INFLUENZA ANTIVIRAL DOMAIN ADMINISTRATION GUIDE

REMAP-CAP INFLUENZA ANTIVIRAL DOMAIN

This domain aims to determine the effectiveness of different antiviral strategies for patients with CAP with confirmed influenza virus infection. In this domain, patients are randomised to receive:

- No antiviral agents, including oseltamivir (no placebo)
- 5 days of oseltamivir
- 10 days of oseltamivir
- Baloxavir marboxil ("baloxavir") on days 1 and 4
- 5 days of oseltamivir + baloxavir on days 1 and 4
- 10 days of oseltamivir + baloxavir on days 1 and 4

Your site may be participating in all six interventions in this domain or as few as two, depending on local practice. All sites must participate in the five-day oseltamivir intervention.

The allocated intervention should be commenced immediately following allocation reveal at the time of randomisation.

NO ANTIVIRAL AGENTS INTERVENTION

Patients allocated to the *No antiviral agents* intervention should not receive any oseltamivir, baloxavir, or other antiviral agents intended to be active against influenza while the patient remains in hospital, up until study day 28. If oseltamivir or baloxavir have been administered or prescribed prior to randomisation, they should be discontinued immediately.

5-DAY OSELTAMIVIR INTERVENTION

Patients allocated to the *5-day course of oseltamivir* are to be prescribed a five-day course commencing immediately after reveal of allocation (do not include a dose administered before randomisation). This course will be continued until at least the end of study day 5, and no longer than the end of study day 6 (i.e. 10 doses with BD administration).

Dosing of oseltamivir is determined by the treating clinician and the following is provided only as a guide.

- The standard dose of oseltamivir for adult patients is 75 mg enterally, twice per day.
- For children, the standard dose of oseltamivir is 6mg/kg/day, divided into two doses.
- No dosage adjustment is suggested for body mass index, pregnancy, or for extracorporeal membrane oxygenation

Dose adjustment for renal dysfunction will be as per local guidelines. If no local guideline exists, recommendations for dosing based on estimated Glomerular Filtration Rate (eGFR) are outlined in the Influenza Antiviral Domain-Specific Appendix.

It will be considered a protocol deviation if during the 5-day course two or more doses of oseltamivir are missed.

Oseltamivir is not required to be continued after hospital discharge, for patients discharged from hospital before the end of study day 5.

INFLUENZA ANTIVIRAL DOMAIN ADMINISTRATION GUIDE

10-DAY OSELTAMIVIR INTERVENTION

Patients allocated to the *10-day course of Oseltamivir* are to be prescribed a ten-day course commencing immediately after reveal of allocation (do not include a dose administered before randomisation). This course will be continued until at least the end of study day 10, and no longer than the end of study day 11 (i.e. 20 doses with BD administration).

Dosing of Oseltamivir is determined by the treating clinician, however guidance relating to dosing is provided in the previous section (five-day oseltamivir intervention).

It will be considered a protocol deviation if during the 10-day course two or more doses of Oseltamivir are missed.

Oseltamivir is not required to be continued after hospital discharge, for patients who are discharged from hospital before the end of study day 10.

BALOXAVIR INTERVENTION

Patients allocated to receive *Baloxavir on days 1 and 4* are to be prescribed Baloxavir as per the following table, on days 1 and 4 after reveal of allocation. A third dose may be administered on day 7 if, in the opinion of the treating clinician, there has been insufficient clinical improvement in the patient's condition.

No dose adjustment is necessary for renal impairment, hepatic impairment, or ECMO.

Baloxavir is not required to be continued after hospital discharge, for patients who are discharged from hospital before the end of study day 4.

Agent	Weight < 40kg	Weight 40 – 80kg	Weight > 80kg
Baloxavir	2 mg/kg once daily (maximum dose of 40 mg)	40 mg once daily	80 mg once daily

5 DAYS OF OSELTAMIVIR + BALOXAVIR ON DAYS 1 AND 4 INTERVENTION

Patients allocated to receive the *5-day course of oseltamivir + baloxavir on days 1 and 4* are to be prescribed both oseltamivir and baloxavir as outlined in the "*5-day oseltamivir intervention*" and "*baloxavir intervention*" sections above.

10 DAYS OF OSELTAMIVIR + BALOXAVIR ON DAYS 1 AND 4 INTERVENTION

Patients allocated to receive the *10-day course of oseltamivir + baloxavir on days 1 and 4* are to be prescribed both oseltamivir and baloxavir as outlined in the "*10-day oseltamivir intervention*" and "*baloxavir intervention*" sections above.

INFLUENZA ANTIVIRAL DOMAIN ADMINISTRATION GUIDE

CONCOMITANT CARE AND PROTOCOL DEVIATIONS

No additional antiviral agents that are intended to be active against influenza should be administered to patients randomised into the Influenza Antiviral Domain while the patient remains in hospital, up until study day 28.

For patients randomised to receive oseltamivir, baloxavir, or both, administration of any antiviral agent that is intended to be active against influenza after the end of the course of the allocated intervention is not permitted and will be considered a protocol deviation.

For patients who are allocated to receive a course of oseltamivir, baloxavir, or both, and are discharged from the randomising location (e.g. ICU or ward) before the end of the allocated course, it is the responsibility of the treating clinician to prescribe the allocated agent to complete the course. However, it is not the responsibility of the treating clinician or research staff to ensure continuation or completion of the course after discharge from the randomising location. It is not a protocol deviation if the course of the allocated intervention is not completed after discharge from the randomising ward or ICU, and continuation of the allocated interventions is a clinical decision at the discretion of the treating clinician in the new location.