Treating Oesophageal Atresia to Prevent Stricture

Title: TOAST - Treating Oesophageal Atresia to prevent Stricture

Full Title: TOAST - A multicentre, randomised trial of gastric acid suppression medication for treating oesophageal atresia to prevent stricture

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2 SUMMARY OF STUDY

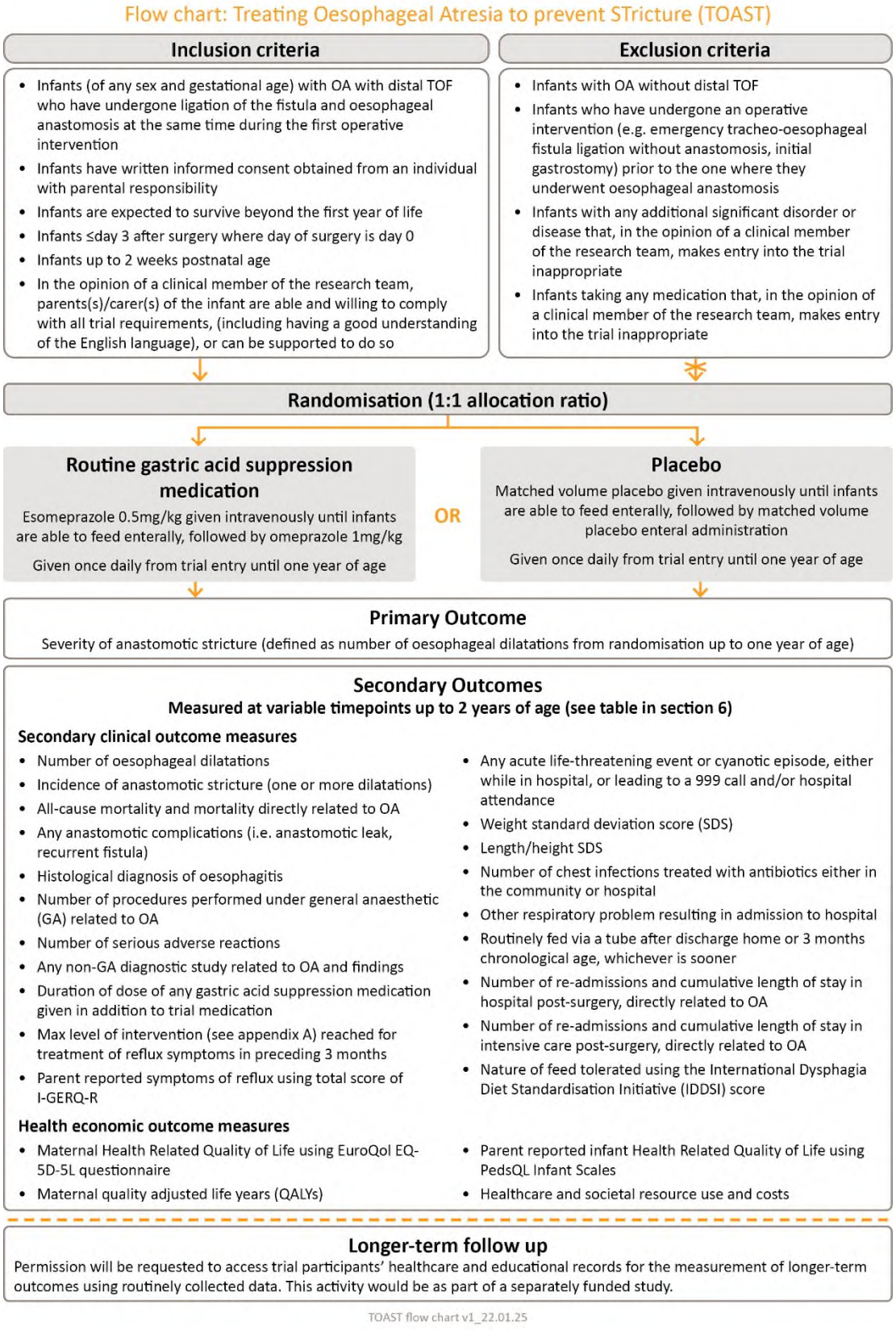
Oesophageal atresia is a rare (about 1 in 2,500–3,000 births) condition where babies are born without an intact oesophagus (swallowing tube) and usually have a connection between their trachea (windpipe) and their stomach instead. It requires urgent lifesaving surgery in the first days of life. In the UK, every year around 150 babies are born with this condition.

The surgery rebuilds the oesophagus, which is usually successful but sometimes there are problems. One of these problems is reflux; where the acid content of the stomach comes back into the oesophagus and can cause regurgitation of feeds and/or damage to the oesophagus. Another problem that sometimes occurs is that the join where the oesophagus has been rebuilt can narrow down (called a stricture) and cause difficulties with feeding and swallowing. It is thought that strictures can be caused or made worse by reflux. Some surgeons who look after these babies use a medication to suppress the acid produced by the stomach even if there are no symptoms of reflux. A major reason for this is to reduce the risk of strictures forming. Despite this being an apparently popular option (about half of babies with oesophageal atresia are treated with this medication) (1) the evidence for using this medication is weak. In fact, some studies of babies with oesophageal atresia have actually found that strictures are more common in babies treated with acid suppression than in those who were not. In addition, there is some suggestion that taking the medicine can increase the chance of certain types of infection.

We want to answer the question, “Should babies born with oesophageal atresia all be treated routinely with antacid medication to reduce strictures?” In this randomised controlled study, babies with oesophageal atresia are allocated at random to either being given acid suppressing medicine or not. They are then followed up for 2 years, including maternal questionnaire collection where possible, to see if they develop a stricture and require any further treatments.

This is a multicentre double-blind, randomised placebo-controlled study. The study includes an 18 month pilot phase, with criteria at the end of this period to decide whether to progress to the main study or not. The study overall has a 5 year recruitment period, where babies are in the study for 2 years, with babies recruited in the last year of recruitment only being followed up until they are 1 year old.

3 FLOW CHART


Flow chart: Treating Oesophageal Atresia to prevent STricture (TOAST)
Inclusion criteria
Infants (of any sex and gestational age) with OA with distal TOF who have undergone ligation of the fistula and oesophageal anastomosis at the same time during the first operative intervention
Infants have written informed consent obtained from an individual with parental responsibility
Infants are expected to survive beyond the first year of life
Infants ≤day 3 after surgery where day of surgery is day 0
Infants up to 2 weeks postnatal age
In the opinion of a clinical member of the research team, parents(s)/carer(s) of the infant are able and willing to comply with all trial requirements, (including having a good understanding of the English language), or can be supported to do so
Exclusion criteria
Infants with OA without distal TOF
Infants who have undergone an operative intervention (e.g. emergency tracheo-oesophageal fistula ligation without anastomosis, initial gastrostomy) prior to the one where they underwent oesophageal anastomosis
Infants with any additional significant disorder or disease that, in the opinion of a clinical member of the research team, makes entry into the trial inappropriate
Infants taking any medication that, in the opinion of a clinical member of the research team, makes entry into the trial inappropriate
Randomisation (1:1 allocation ratio)
Routine gastric acid suppression medication
Esomeprazole 0.5mg/kg given intravenously until infants are able to feed enterally, followed by omeprazole 1mg/kg
Given once daily from trial entry until one year of age
OR
Placebo
Matched volume placebo given intravenously until infants are able to feed enterally, followed by matched volume placebo enteral administration
Given once daily from trial entry until one year of age
Primary Outcome
Severity of anastomotic stricture (defined as number of oesophageal dilatations from randomisation up to one year of age)
Secondary Outcomes
Measured at variable timepoints up to 2 years of age (see table in section 6)
Secondary clinical outcome measures
Number of oesophageal dilatations
Incidence of anastomotic stricture (one or more dilatations)
All-cause mortality and mortality directly related to OA
Any anastomotic complications (i.e. anastomotic leak, recurrent fistula)
Histological diagnosis of oesophagitis
Number of procedures performed under general anaesthetic (GA) related to OA
Number of serious adverse reactions
Any non-GA diagnostic study related to OA and findings
Duration of dose of any gastric acid suppression medication given in addition to trial medication
Max level of intervention (see appendix A) reached for treatment of reflux symptoms in preceding 3 months
Parent reported symptoms of reflux using total score of I-GERQ-R
Any acute life-threatening event or cyanotic episode, either while in hospital, or leading to a 999 call and/or hospital attendance
Weight standard deviation score (SDS)
Length/height SDS
Number of chest infections treated with antibiotics either in the community or hospital
Other respiratory problem resulting in admission to hospital
Routinely fed via a tube after discharge home or 3 months chronological age, whichever is sooner
Number of re-admissions and cumulative length of stay in hospital post-surgery, directly related to OA
Number of re-admissions and cumulative length of stay in intensive care post-surgery, directly related to OA
Nature of feed tolerated using the International Dysphagia Diet Standardisation Initiative (IDDSI) score
Health economic outcome measures
Maternal Health Related Quality of Life using EuroQol EQ-5D-5L questionnaire
Maternal quality adjusted life years (QALYs)
Parent reported infant Health Related Quality of Life using PedsQL Infant Scales
Healthcare and societal resource use and costs
Longer-term follow up
Permission will be requested to access trial participants' healthcare and educational records for the measurement of longer-term outcomes using routinely collected data. This activity would be as part of a separately funded study.
TOAST flow chart v1_22.01.25

4 SYNOPSIS

Study Title	**TOAST** - A multicentre, randomised trial of gastric acid suppression medication for treating oesophageal atresia to prevent stricture
Internal ref. no. (or short title)	**TOAST** - **T**reating **O**esophageal **A**tresia to prevent **ST**ricture
Study registration	ISRCTN 96912679
Sponsor	University of Oxford
Funder	NIHR131136
Clinical Phase	Phase III
Study Design	Multicentre double-blind, randomised placebo-controlled trial (with an internal pilot and health economic evaluation)
Study Participants	Newborn infants with oesophageal atresia and distal tracheo-oesophageal fistula undergoing surgical repair
Sample Size	211 infants
Planned Study Period	The planned study period is from 01/07/2025 to 31/10/2031. Individual participants will receive the intervention as soon as possible after surgical repair until 1 year chronological age. The final follow-up assessment will be conducted at 2 years chronological age (for approximately 80% of infants)
Planned Recruitment period	60 month recruitment period (including an 18 month internal pilot period), planned 01/07/2025 – 30/06/2030
Primary Objective	To compare the severity (defined as the number of dilatations performed) of anastomotic stricture during the first year of life in infants randomised to receive routine gastric acid suppression medication versus those randomised to matched placebo.
Secondary Objectives	To compare the severity and incidence of anastomotic stricture during the first 2 years of life in infants randomised to receive routine gastric acid suppression medication versus those randomised to matched placebo Outcomes include: ● Number of oesophageal dilatations ● Incidence of anastomotic stricture (one or more dilatations) ● Histological diagnosis of oesophagitis
	To investigate the influence of routine gastric acid suppression medication versus matched placebo on other important clinical outcomes in infants randomised to receive routine gastric acid suppression medication versus those randomised to matched placebo at 1 and 2 years of age. Outcomes include: ● All-cause mortality ● Mortality directly related to OA ● Any anastomotic complications (i.e., anastomotic leak, recurrent fistula)

	● Number of procedures performed under general anaesthetic (GA) related to OA (e.g. upper gastrointestinal (UGI) endoscopy, bronchoscopy/ microlaryngobronchoscopy (MLB), oesophageal manometry, gastrostomy, fundoplication) ● Number of serious adverse reactions ● Any non-GA diagnostic study related to OA (e.g. contrast study, pH impedance study), and findings ● Duration of dose of any gastric acid suppression medication given in addition to study medication ● Max level of intervention (based on the treatment flow diagram – see appendix A) reached for treatment of reflux symptoms in preceding 3 months (described using summary statistics) ● Parent-reported symptoms of reflux using total score of I-GERQ-R ● Any acute life-threatening event or cyanotic episode, either while in hospital, or leading to a 999 call and/or hospital attendance ● Weight standard deviation score (SDS) ● Length/height SDS ● Number of chest infections treated with antibiotics either in the community or hospital ● Other respiratory problem resulting in admission to hospital ● Routinely fed via a tube (nasogastric or gastrostomy) after discharge home or 3 months chronological age, whichever is sooner ● Number of re-admissions to hospital directly related to OA ● Cumulative length of stay in hospital post-surgery, directly related to OA ● Number of re-admissions to intensive care directly related to OA ● Cumulative length of stay in intensive care post-surgery, directly related to OA ● Nature of feed tolerated using the International Dysphagia Diet Standardisation Initiative (IDDSI) score
	To investigate the cost and consequences of routine gastric acid suppression medication versus matched placebo.
Intervention(s) IMP	Esomeprazole (0.5mg/kg intravenously) once daily until infants are able to feed enterally followed by omeprazole (1mg/kg orally) once daily until 1 year of age
Comparator	Matched volume placebo given intravenously once daily until infants are able to feed enterally followed by matched volume placebo enteral administration, once daily until 1 year of age

5 ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol 5 Dimension 5 Level Questionnaire
GA	General Anaesthetic
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
GP	General Practitioner
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDDSI	International Dysphagia Diet Standardisation Initiative
I-GERQ-R	Infant Gastroesophageal Reflux Questionnaire Revised
IMP	Investigational Medicinal Product
IP	Intellectual Property
IV	Intravenous
MHRA	Medicines and Healthcare products Regulatory Agency
MLB	Microlaryngobronchoscopy
MP	Monitoring Plan
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research

NNU	Neonatal unit
NPEU	National Perinatal Epidemiology Unit
OA	Oesophageal Atresia
PedsQL	Pediatric Quality of Life Inventory
PI	Principal Investigator
PMG	Project Management Group
PPI	Patient and Public Involvement
QALYs	Quality Adjusted Life Years
RA	Risk Assessment
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGEA	Research Governance, Ethics & Assurance
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDS	Standard Deviation Score
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TOF	Tracheo-oesophageal fistula
TOFS	Charity providing support to families affected by Oesophageal Atresia and Tracheo-oesophageal fistula (https://tofs.org.uk/)
TMF	Trial Master File
TSC	Trial Steering Committee
UGI	Upper Gastrointestinal

6 BACKGROUND AND RATIONALE

Oesophageal atresia (OA) is a rare congenital anomaly affecting 1 in 2,500–3,000 live-born babies worldwide, approximately 150 cases per year in the UK (1). Previously a condition with high mortality, survival has improved and the focus has shifted from ensuring survival to reducing morbidity, achieving excellent clinical outcomes and optimising quality of life. In this context, it is imperative to assess interventions consistent with these new aims, particularly since affected infants may have multiple morbidities due to a number of co-existing medical problems.

In infants born with OA there is no communication between the upper oesophagus and the stomach and surgical repair of this congenital anomaly is required for survival. This is usually done in the first few days (up to one week) of life, aiming to join the upper and lower oesophageal segments, thereby creating a continuous oesophagus and allowing feeding via the normal route into the stomach. Following this repair, a frequent complication is the formation of a stricture at the anastomosis between the upper and lower oesophageal segments. This occurs in 30–44% of cases (some series as high as 60%) and causes significant burden for infants, parents, families and the healthcare service (2). The burden of healthcare is already high for parents of a child born with OA: these infants often have multiple morbidities with 50% being born with an additional congenital anomaly (3).

Not every infant will develop a stricture but once a stricture is present, it may cause significant difficulty with swallowing and feeding as food does not pass easily down the repaired oesophagus. The most obvious effect of this is that the infant develops difficulty with feeding, which becomes slow and there may be choking and regurgitation. Many infants, however, have more significant difficulties. At times, infants may be at acute risk of aspiration (feed going into the windpipe and causing suffocation). As a result, all parents of an infant born with OA are taught infant resuscitation skills prior to discharge and it is not uncommon for a parent to have to use this training. The lack of adequate nutrition means that infants suffering from stricture often suffer from faltering growth (lack of growth and development), sometimes weight loss and, ultimately, may be at risk of delayed neuro-cognitive development. The disease burden and stress on the family can thus be very high, which may be compounded by a requirement to take extra days of child-related sick-leave to attend hospital.

Infants who develop an anastomotic stricture typically require admission to hospital for investigation followed by a surgical procedure. The standard approach to treating a stricture is dilatation of the narrowed segment, where the narrowing is mechanically stretched open, which is performed under general anaesthesia. Whilst some infants only require one or two dilatations, there are a number of infants who require many more. A UK-wide study found that in infants with a stricture the median number of dilatations in the first year of life was three, but one quarter of infants with a stricture received more than five dilatations in the first year of life (1). This need for repeated hospital attendances, many of which are unscheduled, places particular additional burden on the family (4).

Stricture following OA repair also creates other significant demands on the healthcare service in terms of resources and cost. Infants with a stricture commonly present to Emergency Departments, requiring expert diagnosis, radiological investigations and treatment. Management of a stricture is typically carried out by a paediatric surgeon, with an affected infant usually requiring an inpatient stay and surgical procedure. The NHS tariff for dilatation of an oesophageal stricture is in excess of £1,500 per episode

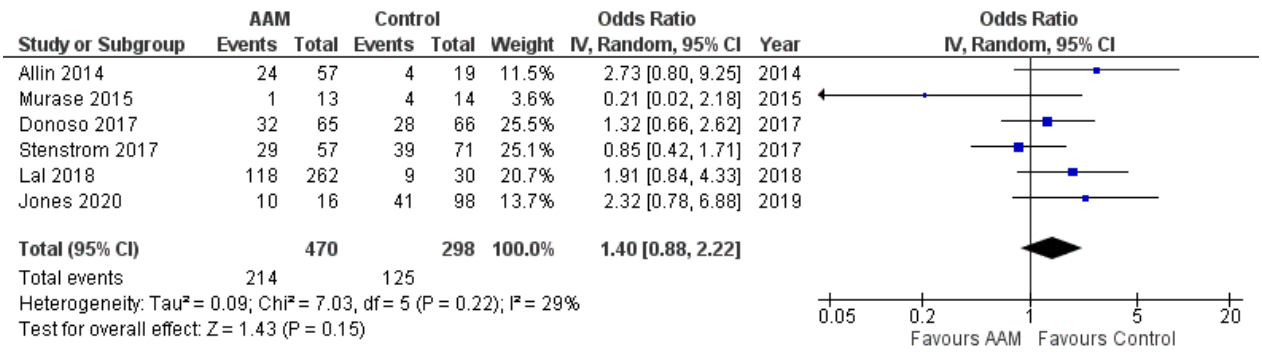
meaning that the healthcare costs of managing strictures following OA repair alone are significant (approximately £250,000 every year just for the babies born that year). Further, local community-based healthcare services including the General Practitioner, Health Visitor Service and Ambulance Services may all be called upon. Thus, the overall impact of anastomotic stricture for the healthcare system is potentially significant. Beyond the healthcare system, there will also be costs to parents and the wider society associated with the disruption to normal life caused by repeated dilatations; parents may need to take time away from work or pay out-of-pocket expenses as a result of their child's condition.

In anticipation of the negative consequences of stricture formation, some paediatric surgeons frequently assume that acid reflux is at least partially responsible for the development of strictures. As a consequence, routine gastric acid suppression medication is often prescribed. Indeed, gastric acid suppression medication is even recommended in international guidelines (5), despite a lack of evidence to support its use. Worryingly, there is some evidence suggesting harm from this type of medication and it has been linked with an increased risk of a number of different types of infection (6-9). Given this conflicting information, there is variation in the practice of gastric acid suppression medication prescription for the prevention of stricture formation.

A review of the literature relating to the use of gastric acid suppression medication in infants with OA reveals that the existing evidence stems from only a small number of observational studies. There are no published RCTs on this matter. Some of these studies are summarised in a systematic review and meta-analysis (2). We have recently updated this meta-analysis with two further datasets (10 and 11). The conclusion of this updated meta-analysis (Figure 1) remains as previously: (i) the quality of evidence is low with no prospective studies; (ii) none of the individual studies demonstrate a benefit of routine gastric acid suppression medication in reducing incidence of anastomotic stricture; (iii) overall, the results do not suggest that gastric acid suppression medication reduces the incidence of anastomotic stricture.

Figure 1 Meta-analysis of observational studies comparing routine Antacid Medication (AAM) with control; outcome is incidence of oesophageal stricture.

Note: 'IV, random' refers to inverse variance (IV) method and a random effects model



Determining if routine gastric acid suppression medication reduces the incidence or severity of anastomotic stricture in infants with OA is imperative if we are to understand how to best treat these infants. The current variation in practice is not justifiable nor evidence-based. A carefully designed and

adequately powered prospective randomised controlled trial is required to answer this question and to help inform evidence-based practice moving forward.

Given the minimal cost of gastric acid suppression medication, the intervention is likely to be cost-effective if clinically effective. Conversely, if found to be ineffective or even harmful, routine use of gastric acid suppression medication should be avoided.

A feasibility study was carried out at the University of Liverpool prior to the start of this study (ethical approval REC.8510). This was a mixed-methods study involving semi-structured interviews with parents of an infant with OA and an online survey, telephone interviews and focus groups with clinicians involved in the treatment of OA infants.

The main findings indicated that parents and most clinicians viewed the TOAST Study as being feasible and acceptable so long as infants can access reflux medication if clinically required (see appendix A). The results from this feasibility study has informed the study protocol and other study documents to ensure the study is family-centred and to assist in clinician engagement.

7 OBJECTIVES AND OUTCOME MEASURES

All outcomes are measured from date of randomisation unless specified in the table below.

Primary objectives	**Primary outcome measures**	**Time point of evaluation**
To compare the severity of anastomotic stricture during the first year of life in infants randomised to receive routine gastric acid suppression medication versus those randomised to matched placebo.	● Number of oesophageal dilatations	Up to 1 year of age
Secondary objectives	**Secondary clinical outcome measures**	**Time point(s) of evaluation**
To compare the severity and incidence of anastomotic stricture during the first 2 years of life in infants randomised to receive routine gastric acid suppression medication versus those randomised to matched placebo	● Number of oesophageal dilatations	Up to 2 years of age
	● Incidence of anastomotic stricture (one or more dilatations)	Up to 1 and 2 years of age

	• Histological diagnosis of oesophagitis	Up to 1 year and 2 years of age
To investigate the influence of routine gastric acid suppression medication versus matched placebo on other important clinical outcomes in infants randomised to receive routine gastric acid suppression medication versus those randomised to matched placebo at 1 and 2 years of age.	• All-cause mortality	Up to 1 year and 2 years of age
	• Mortality directly related to OA	Up to 1 year and 2 years of age
	• Any anastomotic complications (i.e., anastomotic leak, recurrent fistula)	Up to 1 year and 2 years of age
	• Number of procedures performed under general anaesthetic (GA) related to OA (e.g. upper gastrointestinal (UGI) endoscopy, bronchoscopy/ microlaryngobronchoscopy (MLB), oesophageal manometry, gastrostomy, fundoplication)	Up to 1 year and 2 years of age
	• Number of serious adverse reactions	Up to 1 year of age
	• Any non-GA diagnostic study related to OA (e.g. contrast study, pH impedance study), and findings	Up to 1 year and 2 years of age
	• Duration of dose of any gastric acid suppression medication given in addition to study medication	Up to 1 year of age
	• Max level of intervention (based on the treatment flow diagram – see appendix A) reached for treatment of reflux symptoms in preceding 3 months (described using summary statistics)	At 3, 6, 9 and 12 months of age

	• Parent-reported symptoms of reflux using total score of I-GERQ-R	At 3, 6, 9 and 12 months of age
	• Any acute life-threatening event or cyanotic episode, either while in hospital, or leading to a 999 call and/or hospital attendance	Up to 1 and 2 years of age
	• Weight standard deviation score (SDS) • Length/height SDS	At 1 year and 2 years of age
	• Number of chest infections treated with antibiotics either in the community or hospital	Up to 1 year and 2 years of age
	• Other respiratory problem resulting in admission to hospital	Up to 1 year and 2 years of age
	• Routinely fed via a tube (nasogastric or gastrostomy) after discharge home or 3 months chronological age, whichever is sooner	Up to 1 year of age
	• Number of re-admissions to hospital directly related to OA	Up to 1 year and 2 years of age
	• Cumulative length of stay in hospital post-surgery, directly related to OA	Up to 1 year and 2 years of age
	• Number of re-admissions to intensive care directly related to OA	Up to 1 year and 2 years of age
	• Cumulative length of stay in intensive care post-surgery, directly related to OA	Up to 1 year and 2 years of age
	• Nature of feed tolerated using the International Dysphagia Diet Standardisation Initiative (IDDSI) score	At 1 year and 2 years of age

Secondary objectives – Health Economics	Health economics outcome measures	Time point(s) of evaluation
To investigate the cost and consequences of routine gastric acid suppression medication versus matched placebo.	• Maternal Health Related Quality of Life using EuroQol EQ-5D-5L questionnaire (see section 13)	At 6, 12, 18 and 24 months of age (infant)
	• Maternal quality adjusted life years (QALYs)	Up to 2 years of age (infant)
	• Parent reported infant Health Related Quality of Life using PedsQL Infant Scales	At 6, 12, 18 and 24 months of age (infant)
	• Healthcare and societal resource use and costs	Up to 1 and 2 years of age (infant)

8 STUDY DESIGN

A multicentre, double-blind, randomised, placebo-controlled trial (with an internal pilot and health economic evaluation). The research will take place in specialist UK neonatal surgical units and in participant homes.

The study flowchart and schedules of events are summarised in sections 3 and 10 respectively.

8.1 Internal Pilot

The total internal pilot phase duration is 18 months which incorporates criteria to evaluate feasibility of recruitment and other study processes listed below.

It is expected that all recruiting sites will be opened to recruitment in the first 6 months and achieve a steady state from then onwards. It is anticipated that 57 infants (27% of the total sample size) (n=211) would be recruited during the 18-month pilot phase.

During the pilot phase, site performance indicator metrics will also be closely monitored. Metrics will assess number of sites opened, processes for local screening (ability to identify and approach parents of eligible cases) and recruitment (ability to successfully enrol those who are approached), and adherence to administration of study medication. Ability to open new centres will be reviewed monthly by the Project Management Group (PMG) during the initial six months. In addition, during the internal pilot, sites will be contacted regularly to discuss any recruitment issues. These discussions will further inform training during the pilot phase and before progression criteria are assessed.

The following pre-defined criteria to determine study progression will be considered by the Trial Steering Committee (TSC):

	Red	Amber	Green
Anticipated pilot RCT recruitment†	<70%	70–99%	≥100%
Number of sites opened	<8	8–11	≥12
Total number of participants recruited	<40	40–56	≥57

Green: continue into the main study
Amber: open new centres, explore and address barriers to recruitment, review in six months
Red: urgent detailed review of options with the TSC and HTA

† Site performance indicator metrics will be monitored after the site has been open for six months. Targeted training will be provided for any site where <75% of eligible infants have been identified and approached or where parental uptake is <50%.

9 PARTICIPANT IDENTIFICATION

9.1 Study Participants

Newborn infants with oesophageal atresia (OA) and distal tracheo-oesophageal fistula (TOF).

9.2 Inclusion Criteria

- Infants (of any sex and any gestational age) with OA with distal TOF who have undergone ligation of the fistula and oesophageal anastomosis at the same time during the first operative intervention
- Infants have written informed consent obtained from an individual with parental responsibility
- Infants are expected to survive beyond the first year of life
- Infants within the end of day 3 after surgery where day of surgery is day 0
- Infants up to 2 weeks postnatal age
- In the opinion of a clinical member of the local research team (appropriately trained and experienced doctor or nurse), parents(s)/carer(s) of the infant are able and willing to comply with all study requirements, (including having a good understanding of the English language), or can be supported to do so (including the use of translation services).

9.3 Exclusion Criteria

- Infants with OA without distal TOF
- Infants who have undergone an operative intervention (e.g. emergency tracheo-oesophageal fistula ligation without anastomosis, initial gastrostomy) prior to the one where they underwent oesophageal anastomosis

- Infants with any additional significant disorder or disease that, in the opinion of the responsible paediatric surgeon or neonatologist, makes entry into the study inappropriate
- Infants taking any medication that, in the opinion of a clinical member of the research team, makes entry into the study inappropriate

10 STUDY PROCEDURES

Procedures	Screening	Baseline	Randomisation	Intervention		Intervention and Data collection***					
	Infants with OA and distal TOF undergoing surgical repair			Post-randomisation	At hospital discharge	3 months of age +/- 2 weeks	6 months of age +/- 2 weeks	9 months of age +/- 2 weeks	12 months of age +/- 2 weeks	18 months of age +/- 4 weeks	24 months of age* +/- 4 weeks
Eligibility assessment	X										
Informed consent		X									
Randomisation			X								
Esomeprazole/ omeprazole/ placebo				X	X	X	X	X	X		
Clinical data collection*****				X	X	X	X	X	X	X	X
Parent-reported outcomes		X				X**	X	X**	X	X	X
Maternal Health Related Quality of Life#		X					X		X	X	X
Adverse events assessments (SAEs, SUSARs etc.)				X	X	X	X	X	X		
Adherence to study medication				X****							

*Data collection at 24 months of age will only occur for participants recruited in the first 48 months of the recruitment period (anticipated 80% of the sample)

** Parent-reported symptoms of reflux using total score of I-GERQ-R and data on overall adherence to medication administration only

*** Time windows are a guidance for sites to maintain visit schedule as much as possible and data collection outside of these will not be reported as protocol deviations. These visits will be conducted in line with routine care visits for this patient population and per local site policy (for example, whether

conducted at outreach clinics, by telephone or video call). Where a visit does not occur or is missed, 3 attempts will be made to invite to a visit and after this data will be recorded as missing data.

****Recorded daily up to 1 month post-discharge/weekly thereafter

***** Data is already collected as part of routine clinical care

Where biological mother has agreed to complete maternal questionnaires.

10.1 Recruitment

Infants will be recruited from specialist UK Neonatal Surgical Units; it is expected that approximately 12–15 units will take part. The study aims to recruit 211 participants in 60 months from the recruitment start date, equating to around 3–4 per month across all sites. Information about the study will be widely available using posters and banners distributed throughout relevant areas in participating hospitals. Eligible infants will be recruited early in life, shortly after their surgical repair, so that the study medication can commence as soon as possible after surgical repair. Eligible infants will be identified by the clinical care team and after parents/carers consent to their participation in the research, will be recruited (by appropriately trained, delegated individuals within the clinical care team at the site). Where a diagnosis of OA is made antenatally, parents may be informed about the study but consent to enter the study will only be sought after surgical repair.

10.2 Continuing Care Sites

The responsibility for complete data collection lies with the recruiting site. Networks of potential continuing care sites will be identified during the set-up of recruiting sites, so that where possible, regulatory and local approvals to continue study-related activities can be obtained in advance of any transfers from the original recruiting sites or admission to a continuing care site during the follow-up phase.

Participating sites will be either:

- A recruiting site where the parent/carers' consent is obtained and participants are recruited, randomised, and commence participation in the study

  OR

- A continuing care site which will continue to administer the study medication if infant is admitted after transfer or readmitted following discharge from the recruiting site.

At any other medical facility, (where permitted by regulations and individual NHS Trust policies, and considered clinically appropriate by the treating clinician), parents/carers will be allowed to continue to administer the study medication themselves, with adherence logged on a bespoke study app (electronic and paper alternatives will be available for those who do not have access to a smartphone).

For further details about commencing the study medication at continuing care sites see section 11: Investigational Medicinal Product.

10.3 Screening and Eligibility Assessment

OA with distal TOF is a rare condition. Infants identified as having the condition will be screened for eligibility by the clinical care team. Parents/carers with legal responsibility will be approached to discuss the study. Eligibility will be reconfirmed at the point of randomisation.

10.3.1 Recruitment to other studies

Co-recruitment of participating infants to other non-interventional studies would generally be permitted. Co-recruitment to another interventional study may be possible following discussion and agreement with the TOAST Chief Investigator if shown not to affect the outcome of this study in any way. The burden to the family of involvement in additional research will also be considered when making a decision.

10.4 Informed Consent

Infants will be identified by a member of the clinical care team as being potentially eligible, with parents/carers willing to discuss the study with a researcher. Parents/carers with legal parental responsibility will be approached by a clinical member of the research team to discuss the study further and to discuss participation. Written and verbal (video) versions of the Participant Information Leaflet and Informed Consent Form will be presented detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that any participant is free to change their consent status for the study at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for change of consent. Parents/carers will be given the opportunity to consider the information, and to ask questions of the research team or other independent parties to decide whether they would like to participate in the study. A trained and delegated individual must obtain appropriate written informed consent from the parent/carer prior to any study-related procedures being undertaken. Where parents/carers do not have a good understanding of English, sites may use the translation and interpreting services which they usually use in clinical practice to communicate about the study.

A parent/carer with legal parental responsibility must sign and date the latest approved consent form; this does not have to be the biological mother. A copy of the completed consent form will be given to the parent/carer. Where biological mothers agree to complete maternal questionnaires, they will be asked to sign a separate section of the same consent form. The biological mother can sign this part at a later date if they are unavailable, and the baby can be recruited into the study before this separate section has been signed. Originals will be stored in the site file, with copies filed in the infant's medical notes, a copy provided to the parent/maternal participant and sent via secure document transfer to National Perinatal Epidemiology Unit Clinical Trials Unit (NPEU CTU), University of Oxford.

10.5 Randomisation

Randomisation of infants will occur using a 1:1 allocation ratio, to either:

- routine gastric acid suppression medication – initially esomeprazole 0.5mg/kg intravenously once daily, until infants are able to feed enterally, followed by omeprazole 1mg/kg enterally once daily up to one year of age

  or

- matched volume placebo given intravenously once daily, until infants are able to feed enterally, followed by matched volume placebo enteral administration once daily up to one year of age.

Study medication will be administered as soon as possible after randomisation.

Randomisation of infants will be managed via a secure web-based randomisation facility hosted by the NPEU CTU with telephone backup available at all times (365 days per year). The randomisation program will use stratified block randomisation to ensure balance between the intervention and control arms with respect to recruiting hospital and prematurity ($<37^{+0}$ weeks; $\geq 37^{+0}$ weeks of gestation).

A statistician or programmer at the NPEU CTU will generate the randomisation schedule and the Senior Trials Programmer will write the web-based randomisation program; both will be independently validated. Packs will be allocated according to the randomisation schedule at the point of randomisation. The Senior Trials Programmer will liaise directly with the packaging and distribution company to supply a list of packs and their allocations. The implementation of the randomisation procedure will be monitored by the Senior Trials Programmer and Trial Statistician throughout the study and reports will be provided to the Data Monitoring Committee (DMC).

10.6 Blinding

Families (i.e. participants) and clinical teams caring for the infant will be blinded to study allocation. Centres will be supplied with sealed numbered indistinguishable packs containing IV esomeprazole or enteral omeprazole, or matched placebo. Once consent and eligibility are established, infants will be allocated a pack containing the study allocation (IMP or placebo) generated by the randomisation program; the study allocation itself will not be revealed. All investigators and CTU staff with the exception of the Senior Trials Programmer and the person (not the Trial Statistician) who generated the randomisation schedule will be blinded to study allocation.

10.7 Emergency Code Breaking

In the event of an emergency, unblinding can be performed by the clinician at the recruiting site by logging into the randomisation website using a single-use access code provided in a sealed envelope. The reason for unblinding must be recorded. Clinicians are reminded to exercise discretion when the allocation has been unblinded.

Clinicians carrying out emergency unblinding must be satisfied that it is a genuine emergency and that knowledge of the treatment allocation (either gastric acid suppression medication or placebo) is essential

to guide the appropriate clinical management of the infant. In most cases, appropriate clinical management will be possible without unblinding, by treating the infant as if they have received gastric acid suppression medication. Clinicians considering emergency unblinding are encouraged to discuss the need to do so with the PI, or another clinician on the delegation log beforehand, if possible and safe to do so. Where appropriate the site can also contact the CI.

Where the infant has been transferred out of the recruiting site for onward care, the treating healthcare professional should contact the PI or any clinician on the delegation log at the recruiting site to unblind. Details of how to do this will be contained in the transfer pack that will be sent with the baby to the new site.

10.8 Subsequent Visits

Study data will be collected during routine clinical follow-up appointments at 3, 6, 9, 12, 18 and 24 months of age. Data will be collected in accordance with the Data Management Plan. Clinical data collected for the study is part of the routine care of these babies. In addition, safety data will be collected as well as parent/carer reported data and maternal quality of life. These visits will be carried out as per local site policy and could occur at the recruiting site, associated locations linked to the recruiting site, continuing care sites or in some cases could be done via telephone. Additional visits may occur if deemed necessary by the clinical team.

Any incidental findings that are identified during the course of the study will be notified to the clinical team looking after the infant in question.

10.9 Withdrawal of Participants/Change of consent

Parents/carers will have the right to change their consent for their infant's participation in the study up until the end of the study. Change of consent will not affect their infant's ongoing clinical care. If an infant is withdrawn from TOAST Study due to an adverse event (AE), this will be followed up by the local research team and TOAST Study team to assess whether a serious adverse reaction (SAR) has occurred. Data collected up to the point of consent change will be used in the study. Change of consent will be recorded on an eCRF and the reason detailed, if it has been provided. Withdrawals will not be replaced as they are accounted for in the sample size calculation.

10.10 Discontinuation of Study Medication

Parents/carers have the right to permanently discontinue administration of the study medication. This will be recorded as a discontinuation of study medication on an eCRF. Discontinuation of study medication will not affect the infant's ongoing clinical care. Data will continue to be collected from the infant's notes and at hospital visits, if parents/carers give permission. Adherence data collection through the app will cease once the NPEU CTU has been notified of the discontinuation of study medication.

In addition, the treating clinician may discontinue the study medication at any time if they consider it to be in the best interests of the infant's health and wellbeing.

As the study is designed in a pragmatic manner, if any number of doses of study medication or placebo are missed then this will not constitute a formal discontinuation of the study medication or change of consent status for the study. Data on adherence to the study medication will continue to be collected. Formal discontinuation or change of consent status for the study will only be applicable if the parent/carer asks to end some or all aspects of participation as per section 10.9. The TOAST Study team will work with the recruiting site team to review adherence to the protocol and where deemed appropriate, the research team or clinical care team will make contact (e.g. phone call, SMS message or email) with the infant's parents to discuss their ongoing participation in the study.

10.11 Definition of End of Study

The end of the study will be defined as the date when the study database is locked. An End of Trial Declaration will be made to the sponsor, Medicines and Healthcare products Regulatory Agency (MHRA) and approving Research Ethics Committee (REC) within 90 days of end of study.

11 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

11.1 Investigational Medicinal Product(s) (IMP) Description

There are two active IMPs and 2 matched placebos, depending on whether the infant is able to take medication enterally or intravenously.

Whilst in the recruiting site NNU, the decision of whether to give the IMP/placebo intravenously or enterally on any given day during the initial hospital admission will be at the discretion of the clinical team guided by the infant's tolerance of enteral feed.

For infants not yet feeding enterally, the IMP is esomeprazole 40mg powder for solution for injection/infusion (off-label PL31750/0049, Sun Pharmaceuticals Industries Europe B.V.) or placebo administered daily until oral feeding is established. The dosage and route of administration is esomeprazole 0.5mg/kg intravenously or placebo at a matched volume. Individual esomeprazole 40 mg vials or matched placebo with tamper evident caps will be packed into shrouding cartons for blinding purposes. Seven vials will then be placed into secondary packaging (study pack). Each vial and pack will be labelled with an Annex 13-compliant label including a pack ID. The intravenous IMP/placebo should be reconstituted using 0.9% sterile sodium chloride solution for injection/infusion, which must be a medicinal product with a Marketing Authorisation – this should be provided by the recruiting hospital, and will not be included in the TOAST medication pack.

For infants feeding enterally when in hospital, and also when discharged home, the IMP is omeprazole 2mg/ml solution (off-label PL34111/0002, Xeolas Pharmaceuticals Limited) or placebo administered daily up to one year of age. The dosage and route of administration is omeprazole 1mg/kg orally or placebo at a matched volume. Individual bottles containing omeprazole or matched placebo will be provided, to be reconstituted into a solution with 64ml of water. Each bottle will be labelled with an Annex 13-compliant label including a pack ID. Individual bottles will be packed into aluminium foil pouches, then six bottles will be placed into secondary packaging (study pack) with an Annex 13-compliant label including a pack ID.

The Reference Safety Information (RSI) will be the latest approved and relevant Summary of Product Characteristics (SmPC) for both esomeprazole and omeprazole (see section 12.5).

11.1.1 IMP supplier

The IMP and matched placebo (both IV and enteral) will be supplied by Sharp Clinical Services (UK) Ltd. in accordance with Good Manufacturing Practice (GMP). Each batch will be released by a Qualified Person (QP) at Sharp Clinical Services (UK) Ltd. prior to dispatch to sites. Omeprazole and matched placebo will be supplied by Sharp Clinical Services (UK) Ltd. via Xeolas Pharmaceuticals. Sharp Clinical Services (UK) Ltd will be handling the labelling for both IMPs and placebos.

11.1.2 Storage of IMP

When in hospital the study IMP will be stored in the pharmacy, with out-of-hours provision in a study-specific locked drug cabinet. Once a baby is randomised study medication will be transferred to the NNU.

The esomeprazole IMP and placebo must be stored at a temperature of 30°C or below before reconstitution and each vial is discarded after use. The omeprazole IMP and placebo must be stored at temperatures below 25°C before reconstitution and between 2–8°C after constitution. The shelf life of each reconstituted bottle of omeprazole will be 28 days from reconstitution.

When the infant is discharged home, study medication (omeprazole/placebo) will be provided from either the NNU or the pharmacy to the parent/carer. It will be reconstituted by the parent/carer at home, then stored in a domestic fridge, and temperature will not be monitored due to the additional burden to parents. Training for reconstitution and administration will be provided to the parent. Further medication will be given to the parent/carer at follow up visits, and where a visit does not occur, study medication may be provided by the site by local appropriate ways.

If an infant is transferred to a continuing care site, the study medication will be transferred with them, with additional medication provided from the recruiting site pharmacy.

11.1.3 Adherence to Study Medication

Study medication will be administered whilst the infant is in hospital. Data on dosage and administration will be collected daily. Following discharge, study medication will be given by the parent/carer and adherence to administration will be collected at predefined intervals via a bespoke app, or on paper as a back-up. More details about the app are in section 19.6. For those who are unable use an app e.g. those without a smartphone, electronic and paper alternatives will be made available.

A symptomatic reflux treatment pathway has been developed in conjunction with clinicians and parents. This guides clinicians in evidence-based treatment of symptomatic reflux and allows the administration of rescue gastric acid suppression (in addition to the study medication) whilst remaining within the protocol. Data will be collected on the need for treatment of symptomatic reflux.

11.1.4 Accountability of the Study Medication

Accountability records will be maintained for stock held at recruiting sites. Families will be advised to dispose of unused study medication by placing in a domestic bin. There will be no IMP and placebo accountability at families' homes or during follow-up visits in line with the pragmatic nature of the study design and to minimise the burden placed on families.

11.1.5 Post-study Medication

There will not be provision of esomeprazole or omeprazole beyond the study period, due to it being routinely available.

11.1.6 Concomitant and Prohibited Medication

Clinicians should refer to the current approved SmPC prior to prescribing concomitant medications.

Omeprazole or other gastric acid suppression medications should be prescribed in accordance with the TOAST Symptomatic Reflux Treatment Pathway, provided this is deemed clinically appropriate by the treating clinician.

In the event of a reported serious adverse event (SAE), all concomitant medication will be detailed on the SAE form.

12 SAFETY REPORTING

12.1 Adverse Event Definitions

Adverse Event (AE)	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 a study 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 study medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: ● results in death ● is life-threatening ● requires inpatient hospitalisation (for a stay more than 24 hours) or prolongation of existing hospitalisation (by more than 24 hours) ● 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 (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the study treatments, based on the information provided.
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 study in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

12.2 Assessment of Causality

The relationship of each adverse event to the study 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 IMP
- **Possibly** – although a relationship to the IMP 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 IMP
- **Definitely** – the known effects of the IMP, its therapeutic class or based on challenge testing suggest that the IMP is the most likely cause

All AEs/SAEs labelled possibly, probably or definitely will be considered as related to the IMP.

12.3 Reporting Procedures for Adverse Events

The safety reporting window for this study for each infant will be from start of study medication up to one year of age. All trials run by the NPEU CTU follow the unit's safety reporting Standard Operating Procedure.

In this population we anticipate day-to-day fluctuations of pre-existing conditions, new 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 events listed in 12.4 will be collected and reported for the study.

12.4 Reporting Procedures for Serious Adverse Events

Due to the established safety profile of the study medication, the only SAEs that will be reported are:

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

While the infant is an inpatient at the recruiting site, sites will report any death or SAR to NPEU CTU as soon as possible and within 24 hours of awareness. Following discharge from recruiting site, SARs will be collected by recruiting sites at 3-monthly follow-up appointments and reported to NPEU CTU within 24 hours of awareness. Sites may use one of the following methods:

- Staff with access to the study electronic database (OpenClinica) should complete the SAE form online. An automatic email notification to the NPEU CTU staff will be triggered for SAEs reported electronically
- Paper or electronic forms, with instructions, will be provided with the study documentation to enable anyone to report an SAE. The completed SAE form must be emailed or uploaded using NPEU CTU systems to NPEU CTU
- Where the above routes are not possible, the SAE may be reported to NPEU CTU by telephone and the SAE form completed by NPEU CTU staff

Follow-up SAE information should be reported as necessary by the site staff and sent back to the NPEU CTU electronically, by email or uploaded using NPEU CTU systems.

12.5 Expectedness

For SAE/SARs that require reporting, expectedness will be determined according to the section 4.8 of the two Summary of Product Characteristics (SmPC).

The esomeprazole and omeprazole being used in the study are licenced products and therefore the SmPCs for the products themselves will be used as the RSI for expectedness.

The RSI used (found in section 4.8 of the SmPCs for each IMP respectively) will be the current Sponsor and MHRA approved versions at the time of the event occurrence. For assessment of expectedness in the Development Safety Update Report, see section 12.7 below.

12.6 SUSAR Reporting

All SUSARs will be reported by the Sponsor or NPEU CTU delegate to the MHRA and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the NPEU CTU is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

NPEU CTU will ensure Sponsor are sent copies of all reports at the time of submission to REC. Treatment codes will be unblinded for these specific participants.

12.7 Development Safety Update Reports (DSUR)

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical study, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

For assessment of SARs in the DSUR, the RSI that was approved at the start of the safety reporting period will be used. When there have been approved changes to the RSI by substantial amendment during the reporting period, the RSI used for the DSUR will differ to the RSI used to assess expectedness at the time of SAR occurrence for SARs which require expedited reporting.

12.8 Safety Oversight

The following events are expected in the infant population, and information will be collected by recruiting site at 3-monthly intervals during the intervention period. They do not require reporting as SAEs as they are collected as outcomes. Data pertaining to these events will be reviewed by the DMC at a frequency to be determined by the DMC (at least annually).

- 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

Parent/carer packs given to families to take home will include information/reminders on the specific events that the research team need to know about.

13 STATISTICS

13.1 Sample Size Determination

The proportion of infants with a stricture is estimated to be between 36–44% (1, 2). The primary outcome (number of dilatations performed) will be analysed as an ordered categorical variable. In a UK study (1), the proportion of infants having 1, 2, 3, 4, 5, >5 dilatations performed in the first year was uniformly distributed. Assuming a stricture event rate of 40% and a uniform distribution across categories 1 to >5, with a 5% two-sided significance level, an odds ratio of 2.7 could be detected with 90% power from a sample of 200 infants (100 per treatment arm). This would result in an increase in the proportion of infants with 0 dilatations from 60% to 80% and a reduction in the proportion with 1, 2, 3, 4, 5, >5 dilatations to between 3% and 4%.

To detect an absolute risk difference of 22% in the proportion of infants with stricture with 90% power (e.g. from 40% to 18%) and allowing for 5% lost to follow-up, a total of 211 infants would need to be recruited.

13.2 Statistical Analysis Plan

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan (SAP) that will be available prior to the first DMC review of interim data. The SAP will be finalised before data lock of the one-year outcomes takes place. Data relating to the one-year outcomes will be locked and analysed prior to the final database lock after collection of the two year outcomes.

13.3 Description of Statistical Methods

For the main study, infants will be analysed on an intention-to-treat basis in the groups to which they are assigned, regardless of deviation from the protocol or treatment received. Infant clinical characteristics at study entry will be summarised by randomised group using counts and percentages for categorical variables, means and standard deviations for normally distributed continuous variables, or medians and interquartile ranges for non-normally distributed continuous variables.

For the primary outcome, the number and percentage (%) of infants with 0, 1, 2, 3, 4, >5 dilatations performed in the first year will be reported and ordinal logistic regression will be used to estimate the odds of receiving one fewer dilatation in the gastric acid suppression medication group compared to the placebo group, assuming that the treatment effect will be proportional across all (ordered) categories. An adjusted odds ratio and 95% confidence interval will be presented, adjusting for the stratification factors used at randomisation (recruiting hospital and prematurity). For the number (%) of infants with a stricture and other secondary dichotomous outcomes, counts and percentages will be reported and adjusted risk ratios with 95% confidence intervals will be calculated using log binomial regression. For continuous outcomes, means and standard deviations will be reported with adjusted mean differences and 95% confidence intervals, estimated using linear regression (assuming residuals are normally distributed). Should this assumption be considered unmet, quantile regression will be used to estimate median difference, and medians and interquartile ranges will be presented instead. A pre-specified subgroup analysis will be conducted for the number of dilatations and incidence of stricture outcomes to investigate

whether the effect of the intervention is consistent across preterm and term infants (<37+0 weeks; ≥ 37+0 week of gestation), and will be assessed using the standard statistical test of interaction.

14 HEALTH ECONOMICS

Parents/carers will be invited to complete questionnaires about their infant as part of the study. Biological mothers will be invited to answer specific questions about themselves and therefore will be asked for their own consent to do this as detailed in 14.1.

14.1 Biological Mother Data Collection

The use of the EQ-5D-5L in this study relates to biological mothers only and this will be explained in the Parent Information Leaflet. Biological mothers of infant participants will be asked their specific consent to complete questionnaires about themselves and will sign a separate section of the main consent form. As the questionnaires will be in English, the mother will need to have a good understanding of the English language or be able to be supported to complete the questionnaires. They will also need to be able and willing to comply with all study requirements, in the opinion of the recruiting clinician.

If the mother consents, they will be sent the EQ-5D-5L questionnaires at the times indicated in section 9 and until the infant is 2 years old. In the final year of recruitment, infants are only followed for 1 year, so the mothers will only complete questionnaires up to 1 year.

If the mother does not want to complete the questionnaires, this will not affect their infant's participation in the study. Mothers can also choose to stop completing the questionnaires at any time and without providing a reason, and this will not affect the infant's further participation in the study.

No safety reporting will be undertaken for biological mothers, who will be completing questionnaires only, and no financial or material incentive or compensation will be provided.

The questionnaires contain questions of a sensitive nature and further action will not take place based on questionnaire responses. These mothers are being cared for by the hospital clinical team as well as midwives/health visitors, and will be encouraged to get in touch with the site clinical staff if they have any concerns about the questionnaires or their responses.

14.2 Health Economics Analysis

A health economic evaluation forms an integral part of the study and will be conducted from the perspectives of the NHS, parents and society. We will follow-up all infants to one year and 80% to two years post randomisation and record information on gastric acid suppression medication, stricture and anastomotic dilatations performed, other hospital admissions, key primary and secondary healthcare contacts, and treatments for symptomatic reflux, respiratory symptoms, and chest infections. These data will be collected using a combination of medical records review and parent self-report at regular intervals during follow-up (6, 12, 18 and 24 months) and will be costed using unit costs from established sources including the new NHS National Cost Collection which is based on Patient-Level Information and Costing Systems (PLICs), the Personal and Social Services Research Unit (PSSRU), and the NHS Electronic Drug

Tariff. To assess the burden beyond the health service, the parent/carer will also be asked about time away from work, any changes to their employment status, and any out-of-pocket expenses arising as a result of their child's condition.

The PedsQL infant scales are validated parent-report questionnaires for health-related quality of life (HRQoL) in infants aged 1–24 months. The questionnaires (covering 1–12 months and 13–24 months) are brief, should take parents only minutes to complete, and include questions on physical functioning, physical symptoms, and emotional, social, and cognitive functioning. Parents will be asked to complete the PedsQL Infant Scales at 6, 12, 18, and 24 months. As the condition of their child is also likely to have a substantial impact upon the HRQoL of parents, we will collect demographic information at baseline and information on maternal HRQoL at baseline, 6, 12, 18, and 24 months using the EuroQol EQ-5D-5L questionnaire (12). This will need to be completed by the biological mother only and will be considered missing data where unavailable. The questionnaire is short, and asks respondents to select one of five pre-specified descriptive levels for each of five dimensions of HRQoL (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The resulting health state description is converted into a single values on a scale where death is anchored at 0 and perfect health at 1, and can be compared with age and sex matched population normative values. The EuroQol EQ-5D is currently the preferred preference-based instrument to measure HRQoL in adults by the National Institute for Health and Care Excellence (NICE) (13).

Capturing health-related quality of life of fathers/other family members was outside the scope of this study as our processes place the mother at the centre of the data collection for the study. We recognise that the quality of life of fathers may also be affected by the main treatment effect but we will not be able to investigate this in this study.

To consider the longer-term impact of the intervention for families and the health service, the principal form of the economic evaluation will be a within-trial cost-consequences analysis with a two-year time horizon. Costs at 2 years will be presented alongside the various key outcomes, for example the number of children developing a stricture, the number of anastomotic dilatations performed, cases of chest infection, maternal HRQoL scores and quality adjusted life years (QALYs), and infant HRQoL scores. This approach will enable various stakeholders (for example parents and clinicians) to contemplate the impact of gastric acid suppression medication on the outcomes of most relevance to them. To complement the study's primary clinical analysis at one year, we shall produce estimates of resource use and costs at one year which will be reported alongside the primary clinical endpoint.

To better understand the burden for families and wider society, healthcare costs will be reported separately from any out-of-pocket expenses incurred by families and any societal productivity losses. When analysing continuous variables (for example costs and HRQoL scores) means and standard deviations will be computed for each study arm and for comparisons between study arms, mean differences and 95% confidence intervals will be used. For categorical outcome variables proportions will be used. Uncertainty around key study parameters will be addressed using sensitivity analysis. All analyses will be conducted and reported in accordance with existing good practice guidelines for economic evaluation (13).

15 DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan and Data Flow document.

15.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. CRF entries will be considered source data if the CRF is the site of the original recording (i.e. there is no other written or electronic record of data). Parent-reported data (for example, adherence data collected via the app, quality of life questionnaires) will be considered source data. Site staff will enter clinical data directly into the clinical database (OpenClinica).

15.2 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections.

Site staff will have authenticated and restricted access to the Clinical Database Management System (OpenClinica), ensuring they are only able to see data on participants recruited at their site. Access to the electronic data is strictly controlled using individual passwords for all staff accessing the electronic databases.

15.3 Data Recording and Record Keeping

Apart from the dosing logs, which will first be recorded on paper, all clinical data will be entered directly into the clinical database (OpenClinica) by the site staff. The clinical database will be validated and maintained in accordance with NPEU CTU Standard Operating Procedures (SOPs). Data will be entered and at the point of entry will undergo a number of validation checks to verify the validity and completeness of the data captured. A separate administrative database application will be used to store the participant's name and any other identifiable details on NPEU servers at University of Oxford. Study participants will be identified by a unique study number, which is used to link the clinical and administrative database applications.

Parents will be invited to download a bespoke study app to monitor daily adherence with the study medication. For those who are unable use an app e.g. those without a smartphone, electronic and paper alternatives will be made available.

Consent forms containing the infant and parent's names will be sent securely to the NPEU CTU. All data will be processed in line with the NPEU CTU Data Management SOPs. It is the responsibility of all parties involved (Sponsor, NPEU CTU, and the NHS organisations) to ensure that confidentiality of participant information is maintained.

Electronic files, such as eCRFs and other electronic or scanned documents containing personal/sensitive information, will be stored on a restricted access (named individuals) server that can be accessed only by members of the NPEU CTU TOAST Study team with permissions to access data at specified levels, held in

a secure location. The data are backed up daily. Authorised access to the NPEU CTU is via an electronic tag entry system and individual rooms are kept locked when unoccupied. Data will be analysed by the statistical team within NPEU CTU, University of Oxford via a secure network, which requires individual login name and password (changed regularly). No data are stored on individual workstations.

Archiving of research data will follow the completion of the study and publication of results for an initial period of 25 years. At this point, the requirements to continue to archive these data will be reviewed in line with the applicable data protection guidelines.

Archiving of identifiable data will follow the completion of the study and publication of results for a maximum of 25 years, to allow for contact in the unlikely event of very long-term treatment effects being discovered. In addition, optional consent for holding identifiable data for potential future research is included in the information provided to parents.

All paper and electronic data will be stored securely in strict compliance with data protection regulations.

15.4 Data Sharing

Any data sharing requests should be submitted to the Chief Investigator and the NPEU for consideration. Access to anonymised data may be granted following review.

15.4.1 Use of personal data to contact parents/carers in future

At the end of the study, where consent has been given, personal data of study participants will remain at the NPEU, University of Oxford as well as being shared with the Chief Investigator at the University of Southampton and the Co-Lead at Evelina London to be able to contact parents/carers to invite them to take part in future research looking into the longer-term effects of oesophageal atresia. Consent to this data sharing will be optional and parents/carers who consent will be free to choose whether or not they want to take part in further research. Future studies will require additional ethical approval.

The NPEU research team are looking for ways to improve the research projects they run using Parent, Patient and Public Involvement and are looking for parents/carers to contact to help with this. Consent for contact details to be kept for these purposes will be optional and parents/carers who consent will be free to choose whether or not to take part if contacted in the future.

16 QUALITY ASSURANCE PROCEDURES

16.1 Risk Assessment

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations and SOPs. A risk assessment (RA) and monitoring plan (MP) will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

16.2 Monitoring

The Principal Investigator (PI) will be responsible for the running of the study at their site. This will include ensuring successful recruitment, staff education and training, and study data completeness and quality.

The NPEU CTU will develop and conduct appropriate central monitoring for the study, based on the RA. Recruitment patterns at sites and within the data will be monitored. Any unexpected patterns, issues, or outlier data will be investigated and may trigger 'for cause' site monitoring. No other routine monitoring or auditing will be conducted unless central monitoring triggers cause to do so.

16.3 Trial Committees

The study will be run on a day-to-day basis by the Project Management Group (PMG), which reports to the Trial Steering Committee (TSC), which in turn is responsible to the NIHR HTA programme. The PMG will consist of the Chief Investigator(s), CTU Director, Clinical CTU Director, Senior Trials Manager, Trial Statistician, CTU IT development Team, PPI representative from the charity TOFS and other project staff. The PMG will meet every month.

To ensure that our research is carried out keeping the interests of parents and families caring for infants born with oesophageal atresia at its centre, we have formed our research team to include a Patient and Public Involvement (PPI) co-applicant. This person is a representative from the Tracheo-Oesophageal Fistula Support charity (TOFS), the parent support group for children born with OA, who is also a parent of a patient (now an adult) born with OA. Thus far this PPI co-applicant has made significant contributions to the proposal by bringing a parental perspective of having a child with OA and providing insight into the acceptability of the care pathways proposed. They have given advice on how and when is the best time to approach parents and importantly helped inform the selection of primary and secondary outcomes.

The Co-Investigator Group (CIG), an extended PMG, will comprise all members of the co-applicant group and the members of the PMG, and will review progress, troubleshoot and plan strategically.

The study will be overseen by a TSC consisting of an independent chair and other members, to include clinicians, statisticians and PPI representatives. Committee members will be deemed independent if they are not involved in study recruitment. The chair and members of the TSC will be nominated as per the guidance outlined by the NIHR HTA for their approval. The TSC will aim to meet in person at least annually.

The TSC will monitor the progress and conduct of the study and advise on its scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC and ultimately carry the responsibility for deciding whether the study needs to be stopped on grounds of safety or efficacy. Details about the roles, responsibilities and conduct of the committee with be set out in a TSC Charter, which will be agreed at the first meeting.

The DMC members will be independent of the study team and the TSC, and will include a chair, clinician and statistician. During the recruitment phase, the committee will meet annually or more often as appropriate, review study conduct, progress, and accumulating data, and make recommendations to the TSC. Details about the roles, responsibilities and conduct of the committee with be set out in a DMC Charter, which will be agreed at the first meeting.

17 PROTOCOL DEVIATIONS

A study-related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process) or from GCP or any applicable regulatory requirements. Any deviations from the protocol will be documented in incident forms and where applicable the relevant corrective and preventative action completed. All incidents will be recorded in an Incident Log database.

18 DATA BREACHES

According to the Information Commissioner's office (ICO), "there will be a personal data breach whenever any personal data is accidentally lost, destroyed, corrupted or disclosed; if someone accesses the data or passes it on without proper authorisation; or if the data is made unavailable and this unavailability has a significant negative effect on individuals".

Suspected personal data breaches must be reported immediately to the University of Oxford's Data Breach Team data.breach@admin.ox.ac.uk

IT security related incidents e.g. malware, hacks to be reported to the Information Security Team (IST): oxcert@it.ox.ac.uk (ext. 82222).

Sites may have reporting obligations within their own organisation as well.

19 URGENT SAFETY MEASURES

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) to protect study participants from any immediate hazard to their health or safety. USMs may be taken without prior authorisation but they should be reported immediately, and not later than 3 days, to the Sponsor, REC and MHRA. This should be followed by submission of a substantial amendment specifically covering the USM related changes. The appropriate NPEU SOP will be followed for this process.

20 SERIOUS BREACHES

A serious breach is defined as "A breach of GCP or the study protocol which is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the study; or

(b) the scientific value of the study".

In the event that a serious breach is suspected the Sponsor must be contacted within one working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, regulatory authority and the relevant NHS host organisation within seven calendar days.

21 ETHICAL AND REGULATORY CONSIDERATIONS

21.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

21.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

21.3 Approvals

Following Sponsor approval, the protocol, informed consent form, parent information leaflet (PIL) and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), Health Research Authority (HRA) (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

21.4 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

21.5 Transparency in Research

Prior to the recruitment of the first participant, the study will have been registered on a publicly accessible database.

Where the study has been registered on multiple public platforms, the study information will be kept up to date during the study and the CI or their delegate will upload results to public platforms within 12 months of the end of trial declaration.

21.6 Participant Confidentiality

The study will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

All personal identifiers will be stored in a separate database also held at the NPEU CTU. These databases will only be linked by the infant's study number. After the study has been completed and the reports published, the data will be archived in a secure physical or electronic location with controlled access.

Where a parent is using the study app, personal identifiable information, including parent's telephone number and email address, will be shared with an app provider called Blue Frontier if required for app troubleshooting during the study. The data will not be shared outside of the UK. The app's main function is to gather study medication adherence, but will also include an optional section for parents/carers to enter helpful notes about their baby, for example their weight or mood. Anything entered on this optional section will not be used in the study. This optional data will be stored in a separate secure location by the TOAST Study team in Oxford and will be deleted at the end of the study. Parents/carers will be able to download a copy of all the data that they have entered and will be prompted to do this at the end of the follow-up period for their child, before the optional data is deleted. Blue Frontier will not have access to the study data nor to the optional section - this data will be held by NPEU.

21.7 Expenses and Benefits

No financial or material incentive or compensation will be provided to parents for enrolling their infant in this study.

22 FINANCE AND INSURANCE

22.1 Funding

This study is funded by the NIHR HTA [NIHR131136]. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

22.2 Insurance

University of Oxford is the sponsor for the study. The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment which is provided.

22.3 Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

23 PUBLICATION POLICY

The success of the study depends on a large number of neonatal surgeons, neonatal nurses, neonatologists, and parents. Credit for the study findings will be given to all who have collaborated and participated in the study, including all local co-ordinators and collaborators, members of the study committees, and the TOAST Study team. Authorship at the head of the primary results paper will take the

form “[name], [name] and [name] on behalf of the ‘The TOAST Collaborative Group’”. The drafting of the paper will be the responsibility of a writing committee. All contributors to the study will be listed at the end of the main paper, with their contribution identified. It is the intention of the TOAST Collaborative Group to publish the protocol and peer-reviewed articles including the analysis of key outcomes. All published material will contain an acknowledgement of funding, as required by the NIHR HTA.

Consideration will be given to publishing the results of the one-year outcomes separately to the results of the two-year outcomes. The health economics outcomes will be published separately.

Parents will be emailed a copy of the study result. Study results will also be disseminated through the study website. A full dissemination plan will be developed by the PMG.

24 DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of Intellectual Property (IP) generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the study.

25 ARCHIVING

Archiving will follow the completion of the study and publication of results, and will take place in accordance with the NPEU SOP for an initial period of 25 years. At this point, the requirements to continue to archive these data will be reviewed in line with the applicable data protection guidelines.

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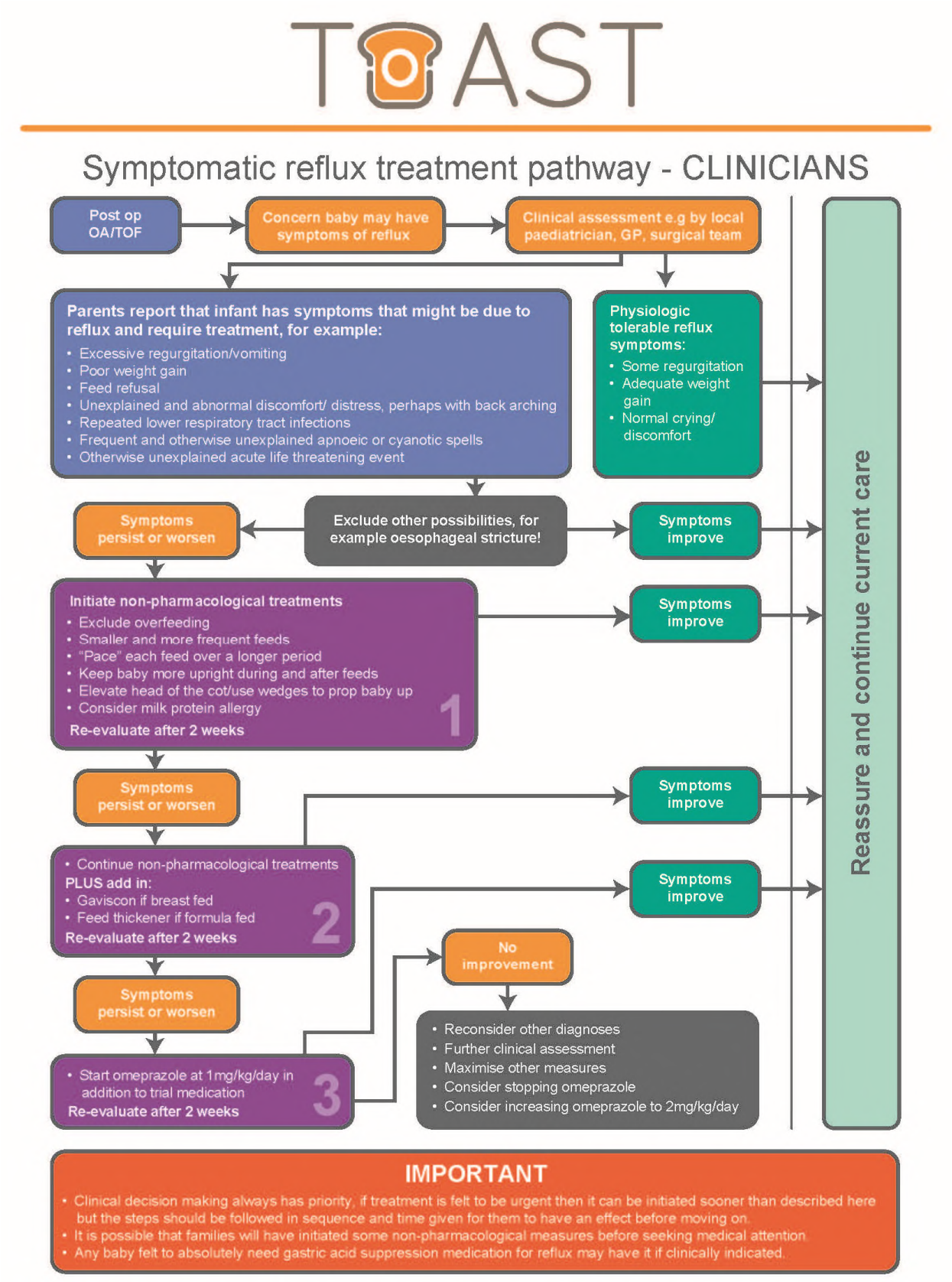
27 APPENDIX A: Symptomatic reflux treatment pathway for clinicians



28 APPENDIX B: Amendment History

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
N/A	v1.0	05/01/2023	Elizabeth Nuthall (Trial Manager)	Original submission to MHRA/REC
N/A	v2.0	03/05/2023	Rachel Williams (Trial Manager)	Revised submission following initial MHRA/REC application
N/A	v3.0	22/05/2025	Hayley Acton (Trial Manager)	Revised submission following withdrawal from MHRA.
Substantial Amendment 1	v4.0	13/10/2025	Hayley Acton (Trial Manager)	• Clarification of intravenous medication reconstitution requirements (Section 11.1) • Co-Lead email address updated (Section 1)

2025-10-06 TOAST Protocol_v4.0

Final Audit Report 2025-11-19

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