Safety & Incident Reporting

The safety reporting window for TOAST Study is **from when the infant starts TOAST medication up to one year of age**.

In this population we anticipate day-to-day fluctuations of pre-existing conditions, and a small number of deaths. As a result, many adverse events are foreseeable due to the nature of the participant population and their routine care/treatment. Consequently, only those adverse events or adverse reactions **identified as serious (SAEs) and related to the trial medication, and all deaths** will be reported for the trial.

Definitions and Acronyms

Adverse Event(s) AE(s)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction AR	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between the TOAST medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the TOAST medication qualify as adverse reactions.
Assessment of Causality	The relationship of each adverse event to the TOAST medication must be determined by a medically qualified individual according to the following definitions: ● **Unrelated** – where an event is not considered to be related to the TOAST medication ● **Possibly** – although a relationship to the TOAST medication cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible ● **Probably** – the temporal relationship and absence of a more likely explanation suggest the event could be related to the TOAST medication ● **Definitely** – the known effects of the TOAST medication, its therapeutic class or based on challenge testing suggest that the TOAST medication is the most likely cause All AEs (SAEs) labelled 'possibly', 'probably' or 'definitely' will be considered as related to the TOAST medication.
Foreseeable	Foreseeable SAEs are those events which are foreseen in the patient population or as a result of the routine care/treatment of a patient.
Investigational Medicinal Product IMP	In TOAST Study there are two active IMPs – esomeprazole and omeprazole - and 2 matched placebos, depending on whether the infant is able to take medication enterally or intravenously.

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Oesophageal Atresia/Tracheo-Oesophageal Fistula OA/TOF	In TOAST Study, the target population are newborn infants with oesophageal atresia and distal tracheo-oesophageal fistula (OA/TOF) undergoing surgical repair.
Reference Safety Information RSI	In TOAST Study, the Reference Safety Information (RSI) will be the latest approved and relevant Summary of Product Characteristics (SmPC) for both esomeprazole and omeprazole.
Serious Adverse Event(s) SAE(s)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction(s) SAR(s)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to the TOAST medication, based on the information provided.
Summary of Product Characteristics SmPC	A document describing the properties and the officially approved conditions of use of a medicine. Summaries of product characteristics (SmPCs) form the basis of information for healthcare professionals on how to use the medicine safely and effectively.
Suspected Unexpected Serious Adverse Reaction SUSAR	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: • In the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product • In the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question.

What to report?

Due to the established safety profile of the TOAST medication, the only SAEs to be reported are:

- **All instances of death, whether related to OA/TOF or not**
- **SAEs that are causally related to the trial medication (SARs – Serious Adverse Reactions)**

For SAE/SARs that require reporting, the Chief Investigator or Safety Delegate will assess the expectedness.

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Safety & Incident Reporting

What NOT to report?

The following events are expected in this population, and data will be collected during the study. These events should NOT be reported as SAEs:

- Anastomotic stricture
- Anastomotic leak
- Recurrent fistula
- Chest infection
- Oesophagitis
- Admission to hospital and/or prolongation of hospital stay
- Acute life-threatening event/cyanotic spell
- Symptomatic gastro-oesophageal reflux

When to report?

While the infant is an inpatient at the recruiting site, report any death or SAR to the TOAST Study team at NPEU CTU as soon as possible and within 24 hours of awareness.

Following discharge from recruiting site, collect SARs at 3-monthly follow-up appointments whilst completing the Outcome CRF and report to NPEU CTU within 24 hours of awareness. Where necessary, e.g. where an infant does not attend a 3-monthly appointment, information should be obtained via a phone-call to the parents, or using electronic patient records and by contacting Continuing Care Sites.

How to report?

- OpenClinica: staff with access to the trial electronic database should complete the SAE form directly onto this database. This will trigger an automatic email notification to the TOAST Study team at NPEU CTU.
    - Follow-up SAE information can be entered directly into OpenClinica
- PDF: editable pdfs with instructions, are provided in the TOAST eISF and on the TOAST website to enable anyone to report an SAE. The completed SAE form must be uploaded via the **NPEU Document Upload Tool**.
    - The TOAST Study team will issue electronic signature requests to PIs/Safety Delegates.
    - If you have follow-up SAE information, complete a new form and or upload via the **NPEU Document Upload Tool**.
- Where the above routes are not possible, report the SAE to the TOAST Study team at NPEU by telephone (**01865 289278** during office hours, or out-of-hours contact the call centre on **0800 138 5451**). Once the NPEU have been made aware, an SAE form must be completed.

Incident Reporting

A trial-related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process) or from GCP or any applicable regulatory requirements.

All deviations from TOAST protocol should be documented on paper or electronic Incident Forms and uploaded via the **NPEU Document Upload Tool.** Please ensure that patient identifying information is not included on the Incident Form.

NPEU CTU staff will complete an assessment and, where applicable, complete the relevant corrective and preventative action plan. Final signed copies should be saved in the eISF.

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