MACROLIDE DURATION DOMAIN ADMINISTRATION GUIDE

MACROLIDE DURATION DOMAIN INTERVENTIONS

This domain aims to evaluate duration of macrolide therapy for patients with severe community-acquired pneumonia.
In this domain participants are randomised to receive:

- Standard course macrolide discontinued between day 3 and day 5
- Extended course macrolide for 14 days or hospital discharge, whichever occurs first

REVEAL OF ALLOCATED INTERVENTION

Participants who are allocated to receive a beta-lactam + macrolide intervention within the Antibiotic Domain may be eligible to receive an allocation in the Macrolide Duration Domain.

For eligible participants, allocation in the Macrolide Duration Domain is obtained by navigating to the *Macrolide Reveal* page on the study database. Reveal of allocation can occur any time after randomisation, until the end of study day 5 but should be done as soon as sufficient information is available. The information required is shown on the following page.

CHOICE OF MACROLIDE AND DOSING

The dose, route and frequency of administration of macrolide antibiotics are not specified in the protocol but the following guidance is provided:

- Initial IV administration is strongly preferred
- The preferred IV macrolide is Azithromycin, but others may be substituted based on local practice
- Preferred enteral macrolide is azithromycin, but enteral clarithromycin or roxithromycin may be substituted
- Erythromycin cannot be used as the intervention macrolide in this domain

The following recommended minimum doses are provided as guidance and should be modified in accordance with local guidelines and/or practice.

Agent	Dose
Azithromycin	500mg daily
Clarithromycin	500mg daily
Roxithromycin	150mg q12hr

The dose of all macrolides is the same for IV and enteral administration. No dose adjustment is required for impaired renal function or if the patient is receiving renal replacement therapy.
A switch from IV to enteral macrolide is permitted once the patient is clinically improving, as determined by the treating clinician.
Azithromycin and Roxithromycin are preferred to Clarithromycin in pregnant participants.

DURATION OF MACROLIDE THERAPY

Duration of macrolide therapy is determined by the study allocation (3-5 vs 14 days), regardless of any other changes to other antibiotics for the treatment of CAP or new infections.

If allocated to the standard course intervention, cease after 3 days or immediately, if allocation is revealed after study day 3. If allocated to extended course intervention, continue for 14 days or until hospital discharge, whichever occurs first.

If the patient is discharged from the randomising clinical area (e.g., ICU or ward) prior to the last day of therapy:

1. Evaluate the patient's QT interval if continuous cardiac monitoring will not be continued
2. Prescribe any remaining duration of macrolide therapy on the medication chart
3. It is not the responsibility of research or medical staff to ensure the macrolide is administered on the ward

Discontinue the macrolide **prior to the completed course, ONLY in the following scenarios:**

- The patient experiences a serious adverse event (SAE) that is thought to be possibly, probably or definitely related to the macrolide
- The treating clinician believes it is not in the patients best interest to continue (for example, new QT prolongation)

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CONCOMITANT CARE

Low dose erythromycin (up to 250mg q6h) to promote gastric emptying is permitted, but alternative agents should be used in preference. Any subsequent change of antibiotics, other than macrolides, based on availability of microbiological data, will be permitted at the treating clinician's discretion.

Please refer to the *Antibiotic Administration Guide* regarding administration of additional antibiotics.

WORK FLOW

