INFLUENZA IMMUNE MODULATION DOMAIN ADMINISTRATION GUIDE

REMAP-CAP INFLUENZA IMMUNE MODULATION DOMAIN

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

- No immune modulation (no placebo)
- Tocilizumab
- Baricitinib

Your site may be participating in all three interventions in this domain or as few as two, depending on local practice.

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

NO IMMUNE MODULATION INTERVENTION

Patients allocated to the *No immune modulation* intervention should not receive any targeted immune modulation therapy intended to be active against influenza while the patient remains in hospital, up until study day 28. Systemic corticosteroids may be administered, either as an allocated intervention in the Corticosteroid Domain of REMAP-CAP, or as determined by the treating clinician.

TOCILIZUMAB INTERVENTION

Patients allocated to the *Tocilizumab intervention* are to be prescribed a single dose of tocilizumab, administered via a intravenous infusion as soon as possible after reveal of allocation.

Dosing of tocilizumab is dependant on age and weight:

- Participants weighing ≥30kg are to be administered a single dose of **8mg/kg** measured or estimated body weight, with a total dose not exceeding 800mg.
- Participants weighing <30kg are to be administered a single dose of **12mg/kg** measured or estimated body weight

The appropriate dose of tocilizumab Is to be mixed in a 100ml bag of 0.9% saline, after removing an equivalent volume of saline (0.4ml/kg) to ensure that the total volume is 100ml when the drug is added.
In participants weighing < 30kg, tocilizumab may be mixed in a 50ml bag of 0.9% saline, if the treating clinician believes that administration in 100ml of saline is inappropriate.

The tocilizumab infusion should then be administered as an intravenous infusion via a peripheral or central line over one hour. It is recommended that the infusion is administered at a rate of 10mls per hour for 15 minutes, and then increased to 130mls per hour for 45 minutes. If the tocilizumab is administered in 50mL, the infusion rate should be half that specified above.
Alternatively, where available, local guidelines may be followed for the administration of the infusion of tocilizumab over one hour.

At the completion of the infusion of study drug, at least 20mls of 0.9% saline should be used to flush the drug through the giving set.

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BARICITINIB INTERVENTION

Patients allocated to the *Baricitinib intervention* are to be prescribed a ten-day course commencing as soon as possible after reveal of allocation.

Dosing of Baricitinib is based on age and renal function:

Age	eGFR	Baricitinib Dose
2 – 9 years	≥60 mL/min/1.73m^2	2mg daily
	≥30 and <60 mL/min/1.73m^2	1mg daily
	<30 mL/min/1.73m^2	Withhold dose
	Receiving renal replacement therapy	Withhold dose
≥ 9 years	≥60 mL/min/1.73m^2	4mg daily
	≥30 and <60 mL/min/1.73m^2	2mg daily
	≥15 and <30 mL/min/1.73m^2	1mg daily
	<15 mL/min/1.73m^2	Withhold dose
	Receiving renal replacement therapy	Withhold dose

For patients who are unable to swallow whole tablets, baricitinib may be dispersed in water and delivered via an enteral feeding tube.

If the required dose is 1mg daily and 1mg tablets are not available, a 2mg tablet may be split using a tablet splitter, with half a 2mg tablet administered daily. Consult your pharmacy and follow relevant precautions before splitting baricitinib tablets. Alternatively, 2mg of baricitinib can be given every second day as an equivalent of a dose of 1mg per day.

CONCOMITANT CARE AND PROTOCOL DEVIATIONS

No additional agents, other than those allocated within REMAP-CAP that are intended to modulate the immune response to influenza should be administered to patients randomised into the Influenza Immune Modulation Domain while the patient remains in hospital, up until study day 28.
The use of corticosteroids, other than those specified by assignment in the Corticosteroid Domain of REMAP-CAP, for a new indication (e.g. bronchospasm or septic shock) is at the discretion of the treating clinician.

For patients who are allocated to receive a course of tocilizumab or baricitinib 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 randomizing team to prescribe the allocated agent to complete the course. However, it is not their responsibility to ensure continuation or completion of the course after discharge from the randomising location. The continued administration of the allocated intervention outside of the participating clinical area is a clinical decision at the discretion of the treating clinician. Under such circumstances, discontinuation of the intervention prior to completion of the course is not considered a protocol deviation.

Any allocated immune modulation intervention should be discontinued if there is development of an SAE which, in the opinion of the treating clinician, could be related to participation in this domain. Allocated interventions may be discontinued at any time by the treating clinician if doing so is considered to be in the best interests of the patient.