSA.

Dosing and titration of the selected ARB agent determined by the treating clinician based on blood pressure and electrolytes. Example dosing algorithms for each ARB agent are listed in Table 4 of the ACE2 RAS DSA.

**Duration of intervention**
Administration is to commence immediately after allocation is revealed. This course will be continued until the end of study day 10 or hospital discharge, whichever occurs first.

The following reasons should prompt discontinuation of an ARB, with recommencement when clinically appropriate:

- **Hyperkalaemia**: serum potassium >5.5 mmol/L, although absolute and relative change in serum potassium should be interpreted in conjunction with urine output and change in serum creatinine
- **Significant renal impairment**: eGFR < 15 ml/min/1.73m², new initiation of renal replacement therapy/dialysis, or deteriorating renal function such as >50% increase in creatinine in 48 hours
- **Significant exposure to other nephrotoxic agents**, including IV contrast medium (noting that exposure to other nephrotoxic agents should only occur if no acceptable alternative exists)
- **Clinically relevant hypotension**, including need for significant escalation in therapies such as the initiation of vasopressor when not previously required

Temporary or permanent cessation of the study intervention for any of the reasons listed above is not a protocol deviation.

**SECTION 5: ARB + DMX-200 INTERVENTION**

**Intervention**
Patients allocated to the *ARB + DMX-200 intervention* are to be prescribed a course of oral ARB and DMX-200 for 10 days post-randomisation.

**Choice of agent and Dosing**
Dosing of the ARB agent should occur as in the ARB only intervention. DMX-200 is administered at a fixed dose of one capsule (120mg) twice daily, at the same time each morning and evening (approximately 12 hours apart). Where possible, patients will take DMX-200 at least 2 hours after any food or at least 30 minutes before the next intake of food. The preferred method of administration is via oral capsules. If oral delivery is not possible the contents of the capsule can be dissolved in at least 15ml water and administered via enteral tube. No titration of DMX-200 dose is required.

**Duration of intervention**
Consideration of temporary discontinuation of ARB therapy should occur as in the ARB intervention outlined above. In these circumstances the ARB should be discontinued, but DMX-200 should continue to be administered.

The development of liver failure or if the patient’s ALT or AST are more than 5x the upper limit of normal, or development of a suspected unexpected adverse reaction (SUSAR) believed to be attributable to the study drug(s) should prompt the permanent discontinuation of both the ARB and DMX-200.

**SECTION 4: CONCOMITANT CARE**

Patients with suspected COVID-19 infection who receive an allocation to an active intervention but who subsequently test negative for COVID-19 infection may have treatment ceased unless the treating clinician believes that doing so is not clinically appropriate. This decision should take into account the known or suspected population incidence of COVID-19 among hospitalised patients and sensitivity of testing for SARS-CoV-2 infection.

For patients allocated to the ARB+DMX-200 intervention, it is requested that AST, ALT, and bilirubin are measured at least once between study days 1 and 5, study days 6 and 10, and study days 11 and 14 post-randomisation. Measurements completed as part of routine care during these periods are acceptable.