COVID-19 ANTIVIRAL DOMAIN ADMINISTRATION GUIDE

SECTION 1: REMAP-CAP COVID-19 ANTIVIRAL DOMAIN INTERVENTIONS

This domain aims to determine the effectiveness of different antiviral strategies for patients with suspected or confirmed COVID-19. In this domain, patients are randomised to receive:

- No antiviral agents active against SARS-CoV-2 (no placebo)
- Lopinavir/ritonavir
- Hydroxychloroquine
- Hydroxychloroquine + lopinavir/ritonavir

Your site may be participating in any combination of these interventions in this domain, depending on local practice. The allocated intervention should be commenced immediately following allocation reveal at the time of randomisation or after obtaining consent, if required.

SECTION 2: NO COVID-19 ANTIVIRAL AGENTS INTERVENTION

Intervention
Patients allocated to the *no antiviral agents* intervention should not receive any antiviral drug intended to be active against SARS-CoV-2 infection.

Discontinuation of intervention
Withholding of antiviral agents for the treatment of COVID-19 is to continue until the end of study day 28 or hospital discharge, whichever occurs first. Administration of antiviral drug for the treatment of COVID-19 after ICU discharge will not be considered to be a protocol deviation.

SECTION 3: LOPINAVIR/RITONAVIR INTERVENTION

Intervention
Patients allocated to the *lopinavir/ritonavir intervention* are to be prescribed course of lopinavir/ritonavir 400mg/100mg administered enterally every 12 hours.

Dosing
Preferred method of administration is two 200/50mg tablets swallowed whole. In patients with a gastric tube who are unable to swallow tablets, preferred method of administration is 5mL of 80/20 mg per mL suspension via gastric tube. **Note that lopinavir/ritonavir suspension may degrade NG tubes if not flushed thoroughly**.
For a patient who cannot swallow whole tablets and when the suspension is not available, four 200/50mg crushed tablets may be administered via enteral tube.

No dose adjustment is required for renal dysfunction or concomitant use of renal replacement therapy. Clinicians should consider dose adjustment in the presence of liver failure.

Duration of intervention
Administration is to commence immediately after allocation is revealed.

This course will be continued until the end of study day 5, regardless of whether the patient remains in ICU.
For patients discharged from ICU between study day 6 and the end of study day 14, cease lopinavir/ritonavir at ICU discharge. If the patient remains in ICU, cease lopinavir/ritonavir at the end of study day 14.
If the patient is readmitted to ICU prior to the end of study day 14, lopinavir/ritonavir should be recommenced.

It will be considered a protocol deviation if two or more sequential doses of lopinavir/ritonavir are missed while the patient remains in ICU, up to the end of study day 14.

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SECTION 4: HYDROXYCHLOROQUINE INTERVENTION

Intervention
Patients allocated to the *hydroxychloroquine intervention* are to be prescribed a course of hydroxychloroquine.

Dosing
A loading dose of 800mg hydroxychloroquine is to be administered enterally, followed by a second dose of 800mg hydroxychloroquine six hours later. Subsequently, 400mg hydroxychloroquine is to be administered every 12 hours for a further 12 doses.
No dose adjustment is required for renal dysfunction or concomitant use of renal replacement therapy. Clinicians should consider dose adjustment in the presence of liver failure.

Duration of intervention
Hydroxychloroquine will be administered until completion of the course detailed above. If the patient is discharged from ICU prior to the end of study day 7, discontinuation of hydroxychloroquine at the time of or after ICU discharge is not considered a protocol deviation.

It will be considered a protocol deviation if more than two sequential doses of hydroxychloroquine are missed while the patient remains in ICU up until the end of study day 7.

SECTION 5: HYDROXYCHLOROQUINE + LOPINAVIR/RITONAVIR INTERVENTION

Patients allocated to the *hydroxychloroquine + lopinavir/ritonavir intervention* will administer both hydroxychloroquine and lopinavir/ritonavir as outlined in the previous sections.

SECTION 6: CONCOMITANT CARE

No additional antiviral agents intended to be active against SARS-CoV-2 should be administered to patients randomised into the COVID-19 Antiviral Domain while the patient remains in hospital up until study day 28.

Patients with suspected COVID-19 who receive an allocation status to one of the active interventions in this domain but for whom all microbiological tests are negative for SARS-CoV-2 infection may have treatment ceased. Ongoing administration of study drug is encouraged as long as there is clinical suspicion of COVID-19. These decisions should take into account the known or suspected sensitivity of testing for SARS-CoV-2.

Concomitant treatment with drugs that are known to interact with lopinavir/ritonavir or hydroxychloroquine must be avoided. If possible, an alternative agent should be considered, allowing for continuation of study drug. If no alternative is acceptable, the treating clinician will need to choose either not to administer the interacting medication or study drug, based on clinical priority.
A list of medications that are commonly used in ICU and are known to interact with lopinavir/ritonavir and hydroxychloroquine are provided as an appendix to the COVID-19 Antiviral DSA. Further information can also be found at http://www.covid19-druginteractions.org/

Some agents in this domain may result in prolongation of the QTc interval. This should be monitored and if necessary study drug can be withheld or ceased. In particular, consider the QTc at ICU discharge when ECG monitoring may cease.