IMP

TOAST

GUIDANCE SHEET 7

Summary

Infants participating in TOAST Study are randomised to either IMP or matched volume placebo, to be administered for 12-months post-surgery. The parents and clinical team will be blinded to the allocation (please refer to **TOAST Guidance Sheet 5: Randomisation**).

During the initial hospital admission, the clinical team will decide whether to give the TOAST medication intravenously or enterally, guided by the infant's tolerance of enteral feed. Whilst an infant is nil-by-mouth, the IMP/placebo will initially be administered intravenously, until they are able to feed enterally.

Intravenous TOAST Medication	Enteral TOAST Medication
0.5 mg/kg intravenously, once daily until infants are able to feed enterally	1 mg/kg enterally, once daily
Use while the infant is nil-by-mouth *(administer as a bolus infusion over 10-30 minutes)*	Use when the infant is able to feed enterally
Each Pack ID refers to 1 box containing 7 single-use vials	Each Pack ID refers to 1 box containing: • 6 bottles of medication • 6 dosing syringes • 6 bottle adaptors • 6 grey replacement caps
Reconstitute with sterile 0.9% sodium chloride for intravenous use, to a strength of 0.5 mg/ml *(refer to instructions below)*	Reconstitute each bottle with 64 ml sterile water *(refer to instructions below). Parents to use 'cooled boiled water' following discharge home.*
Store at room temperature, discard excess once reconstituted	Store at room temperature until reconstituted, then in a fridge for up to 28 days. Discard any remaining medication after 28 days and reconstitute a new bottle.

Who can Prescribe?

Staff prescribing TOAST Study medication must be authorised on the Delegation Log. Nurses or pharmacists may be authorised on the Delegation Log provided this is within local hospital practice.

How to Prescribe

Following randomisation, prescribe the TOAST Study medication as soon as possible. Enter the prescription electronically or on the infant's drug chart as follows:

- While nil-by-mouth:
  "TOAST Study medication [enter alpha-numeric pack code (A1234)] reconstituted according to instructions, 1 ml/kg intravenous once a day"

- When tolerating enteral medication:
  "TOAST Study medication [enter alpha-numeric pack code (A1234)] reconstituted according to instructions, 0.5 ml/kg oral/ng once a day"

The TOAST medication should be continued until 1 year of age.

TOAST is funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme (project reference 131136).
The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

FUNDED BY NIHR | National Institute for Health and Care Research

NPEU Clinical Trials Unit

OXFORD POPULATION HEALTH NPEU

Who Can Prepare, Administer and Dispose of Medication?

Staff preparing, administering and disposing of TOAST Study medication at bedside **must** have completed:

- Any training required by their local hospital,
- TOAST-specific training (including reading and signing '**TOAST for Neonatal Bedside Staff: Study Summary and Preparation, Administration and Disposal of Allocated IMP**' and this Guidance Sheet)
- Be authorised by the PI (or delegate) on the Delegation Log.

You may also find it helpful to shadow a delegated colleague while they prepare/administer the TOAST Study medication.

How to Prepare TOAST Medication

The volume of TOAST medication to be administered will be determined according to the infant's current weight. .

Infants will be allocated two Pack ID numbers during randomisation. These numbers will correspond to one pack containing 7 single-use vials of 40 mg esomeprazole or placebo, and one pack containing 6 bottles of omeprazole or placebo, syringes, adaptors and replacement caps. Write both Pack ID numbers on the infant's **TOAST Daily Dosing Log**.

Select the type (intravenous or enteral) and volume of medication to give based on the infant's current feeding and working weight.

Intravenous TOAST Medication

Once daily until infants are able to feed enterally, until 1 year of age

Each vial provides up to one dose of medication, therefore each pack, containing 7 vials, can provide up to 7 days' worth of intravenous medication. Packs should be stored at room temperature in the neonatal unit. Each vial is concealed in a cardboard carton to prevent unblinding, with the stopper accessible to allow reconstitution.

Do not remove the tamper-proof sticker on the cardboard carton.

7 vials in secondary packaging

Vial in cardboard blinding shroud

GUIDANCE SHEET 7

TOAST is funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme (project reference 131136).
The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

FUNDED BY NIHR | National Institute for Health and Care Research

NPEU Clinical Trials Unit

OXFORD POPULATION HEALTH NPEU

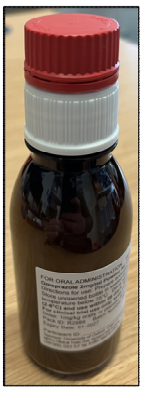
The cardboard shroud should not be removed during reconstitution, administration or disposal of the TOAST intravenous medication.
It is important to follow the steps below exactly to ensure adequate reconstitution of the blinded vial of TOAST intravenous medication:

1. Remove the grey cap from the top of the vial and clean the stopper as per usual practices.
   Do not remove the cardboard blinding shroud
2. Reconstitute the medication vial with 5 ml of 0.9% sodium chloride (with marketing authorisation) to obtain a solution containing 8 mg in 1 ml (or placebo).
3. Invert the vial 5 times to dissolve the powder.
4. Allow the vial to stand for at least 5 minutes to allow the powder to dissolve.
   Use the TOAST digital timer
   Follow steps 3 and 4 exactly, as you will not be able to visually check that the powder has dissolved due to study blinding
   You now have 5 ml medication in the vial at a concentration of 8 mg/ml.
5. Withdraw 1 ml of the medication solution from the vial into a syringe and add a further 15 ml of 0.9% sodium chloride. The resultant solution has a total volume of 16 ml and contains 0.5 mg in 1 ml (or placebo).
6. Move the syringe gently to disperse the solution evenly.
7. Withdraw the required volume of medication according to the prescription from the syringe prepared in Step 5 into a new syringe. Discard any remaining solution.
8. Administer as a bolus infusion over 10 to 30 minutes, **as soon as possible and within 2 hours of reconstitution.**

Dispose of the vial (including any excess) via normal waste routes. Should the participant be nil-by-mouth for longer than 7 days, additional TOAST intravenous medication can be allocated on the randomisation website *(*please refer to **TOAST Guidance Sheet 5: Randomisation**).

<u>Enteral TOAST Medication</u>
Once daily while able to feed enterally, until 1 year of age
Each bottle (sealed in a foil pouch) contains 28-days supply of enteral medication, therefore each pack of 6 bottles contains 6-months supply. Packs can be stored at room temperature in the neonatal unit. Once a bottle is reconstituted, it should be stored in the fridge for 28 days. After 28 days, any leftover medication should be discarded according to normal waste routes and a new bottle of enteral medication reconstituted.

Secondary packaging



6x bottles in foil pouch, 6x oral syringes, 6x bottle adaptors, 6x grey lids

GUIDANCE SHEET 7

TOAST is funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme (project reference 131136).
The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

FUNDED BY NIHR | National Institute for Health and Care Research

NPEU Clinical Trials Unit

OXFORD POPULATION HEALTH NPEU

To reconstitute a bottle of TOAST enteral medication:

1. Remove a bottle from the foil pouch.
2. Check that the tamper-evident seal on the bottle is still intact. If the seal looks damaged, do not use the medication and contact the TOAST Study team.
3. The bottle is a two-compartment system and contains powder in both the red cap and the bottle. Shake the bottle for 10 seconds to loosen the powders.
4. Twist the red cap anti-clockwise until the seal is broken. The powder and a red mixing disc will drop from the red cap into the bottle. The red mixing disc should remain in the bottle, and should not be removed after reconstitution.
5. Twist the red cap back to the original position, making sure it is securely fastened onto the bottle.
6. Shake the bottle vigorously for 10 seconds to mix the powders.
7. Tap the base of the bottles 3 times to make sure all powder is in the bottle and not in the cap.
8. Reconstitute the powder with 64 ml sterile water (boiled and cooled water to be used by parents at home) using a suitable measuring device.
9. Securely fasten the red cap onto the bottle and shake vigorously for 30 seconds.
10. Finally, attach the bottle adaptor. To do this, remove the cap and red ring and throw these away. Insert the colourless, transparent bottle adaptor, and replace the red cap with the grey plastic screw cap. Leave the medication at room temperature for 15 minutes before use, to reach its final consistency.

The dosage for the enteral medication is 1 mg/kg, and the concentration is 2 mg/ml. The volume to be given is 0.5ml/kg, which can be given according the prescription.

Teaching Parents

Please demonstrate reconstitution and administration of the enteral medication to parents before discharge home. If several doses are administered during their stay, use a 'see one, do one' approach. Training should be confirmed on the TOAST Contact Details form (part of the TOAST Randomisation website). Provide parents with the **TOAST Medication Guide for Parents** leaflet as part of their Discharge pack. They can also view the **Trial Medication Video** on the TOAST website, which they can access via the TOAST app.

IMP Administration

Record administration of TOAST Medication on the **Daily Dosing Log**. Paper copies of can be found in the TOAST Document box. Completed Daily Dosing Logs should be inputted onto the study database – OpenClinica – by a staff member listed on the TOAST Delegation Log.

Always check that the 4-digit Study Number listed on the TOAST medication label matches the Study Number of the TOAST participant prior to administering the IMP.

<u>Intravenous TOAST Medication</u>

Once the solution has been prepared and the volume calculated, administer into the infant's existing intravenous line as per local practices.

TOAST is funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme (project reference 131136).
The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

FUNDED BY NIHR | National Institute for Health and Care Research

NPEU Clinical Trials Unit

OXFORD POPULATION HEALTH NPEU

Enteral TOAST Medication

Once the volume is calculated, insert the syringe (provided in medication pack) into the bottle adaptor and turn the bottle upside down. Draw a small amount of medication into the syringe and push the plunger upward to send the medication back into the bottle, in order to remove any bubbles. Pull the plunger down to draw the correct volume, then turn the bottle back so it is the right way up and remove the syringe. Administer the medication to the infant. Secure the lid on the bottle and return it to the fridge. Administration of the medication to the infant should follow local practice.

Pausing IMP Administration

Should a TOAST participant be readmitted to hospital following discharge home, or it is not possible to administer enteral TOAST medication for a clinical reason, you should not switch back to administering intravenous TOAST medication. Please let the TOAST Study team know that a pause in IMP administration is required.

IMP Issues

Should there be a problem, for example, a vial breaks, use the next vial in the pack. If all vials/bottles in the pack are used, log-in to the TOAST Randomisation website to allocate a new pack to that participant (please refer to **TOAST Guidance Sheet 6: Pack Management and Pharmacy**).

Should you need assistance allocating a new pack, or encounter further problems please contact the TOAST Study team on 01865 289278 during office hours. If an emergency occurs outside of office hours, contact the out-of-hours call centre on 0800 138 5451 (please refer to **TOAST Guidance Sheet 14: Emergency Queries and Unblinding**).

Missed Doses and Discontinuation of Intervention

A missed dose does not constitute a permanent discontinuation of TOAST medication (please refer to **TOAST Guidance Sheet 13: Discontinuation of Medication and Change of Consent**).

TOAST is funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme (project reference 131136).
The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

FUNDED BY NIHR | National Institute for Health and Care Research

NPEU Clinical Trials Unit

OXFORD POPULATION HEALTH NPEU