Treating Oesophageal Atresia to prevent STricture (TOAST)

TOAST feasibility study protocol

This protocol outlines a mixed methods feasibility element of the Treating Oesophageal Atresia to prevent STricture (TOAST) study. Findings from this initial work will be used to develop a multicentre pragmatic blinded randomised controlled trial (RCT), which will be outlined in a separate protocol.

RESEARCH REFERENCE NUMBERS

PROTOCOL VERSION NUMBER AND DATE

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National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (Project: NIHR 131136)

CHIEF INVESTIGATOR

Professor Nigel Hall and Mr Iain Yardley (Co- CI)

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Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to appropriate research governance frameworks and any subsequent amendments of regulations, GCP guidelines, the Sponsor's SOPs and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

.....

Name (please print):

Position:

Chief Executive

Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

Position:

Chief Investigator

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KEY CONTACTS

Chief Investigator	Professor Nigel Hall (Co-CI) Faculty of Medicine Mailpoint 816, University Surgery Unit Southampton General Hospital Tremona Road Southampton SO16 6YD Mr Ian Yardley (Co-CI) Evelina London Children's Hospital St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH
Qualitative study Lead Investigator	Dr Kerry Woolfall University of Liverpool Block B, Waterhouse Building Liverpool Tel: 0151 794 4634 Email: K.Woolfall@liverpool.ac.uk
Qualitative study main contact	<*Research Associate name to be inserted*> University of Liverpool Block B, Waterhouse Building Liverpool Tel: <*Telephone number to be inserted*> Email: <E*mail address to be inserted*>
Funder(s)	NIHR Health Technology Assessment Programme Tel: 02380 59 5656 Email: netsmonitoring@nihr.ac.uk

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Clinical Trials Unit	NPEU Clinical Trials Unit

STUDY INVESTIGATORS

Name	Department	Organisation
Professor Nigel Hall	Faculty of Medicine	University of Southampton
Mr Iain Yardley	Paediatric Surgery	Evelina London Children's Hospital
Professor Ed Juszczak	Nuffield Department of Population Health	University of Oxford
Professor Marian Knight	Nuffield Department of Population Health	University of Oxford
Dr Louise Linsell	Nuffield Department of Population Health	University of Oxford
Dr Kerry Woolfall	Department of Public Health, Policy and Systems	University of Liverpool
Professor Charles Roehr	Nuffield Department of Population Health	University of Oxford
Professor Oliver Rivero-Arias	Nuffield Department of Population Health	University of Oxford
Mr Gavin Parker	N/A	PPI based in England
Mr John Pearce	N/A	PPI based in England

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Abbreviations

NHS National Health Service

PICU paediatric intensive care unit

RCT randomised controlled trial

REC Research Ethics Committee

SMG study management group

General information

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This document describes the TOAST qualitative study and provides information about procedures for the study. Participant recruitment will be undertaken in compliance with this document.

This protocol outlines a mixed methods feasibility element of the Treating Oesophageal Atresia to prevent STricture (TOAST) study. Findings from this initial work will be used to develop a multicentre pragmatic blinded randomised controlled trial (RCT), which will be outlined in a separate protocol.

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1 STUDY SUMMARY

1.1 Protocol summary

Title:	Treating Oesophageal Atresia to prevent STricture (TOAST)
Short title:	TOAST feasibility study
REC number:	8510
Funder name and reference:	NIHR Health Technology Assessment Programme reference: NIHR131136
Study design:	Mixed methods
Study objectives:	1. To review and explore acceptability of the proposed trial 2. To review and explore potential barriers and solutions to recruitment and approaches to consent, including acceptability of an opt-out consent model, timing of approach, parental decision making, practitioner equipoise, trial information materials and practitioner training needs 3. To review and explore with parents important, parent-centred, primary and secondary outcomes for a definitive RCT
Recruitment	We will recruit parents and practitioners through online routes and our networks
Population:	Parents of recent infants born with oesophageal atresia, including those with/without stricture and those who did/did

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	not receive routine antacid medication. Medical practitioners (surgeons and neonatologists) and nurses (neonatal surgical specialist nurses) caring for infants with oesophageal atresia.
Planned sample size:	15-25 parents and at least 50 practitioners from approximately 18/25 (75%) of UK units
Duration:	9 months
Follow up duration:	No follow up
Planned study period:	March 2021- November 2021

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2 BACKGROUND INFORMATION

2.1 Introduction and rationale

What is the problem being addressed?

Oesophageal atresia is a rare congenital anomaly affecting 1 in 2,500–3,000 live-born babies worldwide, approximately 150 cases/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 a multiple morbidities due to a number of co-existing medical problems. Infants who develop an anastomotic structure 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.

Determining if routine antacid medication reduces the incidence or severity of anastomotic stricture in infants with oesophageal atresia is imperative if we are to understand how to best treat these infants and optimise their chances of the best possible outcomes. As a rare disease, conditions like oesophageal atresia are often overlooked in research agendas, yet current variation in practice is not justifiable nor evidence based. This was recognised in the evidence review that informed the commissioning brief for this commissioned call. We believe it is imperative to rigorously investigate the effectiveness of interventions in infants with oesophageal atresia in our objective to provide them with the best possible outcomes.

As such, if routine antacid medication were found to be effective at reducing incidence or severity of strictures surgeons would be able to confidently prescribe antacid medication and, importantly, their use could be justified in all infants following oesophageal atresia repair. Given the minimal cost of antacid medication, the intervention is likely to be cost effective if clinically effective. Conversely, if found to be ineffective or even harmful, routine use of antacid medication should be avoided. In addition to the clinical justification for this research there is also an economic argument to be made for both the healthcare system, society and families of affected infants. A reduction in number of dilatations even a median of one dilatation per oesophageal atresia case would result in significant savings to the healthcare sector and wider society over time.

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A review of the literature relating to the use of antacid 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. There is a very clear need to 1) understand the role of antacid medication in the care of infants with oesophageal atresia, 2) generate high-grade evidence to advise guideline generating bodies for or against the recommendation of antacid medication, 3) to equip health-care providers with reliable knowledge, derived from performing a large RCT on the use of antacid medication, to, ultimately, 4) allow for uniform, standardised postoperative treatment of infants born with oesophageal atresia. The generation of this knowledge would help to avoid confusion among care-providers and parents concerning the validity of antacid medication prescription in this patient group and ultimately generate a better understanding of antacid medication's role in the development of strictures to significantly benefit patients, families and the healthcare system.

Clinical trials, such as the proposed TOAST trial, are expensive and the chances of successful completion are improved if they are deemed to be acceptable to families and practitioners and feasibility and pilot testing of certain key parameters can be clearly demonstrated.

2.2 Aims and objectives

Aim

To undertake a mixed-methods feasibility study involving practitioners and parents to inform the design and successful conduct of the TOAST trial.

Objectives:

1. To review and explore acceptability of the proposed trial including population of infants for inclusion, type, dose and duration of antacid medication and treatment pathways
2. To review and explore potential barriers and solutions to recruitment, retention and approaches to consent, including acceptability of an opt-out consent model, wording

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and format of information materials, timing of approach, parental decision making, practitioner equipoise, trial information materials and practitioner training needs

3. To review and explore with parents important, parent/family centred, primary and secondary outcomes for a definitive RCT.

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3 STUDY DESIGN AND CONDUCT

3.1 Study design and setting

We will use a mixed methods study design including a survey, interviews and a focus group and practitioners and interviews with parents. This feasibility work will be led by Dr Kerry Woolfall (KW) and the TOAST Research Associate (RA).

3.2 Eligibility criteria

Inclusion criteria:
Parents of recent infants born with oesophageal atresia, including those with/without stricture and those who did/did not receive routine antacid medication in the last three years.

Medical practitioners (surgeons and neonatologists) and nurses (neonatal surgical specialist nurses) caring for infants with oesophageal atresia.

Exclusion criteria:
Parents/Legal representatives who do not speak English.

3.3 Recruitment and sampling

Parents

The research associate (RA) will contact gatekeepers (e.g. charity leads/Chief Executive Officers) of patient support groups for oesophageal atresia infants and ask them to place the TOAST online recruitment advert on the support group's website and/or social media pages. The RA will also send targeted invitations via support group websites, including our collaborating charity TOFS (https://www.tofs.org.uk/home.aspx), and disseminate the advert widely on relevant social media pages for OA infants using hashtags and tagging.

The online advert will contain information and contact details for parents to register their interest in taking part in an interview. TOFS will also send a TOAST email invitation to

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participate to their members. A link to the study website (insert link) will provide additional information about the study, including the Participant Information Sheet (PIS).

Practitioners

We will send email invitations including study PIS via our networks/national associations and use social media to invite a mix of surgeons/neonatologists/specialist nurses from a range of UK hospitals to complete an online survey and/or register their interest in taking part in an online focus group. Social media adverts will include a description the purpose of the study, what is involved, a link to the survey and RA contact details to register interest in an interview or focus group. A link to the study website will provide additional information about the study including the PIS.

We will purposively sample approximately 5-7 questionnaire participants who raise concerns about the proposed trial design and invite them to participate in a telephone interview. The interviews will aim to further explore their concerns and discuss potential ways these could be addressed to assist 'buy in'. Findings from the online survey, practitioner interviews and parent interviews will be used to inform the practitioner focus group topic guide with specific issues and potential solutions discussed to inform the trial design.

Additional social media advertising and emails may be used to recruit to the focus group if an insufficient sample (e.g. less than 8-10 people) are recruited via questionnaire completion.

Arranging interviews and focus group

The RA will check eligibility and send a PIS to all parents and practitioners who register interest in participating. The RA will then arrange a suitable time for an online interview or focus group (practitioners only) via Zoom or Microsoft Teams.

A copy of the draft TOAST trial Participant Information Sheet and TOAST outcomes list will be sent to parents via email. Parents/Legal representatives will be asked to read this PIS and outcomes list before the scheduled interview. Parents/Legal representatives who do not meet the eligibility criteria, or register after the target sample size (15-25 depending upon data saturation point) has been reached, will be thanked for their time and will take no further part in the study.

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A similar process will be followed to arrange practitioner interviews and focus group although a brief outline of the proposed trial will be shared prior to interview rather than PIS and outcomes list described above.

3.4 Informed consent

Practitioner questionnaire

At the beginning of the questionnaire a series of consent statements and check boxes will be used to seek consent for participation.

Telephone interviews

The RA will begin the telephone interview by explaining the aims of the study, providing an opportunity for questions and verbally obtaining informed consent for the study. This will involve the RA reading each aspect of the TOAST Practitioner Consent Form to participants, including consent for audio recording and to receive a copy of the findings when the study is complete. The RA will tick each box on the consent form when the participant provides verbal consent. Informed consent discussions will be audio recorded for auditing purposes.

After the interview is complete the RA will sign the consent form and send a TOAST Feasibility study Participant thank you letter including a copy of consent from. Parents will be sent and a £30 Amazon voucher to thank them for their time.

Practitioner focus group

The consent form will be emailed to practitioners in advance of the focus group and written informed consent will be sought. Practitioners will be asked to electronically sign the consent form and return it to the RA via email before the scheduled focus group.

3.5 *Questionnaire conduct*

The questionnaire will be on an online platform (e.g. Survey Monkey or Quatrics) and contain researcher derived questions to address the study aims. This will include an outline of the trial and questions to assess views on trial acceptability, inclusion/exclusion criteria as well as crucial 'buy in'.

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3.6 *Focus group and interview conduct*

Parent interview conduct

The RA will check that the parent has had sufficient time to read the example TOAST Pilot Study Participant Information Sheet. The interview will then commence using the interview topic guide which will explore parents' views on:

- acceptability of the proposed trial design and procedures such as type and dose, frequency, delivery and length of trial intervention;
- wording and format of participant information materials;
- consent decision-making; the approach to parents regarding enrolment and consenting processes;
- potential barriers to recruitment and retention; and
- parent/family-centred primary and secondary outcome measures for a definitive trial.

Practitioner focus group and interview conduct

Practitioner focus group and interview topic guides will be developed using early parent interview and practitioner questionnaire findings.

Consent will also be checked verbally before the focus group begins including consent for recording the focus group. The focus groups will commence using the focus group topic guide to explore clinicians' views on:

- trial feasibility and acceptability;
- design aspects and additional clinical questions, such as type, dose and delivery of trial intervention; and
- equipoise of clinicians, including willingness of clinicians to approach parents to participate/randomise infants and practitioner training needs.

For interviews the RA will use an interview topic guide to cover the same areas outlined for focus groups but will also draw on the participants questionnaire responses, requesting further details of concerns raised and discussing any potential changes to the trial design or conduct that may help address such concerns.

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3.7 Sample size

We will use snowball sampling for the practitioner survey and aim to include approximately 50 practitioners representing 75% of UK units (e.g. 18/25 of the UK units). Interviews will be conducted with 5-7 questionnaire participants. We anticipate 8-10 medical practitioners and nurses caring for children with oesophageal atresia infants will attend the focus group.

Parent interviews will continue to be conducted until data saturation is reached. This is when the major themes identified in new data are reoccurring from previous participants/ transcripts and no new major themes are being discovered. Based on previous, similar studies [1-3] this is anticipated to be approximately 15-25 parents/legal representatives.

Data analysis

Interviews and focus groups will be transcribed, checked and anonymised as the study progresses. QSR NVivo software will be used to assist in the organisation and indexing of qualitative data. Whilst reflective thematic analysis[4, 5] will be informed by the constant comparison approach of grounded theory, the focus will be modified to fit with the criterion of catalytic validity, whereby findings should be relevant to future research and practice (i.e. the design of the TOAST trial). Findings from the interviews and focus groups will be fed into the design (including patient information materials), approach to consent and training for site investigators.

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4 STUDY MANAGEMENT

Professor Nigel Hall will take overall responsibility for the TOAST Feasibility study management and overseeing progress against timelines/milestones.

All day-to-day management of will be the responsibility of KW and the Study Management Group (SMG). The SMG will meet regularly to review progress of the study against timelines/milestones.

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5 ETHICAL APPROVAL

This protocol, the PISs, consent forms and other study-related documents will be reviewed and approved by the University of Liverpool Ethics Committee with respect to scientific content and compliance with applicable research regulations involving human subjects. Any modification to the protocol and/or study-related documents which may impact on the conduct of the study, potential benefit to patients or patient safety will require a formal amendment. Such amendments will be submitted for approval by the ethics committee.

The Chief Investigator will require a copy of the relevant local approvals prior to any participant identification at the site. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

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6 CONFIDENTIALITY, DATA STORAGE AND CONSENT WITHDRAWAL

Names and full addresses (postal and email) will be collected from participants whom wish to take part in an interview or focus group. These details will be used to contact them to arrange interviews/focus group and send copies of the consent form and study findings (if participants request a copy). These contact details collected will not be used for any other purpose. All personal data will be held at the University of Liverpool. No personal data will be transferred electronically between sites. All files bearing participant identifiers (e.g. contact details) will be destroyed at the end of the study and only participants' consent forms will be retained. Audio recordings of interviews/focus group will be uploaded by the RA securely to a professional transcription company (Transcription UK) website in accordance with the Data Protection Act 1998. Interview audio recordings will be anonymised by the TOAST RA as soon as the transcript is received from the professional transcription company. Any names or potentially identifying information will be removed. Audio recordings will be deleted when the TOAST researcher has checked transcripts against the audio recordings for accuracy. Audio recordings of consent for telephone interviews will be held for auditing purposes.

All data will be securely stored in an encrypted electronic file. The digital audio recordings are likely to contain details that could identify participants. Audio recordings of interviews/focus group will be anonymised during transcription. All original files will labelled with a unique identity number, encrypted and held on password protected University of Liverpool desktop computers. As soon as the digital recordings have been transcribed, the digital files will be archived securely at the University of Liverpool. Publication of direct quotations from participants is necessary to report the results of qualitative research, but no identifying information will appear in transcripts and therefore none will appear in quotations. The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Participation will be entirely voluntary and parents/guardians will be able to withdraw at any time without giving a reason by contacting the RA or KW. This is described in the PIS.

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7 RISKS AND BENEFITS

There is no foreseeable risk to participants. However, due to the emotive nature of the research setting it is acknowledged that there is a slight risk that the research may be burdensome for parents. Therefore a number of steps have been taken to help minimise potential burden.

KW is experienced in the design and administration of interviews with vulnerable groups, including bereaved parents, on emotive topics, therefore all questions and prompts will be designed with the aim of reducing stress or personal intrusion. Participants will be able to select the time and date of the telephone interview. All interviews will be semi-structured yet conducted in a flexible manner to encourage narrative production and enable the interviewer to change topic if the participant seems to be upset. Participants will be told that they can stop the interview at any time.

We do not anticipate that participants in this study will benefit directly, but many people find that taking part in studies of this sort is useful because they have a chance to air their views, reflect on their experiences and ultimately contribute to the design of a clinical trial to improve the treatment of seriously ill children.

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8 DECLARATION OF INTERESTS

None

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9 Sponsorship and indemnity

Not applicable as no direct access to NHS patient or medical records.

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10 Dissemination policy

The progress and results of the TOAST feasibility study will be widely disseminated through participating sites to inform trial recruitment and externally via a paper, to parents through the charity TOFS and social media, NIHR HTA report and a relevant academic conference.

10.1 Progress of the study

To ensure all stakeholders are kept aware and informed, ongoing progress of the study will be disseminated to: participating units through emails and telephone; to the wider clinical community through relevant professional newsletters, professional meetings; and to consumers/participants via the study website/Twitter and Facebook page.

10.2 Study Results

Interim findings from this qualitative study will be fed into the TOAST trial (described in a separate protocol). Overall findings will be fed into a report for the NIHR HTA Programme describing parents' and practitioners' views on the acceptability of the trial, approach to consent and patient centred outcome measures. Findings from this study will also be written up for publication in an open access, peer-review journal and disseminated via social media and presentation at relevant medical conferences. A participant version of the findings will be written and sent to participants who consented to receiving a copy.

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11 REFERENCES

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5. Braun, V., et al., *Thematic Analysis*, in *Handbook of Research Methods in Health Social Sciences*, P. Liamputtong, Editor. 2019, Springer Singapore: Singapore. p. 843-860.

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