Timing of Stoma Closure in Neonates (ToSCiN)

SHORT STUDY TITLE / ACRONYM

ToSCiN

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CHIEF INVESTIGATOR

Mr Nick Lansdale

SPONSOR REPRESENTATIVE

Dr Lynne Webster

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 the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial 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:

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Name (please print):

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Position:

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Chief Investigator:

Signature: Date:

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General information

This document describes the Timing of Stoma Closure in Neonates (ToSCiN) study and provides information about procedures for the study. Participant recruitment will be undertaken in compliance with this document.

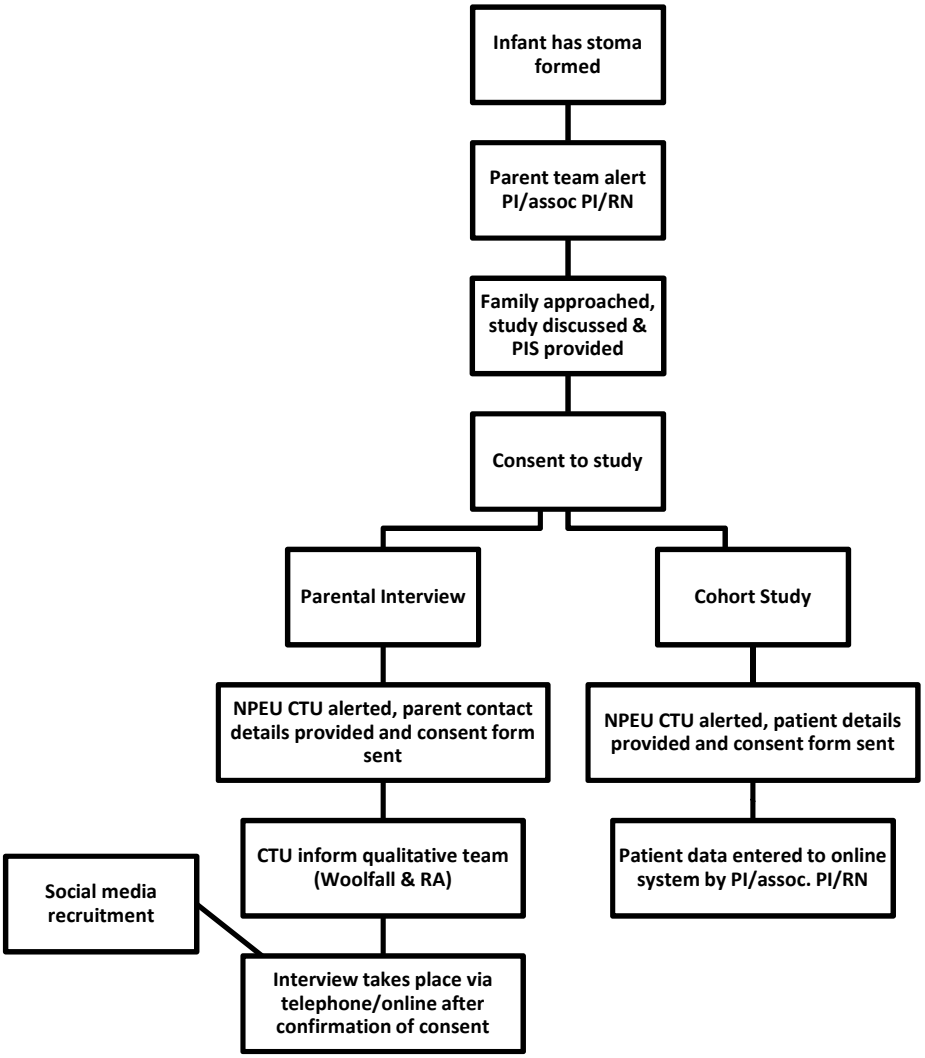
This project will be conducted in accordance with the study protocol and the ethical principles outlined by Good Clinical Practice (GCP) and the Declaration of Helsinki in its most current version.

1. STUDY SUMMARY

1.1. Protocol summary

Title:	Timing of Stoma Closure in Neonates (ToSCiN)
Short title:	ToSCiN
REC number:	20/LO/1227
Sponsor name	Manchester University NHS Foundation Trust
Funder name and reference:	NIHR Health Technology Assessment Programme (project NIHR 128617)
Study design:	Mixed methods comprising three parallel work-streams (WS) incorporating clinician survey; observational cohort study, interviews, focus groups and database analyses.
Study objectives:	1. To establish current UK practice for stoma closure in neonates 2. To determine whether there is equipoise amongst clinicians over when it is best to close stomas in neonates 3. To define 'early' and 'late' stoma closure for a potential trial 4. To define a population of neonates for inclusion in a trial 5. To establish the most appropriate design and outcome measures for a trial 6. To determine the willingness of parents, neonatal surgeons and neonatologists to include neonates in a trial and identify potential barriers to recruitment 7. To assess the suitability of using routinely collected data for gathering clinical information for a trial
Study centres:	Participants identified through (n ≤ 10) neonatal surgical units across the UK and via social media/online support groups
Population:	WS 1: neonatologists, neonatal surgeons, neonatal dieticians and neonatal surgical nurses WS 2: neonates who have recently had a stoma formed, their parents and the clinicians looking after them WS 3: three existing databases
Planned sample size:	WS 1: >75 survey responses WS 2: 30-56 infants
Follow up duration:	No follow up
Planned study period:	March 2020 – October 2022

1.2. Study flowchart (Work-Stream 2)



2. BACKGROUND INFORMATION

2.1. Introduction and rationale

Neonates undergoing emergency surgery on their abdomen frequently require stomas to be formed. Whilst stomas can be life-saving, they pose a number of challenges including fluid and electrolyte imbalance; local wound and skin problems; malnutrition and growth failure.[1-3]. Reversing (closing) these stomas with a second operation is therefore an essential part of the infant's recovery. The timing of this closure is known to be highly variable and the best time to do it remains unclear, with conflicting evidence from published studies and reviews.

A systematic review and meta-analysis from 2017 looked at the timing of stoma closure in infants with necrotising enterocolitis (NEC): 6 articles were included (n=280 infants) comparing early stoma closure (before 8 weeks from formation) with late stoma closure (after 8 weeks).[1] It is likely this review is compromised by a high risk of bias and all studies except one were retrospective. Three of the included studies (n=124) were published in the 1980s and it is likely that care practices have changed since then. The review found that total duration of parenteral nutrition was similar in infants with early versus late closure. Likewise, total length of hospital stay (pre- and post-stoma closure) was not influenced by timing of closure. Included studies also reported similar complication rates after stoma closure between early and late groups.

Other studies have reported conflicting results: a retrospective study from Canada (2009) compared infants who had the stoma closed within 10 weeks (n=13) and after 10 weeks (n=24). Infants with earlier closure had a longer postoperative duration of mechanical ventilation, longer need for parenteral nutrition, and longer hospital stay.[4] Conversely, no differences were observed in survival rates or complications. The opposite results were reported in 2012 by a retrospective Dutch study comparing stoma closure before (n=13) or after 6 weeks (n=62).[5] It reported no differences between the two groups in terms of postoperative adhesions, costs of hospital stay, surgical interventions, and outpatient clinic visits. The authors concluded that, after stabilisation of the patient, the stoma closure could be considered within 6 weeks. A North American study (2015) compared stoma closure before (n=7) or after 8 weeks (n=37) and reported no differences in parenteral nutrition duration and associated cholestasis, duration of mechanical ventilation, the incidence of bowel adhesive obstruction, morbidity and mortality after closure.[6] It demonstrated the duration of hospital admission was shorter in infants who had the stoma closed earlier. A retrospective review of

infants (birth weight <1000g) with stomas (n=55) favoured waiting for stoma closure until a minimum weight was attained.[7] Higher postoperative complications were reported in those <2100g at closure (66.7% vs 10.8%, p < 0.001). Operative time, ventilation, hospital stay and parenteral nutrition use were all longer in those <2100g.

More recently, two conference abstracts (including 3 UK units) reported retrospective data for preterm infants (n=34 and n=76).[8,9] Both report a wide variability in time to closure (27–394 and 21-469 days). Both describe significant stoma morbidity, including stoma complications 7/34 (21%); severe growth failure 46/76 (61%) and emergency readmission in 10% of those discharged prior to closure. These recent studies have important limitations, critically low numbers and the inability to account for important confounders such as disease severity and gestational age. As the authors highlight however, these studies do demonstrate clearly, the potential risks and benefits of early closure.

The above studies demonstrate the existing evidence is of low methodological quality and is conflicting in its assessment of the risk/benefit profile of early vs. late stoma closure. It does however, highlight the morbidity of stomas in infants and the marked variability in practice.

Determining the best time to close stomas in neonates is imperative as it has significant implications for:
i) their health outcomes (short-term e.g. avoiding complications, and long-term e.g. tackling growth failure, which impacts neurodevelopment);[1-10]
ii) families (e.g. reduced NICU stay/healthcare burden/time off work); and
iii) health providers (reduced costs e.g. NICU bed days, parenteral nutrition use and reoperation).

In addition, reducing unwarranted variability in surgical care, such as that highlighted above, is a key priority for the NHS at present; setting standards for a more consistent approach requires a robust evidence base.[11] In order to determine, with certainty, what the optimal timing of closure is, a clinical trial is required. Such a trial is likely to be highly challenging due to: i) the patient group e.g. marked heterogeneity of underlying disease and co-morbidities; ii) clinician factors e.g. willingness to recruit; and iii) parent factors e.g. trial acceptability.

Given that infants have stomas formed for a range of diseases (e.g. necrotising enterocolitis, spontaneous intestinal perforation, jejuno-ileal atresia, meconium ileus and complicated gastroschisis) and are themselves very different (e.g. premature vs. term, varying weights/sizes, an isolated problem vs. multiple co-morbidities), it is imperative we are able to

describe the characteristics of these patient groups; how many are treated each year in the UK and which groups should and could be included in a trial. This study aims to tackle these potential challenges and hence determine if a trial comparing early and late stoma closure is feasible.

2.2. Aims and objectives

Aim

The study aims to answer the question: is it feasible to conduct a clinical trial comparing 'early' vs. 'late' stoma closure in neonates?

Objectives

The specific objectives of the study are:

1. To establish current UK practice for stoma closure in neonates

2. To determine whether there is equipoise amongst clinicians (neonatal surgeons, and neonatologists) and allied health professionals (specialist nurses and dieticians) over when it is best to close stomas in neonates

3. To define 'early' and 'late' stoma closure for a potential trial.

4. To define a population of neonates for inclusion in a trial (in whom there is significant uncertainty over timing) and determine how many infants are eligible for inclusion.

5. To establish the most appropriate design and outcome measures for a trial.

6. To determine the willingness of parents, neonatal surgeons and neonatologists to include neonates in a trial that would randomise to 'early' or 'late' stoma closure and identify potential barriers to recruitment.

7. To assess the suitability of using routinely collected data for gathering clinical information for a trial.

3. WORK-STREAM 1: SURVEY OF CLINICIAN AND ALLIED HEALTH PROFESSIONAL PERSPECTIVES ON NEONATAL STOMA CLOSURE

3.1. Study design and setting

An online survey of clinicians and allied health professionals from neonatal surgical units across the UK, who are involved in the care of newborn infants requiring formation of a stoma.

3.2. Eligibility criteria

Inclusion criteria: Neonatologists in surgical NICUs, neonatal surgeons, neonatal dieticians and neonatal surgical nurses.

3.3. Recruitment and sampling

Potential participants will be identified via promotion through two national organisations: (i) The British Association of Paediatric Surgeons; and (ii) British Association of Perinatal Medicine and personal contacts of the study team, ensuring representative sampling (e.g. geographical area and healthcare professional type). Invitation to complete the survey will be via email.

3.4. Informed consent

Voluntary completion of the online survey will be considered as consent for the anonymous use of provided data for the purposes of the study.

3.5. Survey design

The survey will be designed by the team of ToSCiN co-investigators in order to meet the aims of the study. The survey will ask a series of questions focusing on the above key objectives and will ask these for a number of different clinical scenarios. The survey will ask participants to choose between options for (i) ‘early’ and ‘late’ stoma closure and (ii) which groups of infants should or should not be included in a trial, and will seek reasoning behind these choices and whether equipoise exists. It will explore the respondent’s current preferences for timing of stoma closure (in different groups), what factors are most important to them when determining when to close a stoma and barriers to achieving the perceived optimal timing. Finally, the survey will ask whether respondents would like to attend the final trial design meeting.

3.6. Survey conduct

The survey will be conducted online (LimeSurvey) and distributed as above by the National Perinatal Epidemiology Unit (NPEU), Oxford.[12] There will be automated email reminders to optimise response rates over a period of 6 weeks. Further reminders will use identified study leads in each centre (centre PIs) to encourage local colleagues to complete. Responses will be downloaded as a spreadsheet of answers and stored on a secure server at the NPEU.

3.7. Sample size

We plan to send the survey to around 300 clinicians, and anticipate a minimum response rate of 25% which would give a sample size of 75.

3.8. Analysis

The survey data will be summarised using appropriate descriptive statistics. Numbers (with percentages) for binary and categorical variables and means (and standard deviations), or medians (with lower and upper quartiles) for continuous variables will be presented. The association between responses to key items will be explored using cross-tabulations and regression analyses. Free text responses will be categorised to identify common themes.

4. WORK-STREAM 2: PARENT AND CLINICIAN PERSPECTIVES REGARDING A CLINICAL TRIAL OF NEONATAL STOMA CLOSURE

4.1. Overall design and setting

WS2 Design

The aim of this work stream will be to determine how clinicians and parents view the prospect of a clinical trial that would randomise these infants to 'early' or 'late' closure. (Please note: the term 'parent' will include 'legal representative' and apply for the remainder of this protocol.) Through the collection of clinical data, it will also identify factors that may influence the timing of stoma closure and outcomes that are likely to be important in a future trial. It will explore which of these factors are considered to be most important when determining when to close a neonate's stoma.

WS2 will involve: (2.1) an observational cohort study of neonates who have had a stoma formed; (2.2) questionnaires for the principal clinicians (surgeon and neonatologist) caring for neonates recruited to the cohort study; (2.3) a qualitative study incorporating (i) focus groups with clinicians and (ii) interviews with parents of neonates who have had a stoma closure.

WS2 will address the following study objectives: determining the presence of clinician equipoise; determining willingness of parents and clinicians to include infants in a trial; defining a population for trial inclusion; and establishing appropriate trial design and outcome measures.

WS2 Setting

WS2 will take place in 6 core neonatal surgical units distributed throughout the UK. If required for recruitment purposes, further surgical centres will be added to this group at a later point.

4.2. Recruitment to WS 2

Inclusion Criteria

Eligible infants will include those having a stoma as part of emergency surgery before 44 weeks post-conceptual age:

- **Group A** preterm infants who have stomas formed for necrotising enterocolitis,

spontaneous intestinal perforation or other intestinal pathology

- **Group B** infants (usually born closer to term) who have congenital anomalies that lead to bowel obstruction (e.g. intestinal atresias; meconium ileus and other conditions such as complicated gastroschisis)

Exclusion Criteria

Cases where a stoma is part of a planned treatment pathway e.g. for an anorectal malformation or Hirschsprung's disease, will not be included in this sample.

Sample size

We will aim to recruit 15-28 infants in each of the above two groups (total 30-56 infants). The study is not a randomized controlled trial and is not powered to detect a difference between treatments, therefore there is no formal sample size calculation performed.

Recruitment Process

When a stoma is formed at one of the study centres and an infant meets the inclusion criteria, a member of the infant's care team already known to the parents will approach the parents as soon as practically possible to discuss the study. The most appropriate time for this initial approach will also take into account the infant's clinical condition and family's needs. If the parents express an interest in the study, a site staff member delegated to take consent will discuss the study further and provide a Participant Information Sheet (PIS) that will provide information on participation in both an interview and clinical data collection (WS2.1).

Consent

A participant consent form will be provided indicating that the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is given for access to medical records for data collection and storage. Parents will be allowed time to read the PIS and have an opportunity to ask any questions they may have about their child's participation in TOSCIN. The consent form will request parent contact details (email and telephone number) for the purpose of arranging interviews and permission to contact at a later date if they wish to receive a copy of the study findings. The consent form should be signed by the parent and a member of the local research team. The original consent form will be sent to the NPEU CTU for archiving, a copy will be given to the parent, and a copy kept in the site file.

Recruitment administration

Once an infant is recruited to the study, a member of the local research team will enter the infant's details (including the date of surgery, parent's name and telephone number, taken from the electronic patient record), and also the email addresses for the lead clinicians for that infant (surgeon and neonatologist), into a secure password-protected web recruitment application hosted by the NPEU CTU and stored on secure servers at the NPEU. An email alert will then be sent to the ToSCiN study team about the recruitment.

4.3. WS 2.1 Observational cohort study

We will prospectively record key clinical and demographic information for each of the infants recruited above. This dataset will comprise factors that could influence the timing of stoma closure and outcomes that are likely to be important in a future trial. It will be designed by the study team using the output from WS 1 to guide this. It is likely to include factors such as: gestation, birth weight, underlying disease (resulting in stoma formation), co-morbidities, ventilatory status, nutritional status (including days of parenteral nutrition, time to full enteral feeds and weight gain), surgical findings (including disease extent), time of stoma closure, length of stay and other surgical factors such as stoma recycling and the results of investigations including contrast studies and biopsies/histology.

Data collection

Data for each infant will be collected by the local research team (PI, trainee associate-PI and CRN research nurses) and entered onto an online custom database (hosted by the NPEU CTU).

Timing of data collection

Broadly speaking there will be two time-points for recording clinical data:

Time-point 1

This will be as soon as possible after the operation to form the stoma. These data will include demographics (e.g. gestation, sex and age at surgery), details of the underlying diagnosis, co-morbidities, status at the time of surgery (e.g. weight, ventilatory and cardiovascular support) and details of the operation (findings and procedure carried out).

Time-point 2

This will be around the time of discharge from hospital. These data will include outcomes such as length of stay, death, number of days invasively ventilated, further surgery (including stoma closure), surgical complications, duration of parenteral nutrition, complications of parenteral

nutrition e.g. liver disease and line sepsis, time to full enteral feeds (if applicable) and growth parameters.

4.4. WS 2.2 Practitioner questionnaire

Design

Online questionnaires will be used at three time-points to explore the viewpoints of the practitioners caring for neonates who meet the inclusion criteria (above) to help establish if the practitioner believes the infant they are caring for is suitable for inclusion in a trial that randomises to 'early' and 'late' stoma closure.

The questionnaire will also seek views on what clinical factors are most important in determining whether or not an eligible infant is suitable for randomisation in a trial, by providing a list of factors for the practitioner to rate as being important or not. Since views on trial suitability and/or acceptability may change over time (as an infant's clinical status changes), this approach of documenting the clinician's views at three separate time-points will help determine the most appropriate time to recruit potential participants in any future trial.

Data Collection

The study team at the NPEU CTU will contact the lead surgeon and neonatologist caring for the recruited infant. They will be asked to complete the first questionnaire soon after surgery. The questionnaire will then be sent at two subsequent time points: an 'early' stoma closure and 'late' stoma closure point.

Reminders will be sent in the form of an email or text message after two days of non-completion. The centre PI will also be contacted so they are aware and can encourage their colleagues to complete the questionnaire. The questionnaires will be distributed through the online custom database hosted by NPEU and the responses will be stored in a secure cloud-based clinical data management application (OpenClinica). Analysis will be performed by NPEU statisticians.

4.5. WS 2.3 Interviews and focus groups

Design

This qualitative work stream will involve interviews with parents of infants with experience of stoma closure and focus groups or interviews with practitioners who participate in WS 2.1.

Interviews aim to review and explore parents' views on the acceptability of a proposed trial that randomises to early and late stoma closure, including potential barriers to recruitment, setting and timing of recruitment, important outcomes and study information. Focus groups and interviews will be conducted towards the end of the nine month data collection period (WS 2.1) to elicit views on willingness to recruit to a potential trial, establish whether or not there is equipoise, definitions of 'early' and 'late' stoma closure and trial design, including outcome measures. Focus group and clinician interview topic guides will be informed by early parent interview findings.

Eligibility criteria

Inclusion criteria

- Parents of premature and term infants who have had an stoma in the last three years
- Clinicians in participating surgical units, who are involved in the treatment of infants requiring emergency stoma closure.

Exclusion criteria

- Parents who do not speak English (however, the infants of non-English-speaking parents could be recruited to WS 2.1 if suitable NHS translation services are available to allow them to give informed consent)

Recruitment to parent interviews

We will recruit parents through two routes to maximise the potential sample within the active recruitment period

Recruitment route 1: WS 2 recruitment

Parents of infants recruited in 2.1 will be invited to participate in an interview. Those who consent to participate will be given a card with the Research Assistant (RA)'s telephone number stated so that they recognise it when they are contacted as outlined below.

Recruitment route 2: Social media

The RA will contact gatekeepers (e.g. charity leads/Chief Executive Officers) of support groups for parents of infants. The RA will ask them to post the ToSCiN Study online advert on the support group's website and/or social media pages (e.g. Bliss charity Facebook and Twitter), as well as post the advert via the social media accounts. The advert will include a

description the purpose of the study and interviews. The advert will also contain information and RA contact details for parents to register their interest in taking part. A link to the ToSCiN study page on the NPEU website will provide additional information about the study including the PIS.

Arranging telephone interviews

The RA will respond to parents' requests to participate by contacting each parent by email or telephone (depending on which contact details are provided). The contact details will be accessed via the ToSCiN study administration data application hosted by the NPEU CTU (infants recruited to WS 2.1 only). Access will be granted to members of the study team based at the University of Liverpool who will be contacting the parents. The researcher will check eligibility. Where parents meet the eligibility criteria, the researcher will arrange a convenient time and date for the telephone interview. If preferable to parents, we will offer the interview via an online platform (e.g. Zoom or Microsoft Teams).

We will employ purposive sampling with the aim of maximum variation strategy ensuring mothers and fathers of patient groups A and B (see 4.2) are represented in the sample as well other factors we anticipate may affect suitability to randomisation e.g. underlying disease, treatment centre and socio-economic variation. Parents who do not meet the eligibility criteria, or register after the target group or data saturation has been reached, will be thanked for their time and will take no further part in the study.

Before interviews, a copy of the ToSCiN Participant Information Sheet will be sent to parents via email or post (whichever is preferred). Parents will be asked to read this PIS before the scheduled interview.

Recruitment to practitioner focus groups and interviews

The RA will identify a suitable date and location at participating sites. Details will be sent to clinicians who registered interest in attending. The aim will be to ensure a mix of surgeons, neonatologists, specialist nurses and dieticians from across participating sites are invited to attend each group. The option to conduct the focus groups online will be available due to the COVID 19 pandemic. For clinicians unable to attend, we will conduct up to 10 telephone interviews.

Informed consent

Telephone interviews

The RA will begin the telephone interview by confirming with the person they are calling that it is the intended participant, before explaining the aims of the study, providing an opportunity for questions and verbally obtaining informed consent for the study. The PIS will have been emailed or posted to the participant in advance for them to read. The RA will read each aspect of the 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. After the interview is complete the RA will sign the consent form and send a copy to the participant.

Focus groups

The RA will seek written informed consent for the study using the ToSCiN Practitioner Consent Form. The participant and the researcher will sign the consent form. If online focus groups are used (due to the COVID-19 pandemic), electronically signed consent forms will be requested from all participants via email before the scheduled focus group. The Practitioner Information Sheet will be sent to all participants by email or post. The RA will then check that participants have had enough time to read the PIS and whether they have any questions. They will then email a copy of the consent form to each participant. Participants will complete and return the consent form, either by printing out, signing, and scanning a copy, or by typing their name and signature into an electronic copy.

Interview and focus group conduct

The RA will check that the parent has had sufficient time to read the ToSCiN Participant Information Sheet. Topic guides will be informed by early WS 1 and early WS 2.1 findings as well as trial feasibility and design in HTA funded studies (FiSh, Fever and EcliPSE).[13,14]

Respondent validation will be used so that previously unanticipated topics will be added to the topic guides and discussed with participants as further interviewing and analyses progress. Interviews will be conducted until data saturation is reached (no new themes are emerging in the analysis of data). Based on previous feasibility studies we anticipate interviewing 15-25 parents, a focus group at each participating site and up to 10 telephone interviews with practitioners unable to attend a focus group.

At the end of the interview a £30 Amazon voucher will be given to the participant to thank them for their time. A ToSCiN Study Participant thank you letter will be posted to participants after the interview, including a copy of the consent form.

Interviews will be recorded using an Olympus digital audio recorder. Audio files and transcripts will be stored in encrypted files on a University of Liverpool drive only accessible to Woolfall and the RA. Audio files will be deleted after they have been transcribed and the transcriptions checked by Woolfall and the RA.

4.6. WS 2 Data Analysis

Woolfall and the RA will carry out analysis of anonymised data from the interviews, questionnaires and focus groups using NVivo 10 qualitative data analysis package. WS 2.1 clinical data will be summarised descriptively and will complement the data analysed in WS 3 to provide an overall picture of the demographic and clinical features of infants with a stoma to inform a potential future trial population. Furthermore, by interrogating these clinical data alongside the responses to clinician surveys and parental interviews, we will be in a position to understand which demographic and clinical features are likely to influence both clinician and parental decision-making regarding suitability for a future trial.

Data from WS 2.2 questionnaires will be summarised in key patient groups and time points so that an assessment can be made of broadly what groups of infants' clinicians would be happy to recruit to a trial, at what time points and which factors contribute to these opinions.

WS 2.3 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. Thematic analysis 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 proposed ToSCiN RCT). 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.

5. WORK-STREAM 3: ANALYSIS OF THREE EXISTING NATIONAL DATABASES

5.1. Overall work-stream design

Analyses of 3 existing databases will be carried out in order to generate quantitative data that will address the following study objectives: establishing current UK practice, defining a population for trial inclusion and providing the number of eligible infants; establishing appropriate trial design and outcome measures; and assessing suitability of using routinely collected data for a future trial.

Analyses will be guided by the results of the clinician survey in WS 1. The survey will indicate which patient factors and clinical outcomes are required to be known in order to design a trial: these data can then be extracted from the three databases. Once it is known which infants clinicians consider to be appropriate for trial inclusion, these complementary databases can be used together to calculate the potential number of eligible infants available for inclusion: Hospital Episode Statistics (HES) will provide denominator data for the total number of infants with a stoma, National Neonatal Research Database (NNRD) will provide the granularity required to deduce the proportion of those who have the clinical characteristics for a trial. The databases will not be linked and analyses will proceed separately.

5.2. Data sources

The National Neonatal Research Database (NNRD)

The NNRD holds data from all infants admitted to National Health Service (NHS) neonatal units in England, Scotland and Wales (approximately 80,000 infants annually; 8,000 less than 32 weeks gestation); all NHS neonatal units in England and Wales have been contributing data to the NNRD since 2012.[15]

Contributing neonatal units are known as the UK Neonatal Collaborative (UKNC). Data are extracted from point-of-care neonatal electronic health records completed by health professionals during routine clinical care. A defined data extract, the Neonatal Dataset of approximately 450 data items, is transmitted quarterly to the Neonatal Data Analysis Unit at Imperial College London and Chelsea and Westminster NHS Foundation Trust where patient episodes across different hospitals are linked and data are cleaned (queries about discrepancies and implausible data configurations are fed back to health professionals and rectified). Data items include demographic and admission items (e.g. maternal conditions,

gestation, birth weight), daily items (e.g. respiratory support, medication, surgery, feeding information), discharge items (e.g. feeding and weight at discharge) and ad hoc items (entered if and when they occur, e.g. suspected infection, ultrasound scan findings, abdominal x-ray findings.

The British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPS-CASS)

BAPS-CASS has been the UK's principal data collection system with which to study the surgical management of a range of neonatal conditions on a population basis.[16] It has conducted a number of prospective, multi-centre cohort studies over the past 10 years. Two of these were of infants with conditions that frequently require stoma formation: necrotizing enterocolitis and meconium ileus.

Hospital Episode Statistics (HES)

Hospital Episode Statistics (HES) is a database containing details of all admissions, emergency department attendances and outpatient appointments at NHS hospitals in England. Data are collected during a patient's time at hospital as part of the Commissioning Data Set (CDS). This is submitted to NHS Digital for processing and is returned to healthcare providers as the Secondary Uses Service (SUS) data set and includes information relating to payment for activity undertaken. It allows hospitals to be paid for the care they deliver. This data can also be processed and used for non-clinical purposes, such as research and planning health services, because these uses are not to do with direct patient care, they are called 'secondary uses'.

5.3. Database analyses

The National Neonatal Research Database (NNRD)

Analyses will be carried out by researchers at the Neonatal Data Analysis Unit (NDAU) at Imperial College London where the database is hosted. These activities will be led by co-investigator Battersby and her team will access and analyse the data. Pseudo-anonymised data will be extracted for infants born and admitted to neonatal units in England and Wales over a six-year period between 2014 and 2019 inclusive. Data for infants with a stoma will be verified with host centres.

Inclusion criteria

Eligible infants of any gestational age within the NNRD who had a stoma formed during neonatal care in England and Wales.

Exclusion criteria

Infants with anorectal malformations and Hirschsprung's will be excluded because stoma closures in these infants are usually part of a planned treatment pathway. Data from Scotland will be excluded.

Outcomes

The primary outcome of the study is time to stoma closure defined as days from initial stoma formation.

We will also determine the following outcomes (as well as any others felt to be important in the clinician survey WS 1): survival; length of hospital stay; duration of parenteral nutrition (PN); time to full enteral feeds; growth; complications of surgery; other adverse events; days of invasive ventilation post-operatively; sepsis; necrotising enterocolitis; chronic lung disease/bronchopulmonary dysplasia (preterm only); brain injury on imaging; retinopathy of prematurity (preterm only).

Statistical Analysis

Descriptive results will be presented using means (standard deviations) or medians (interquartile ranges) for continuous variables and proportions for categorical variables. For comparisons between different subgroups of infants, the Chi-squared test will be used for categorical data and the t-test or Wilcoxon rank-sum test for continuous variables. Regression analysis will be used to explore factors associated with timing of stoma closure.

Missing data

We expect missing data from infants that are transferred to surgical centres not co-located within a neonatal unit as they do not submit data to NNRD. These include Great Ormond Street Hospital, Sheffield Children's Hospital, Birmingham Children's Hospital, Alder Hey Children's Hospital. However, we expect that the majority of infants should be repatriated back to neonatal units for post-surgical management.

To maximise data completeness and accuracy, we will verify data for infants with a stoma with host centres.

The British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPS-CASS)

Analyses of data from two previous studies (stored on a secure encrypted server) will be carried out by co-investigators at the University of Oxford. The study on necrotising

enterocolitis (NEC, 2013-14) comprised 236 infants (159 had a stoma) and the study on meconium ileus (2014-2016) comprised 72 infants (21 had a stoma) will be used for this purpose.[16] These cohorts will be reviewed to determine factors including: (i) background characteristics e.g. sex, gestation and birth weight; (ii) operative details e.g. age, findings, type/position of stoma and remaining bowel length; (iii) operative complications including wound infection, adhesive obstruction, stoma 'complications' and need for reoperation within 28 days; (iv) timing of stoma closure; and (v) clinical outcomes e.g. need for parenteral nutrition at 28 days, length of stay and death during hospital stay.

Hospital Episode Statistics (HES)

HES data will be analysed by co-investigator Goldacre via an anonymised, linked dataset (single record for each individual) for 10 years (2006-2016). The data will be stored on a secure encrypted server and will be accessible only by Goldacre. Using OPCS codes for stoma formation and age under 4 weeks (corrected for gestation using maternal data 'tail'), we will establish the number of infants that underwent stoma formation in the neonatal period. ICD-10 codes will be used to establish their primary diagnoses and the timing of stoma closure will be established using OPCS codes. Other outcomes such as death in hospital prior to closure, death before 1 year; LOS (total for that period), operations within 28 days; death within 28 days of operation, total length of stay in hospital in first year of may also be collected if deemed to be important by the results of the survey (WS 1).

These data will provide an overview of current practice and an indication of the number of infants in England eligible for inclusion in a trial. Importantly it will allow us to capture timing of stoma closure for those discharged from the neonatal unit prior to this and hence missed by NNRD.

5.4. Outputs

Summary data from the above analyses will provide a description of the population of infants having stoma formation and subsequent closure in the UK (England for HES) and their clinical course. Specifically, it will: (i) provide characteristics of those having surgery and the number of infants with those particular characteristics; (ii) include details of current surgical practice in the UK; and (iii) give an indication of factors associated with an early or late closure (e.g. gestation or diagnosis), thus helping define a population for trial inclusion and identify how many eligible infants there are likely to be. Furthermore, WS 3 will provide data for outcomes that are likely important for a future trial (and hence could contribute to a sample size calculation).

6. TRIAL DESIGN MEETING

The output of WS 1-3 will be amalgamated and used to inform a one-day trial design consensus meeting at the end of the study, coordinated by NPEU study team and the co-investigator group. All potential trial collaborators and PPI partners will be invited. The aim of the meeting will be to gain agreement on aspects of design and conduct of a future trial (amongst those very people we anticipate will be partners in its delivery). It will make use of an electronic voting system to gain consensus when required. The format for the meeting will be as follows:

1. A summary of qualitative and quantitative data obtained in WS 1-3 will be presented, with opportunity for open discussion. A final decision will be reached by consensus on whether or not a trial is feasible.

2. If a trial is deemed feasible, the next part of the meeting will be to consider and reach agreement on the preferred trial design. Based on the results of WS 1-3, a number of options for each of the design elements below will be put forward to the group and agreement reached where possible.

i) study design (e.g. individual versus cluster randomisation)

ii) patient group (inclusion and exclusion criteria)

iii) intervention and comparator (timing of early and late stoma closure)

iv) primary and important secondary outcome measures (and how to record them)

v) approach to recruitment and consenting (including timing)

Key outputs

By the end of this meeting we aim to have a consensus assessment of whether or not a trial is feasible and if so, to have the required information to be able to form the outline of a suggested trial protocol.

7. PATIENT AND PUBLIC INVOLVEMENT

7.1. Involvement in funding application and study design

The co-applicant group included a parent of a baby who had a stoma as a newborn and who had also previously successfully advised research projects. She brought personal experience and an understanding of how to engage potential participants. She was involved in the application in the following ways: (i) discussing her research priorities with the CI which then influenced the study design and (ii) reading through and modifying the plain English summary.

The Parent Advisory Group (PAG) set up in 2012 to inform Marian Knight's NIHR Professorship work on paediatric surgery was also consulted regarding their viewpoints on being involved in focus groups and interviews.

7.2. Involvement during the project

The charity Bliss (charity for babies born premature or sick) are supporting and assisting with the project as detailed below.

The Study Steering Committee (SSC) will include a parent of a child who had a stoma as a newborn baby.

A further group of parents who have all had infants with a stoma have been identified and will form the Parent Advisory Group specifically for the ToSCiN study. This group will meet a total of three or four times during the study but predominantly early on to advise on the study materials (PIS, consent forms and topic guides), provide input into the wording of interview topic guides for the parental interviews, and advise on appropriate ways of approaching parent participants to optimise engagement. The group will be convened by Hall and supported by Bliss staff. They will attend the final study meeting where they will play an important role in: (i) helping to determine whether a trial is acceptable to parents and hence feasible; (ii) influencing a potential future trial's design (particularly how infants are recruited).

Research findings will be disseminated to patients and the public through social media channels including those established by Bliss.

8. STUDY MANAGEMENT

Clinical Trials Unit (CTU) - The NPEU will manage the overall project, undertake the clinician survey, organise the trial design meeting and enable data collection.

Sponsor – Manchester University NHS Foundation Trust is the nominated sponsor for the proposed study.

Project Management Group (PMG) - the study will be run on a day-to-day basis by this group which reports to the Study Steering Committee (SSC), which in turn is responsible to the NIHR HTA programme. The core PMG will consist of the Chief investigator, the Lead for Qualitative Work, the CTU Clinical Director, the Senior Trials Manager, the Study Coordinator, the Trials Programmer, and other project staff. The core PMG will meet every month.

Co-Investigator Group (CIG) - this extended PMG will meet every two months initially, three-four months subsequently, and will comprise all members of the co-applicant group and the members of the core PMG to review progress, troubleshoot and plan strategically.

Study Steering Committee (SSC) will include an independent chair, at least two other independent members, a PPI representative(s), and the Chief investigator. We have identified and have agreement from individuals suitable to sit on the SSC, pending NIHR ratification. The SSC will review the progress of the trial and report on progress to the funder. Observers from the HTA programme will be invited to attend SSC meetings.

We do not anticipate the need for a Data Monitoring Committee as all included work in WS 1 and 2 is survey- or questionnaire-based; in the unlikely event of unexpected outcomes resulting from the questionnaires we would take advice from the SSC.

9. ETHICAL APPROVAL

This protocol, patient information resources (e.g. PISs), consent forms and other study-related documents will be reviewed and approved by the NIHR HTA Programme and an NHS Research Ethics Committee (REC) 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 NHS REC.

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.

Existing Database Approvals

The Neonatal Data Analysis Unit (NDAU) holds UK Research Ethics Committee approval, 16/LO/1093, and Confidential Advisory Group (CAG) approval, ECC 8-05(f/2010), to form the NNRD.

BAPS-CASS has been approved by the NRES Committee South Central-Oxford A (Ref: 12/SC/0416).

The linked HES and mortality data has been supplied by NHS Digital with signatories Garry Coleman (NHS Digital), Richard Langley (HSCIC), Sophie Baines (University of Oxford) for application “Epidemiological and health services research using routine NHS data: work programme of the Unit of Health-Care Epidemiology, Oxford University” and application reference number DARS-NIC-315419-F3W7K.

10. CONFIDENTIALITY, DATA STORAGE AND CONSENT WITHDRAWAL

WS 2.1 Observational study

Identifiable data will be collected for patients recruited in WS 2.1; this will include name, date of birth, NHS number, parent's name and contact details; these details are required for the contacting the parents in WS 2.3. When consent has been taken a member of the local site study team will enter the data into the secure web recruitment application hosted by the NPEU CTU; once the data has been entered, the application will generate a unique study ID number. This study number will be indicated on the consent form, which will be archived at the CTU. The data will be stored on servers hosted by the NPEU and only accessible via the study administration database application (TADA). The NPEU CTU will give access to members of the study team at the University of Liverpool who will be contacting the parents in WS 2.3.

Observational data will be collected at three time points, and entered into a secure cloud-based clinical data management application (OpenClinica). Data will be entered by trained members of the local study team.

Archiving will be carried out in accordance with NPEU standard operating procedures (SOPs) for a minimum of 25 years.

The Chief Investigator and CTU will preserve the confidentiality of participants taking part in the study and will not disclose or reproduce any information by which participants could be identified.

WS 2.2 Practitioner questionnaire

Data will be entered into OpenClinica at three time points by the infant's lead surgeon or neonatologist. Only the members of the NPEU CTU study team and site staff responsible for entering data will have access to the infant's data.

WS 2.3 Qualitative Study

Names and full addresses (postal and email) will be collected from participants who wish to take part in an interview. These details will be used to contact them to arrange interviews and send copies of the consent form and study findings (if participants request a copy). We will also seek consent to contact parents in the future about related studies. The 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 and focus groups will be uploaded by the RA securely to a professional transcription company website (UK Transcription) in accordance with the Data Protection Act 2018. Interview audio recordings will be anonymised by the ToSCiN 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 ToSCiN researcher has checked transcripts against the audio recordings for accuracy. Audio recordings of consent for interviews will be held for auditing purposes.

All data will be securely stored in a locket cabinet or in an encrypted electronic file. The digital audio recordings are likely to contain details that could identify participants. Audio recordings of interviews and focus groups will be anonymised during transcription. All original files will be 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 deleted. 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.

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 Woolfall. This will be stated in the consent form.

The datasets for each work-stream will remain stored at their host institutions as outlined above and the members of the research team based there will provide summary data and analysis for publications as required. There will be no final data transfer combining the data into one raw dataset.

11. 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. Therefore a number of steps have been taken to help minimise potential burden.

Woolfall 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.

A distress protocol is also in place if a participant does become distressed during an interview. The protocol includes a number of steps: first, the interview is immediately suspended by the researcher (and the recording device switched off) to give the participant time to recover. The researcher and participant collaboratively decide upon their ability to continue the interview following this period. If the participant continues with the interview, the researcher ensures that the interviewer does not terminate the conversation whilst the participant is distressed. If the participant feels unable to continue, the researcher offers to contact a family member or friend. The researcher will not directly provide mental health advice, but directs participants to relevant support services outlined in the participant information sheet. Participants will never be left in a distressed state. If the participant consents, a courtesy call will be made in the following days to ensure that the participant is no longer distressed. The appointed researcher will have relevant experience of conducting interviews and will receive additional training from Woolfall, including use of the distress protocol.

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.

12. DECLARATION OF INTERESTS

None

13. SPONSORSHIP AND INDEMNITY

Manchester University NHS Foundation Trust is the Sponsor for the ToSCiN study and holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study.

14. FUNDING

This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (project reference NIHR 128617). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

A written agreement with the site PI's institution and Manchester University NHS Foundation Trust will outline the funding arrangements to sites. The SSC will meet and review the financial aspects of the study at least annually and report to the Sponsor.

15. DISSEMINATION POLICY

Social Media

We will set up a study Twitter account and use established links to professional and patient Twitter groups to create a network of interested parties. We will then post regular updates of study progress. This approach will be further advised by our Parent Advisory Group.

Patients support groups

We will invite the charity Bliss's established parent groups to disseminate our results to a wide network of parents.

Open access publication

We intend to produce approximately four publications from the results of this study and publish these in open access journals that ensure outreach to the most relevant readership e.g. the Archives of Diseases in Childhood, Fetal and Neonatal Edition. A final report will also be published in the NIHR HTA journal.

Conference presentation

We intend to present our study findings at the British Association of Paediatric Surgeons' Annual Congress and neonatal meetings including the Neonatal Society Meeting, the British Association of Perinatal Medicine (BAPM) Annual Meeting and the Royal College of Paediatrics and Child Health Annual Meeting.

Feedback to professional groups

Our study team are active in UK neonatal and neonatal surgical communities: they will provide ongoing updates to the wider group of clinicians across the UK. These updates can be provided at regular established meetings including the National Paediatric Surgery Research Collaborative (chaired by Co-Applicant Hall); BAPS-CASS steering group (chaired by Co-Applicant Knight); and neonatal study group meetings (the Neonatal Nutrition Network N3 of which Gale and Battersby are members and the NIHR Neonatal Clinical Studies Group of which Gale is a member). The principal impact of our study will be its effect on determining whether or not a definitive trial can go ahead: if we demonstrate that a trial is feasible then we would disseminate our findings to potential funders in order to explore the options of funding a trial. We would use our findings from this study to put ourselves in the best possible position to carry out a successful trial by being armed with the required information with which to optimise the trial design and recruitment process.

16. AUDITS

The study will be subject to the audit and monitoring regime of Manchester University NHS Foundation Trust in line with applicable MFT SOPs and policies. The study will have, as a minimum, an annual survey sent out for completion by a member of the research team.

The project was peer-reviewed by external reviewers as part of the funding application.

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18. APPENDIX 1 PROTOCOL VERSION HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
N/A	1.0	07-Oct-2020 (note: never released to sites; submitted for REC review)	N/A	N/A – first version of document
N/A – amended as part of initial REC application	2.0	03-Dec-2020	Madeleine Hurd	Provided additional detail on data management as requested by REC, including confirmation interview audio files would be deleted post-transcription. Updated information on data collection to match current plan for the study (following completion of WS 1 and development of data collection forms for WS 2). Clarified how parents will be approached. Included mention of use of telephone number card. Minor corrections throughout.
Non-substantial amendment 3	3.0	20-Dec-2021	Madeleine Hurd	Updated study end date from February 2022 to October 2022 following approval of no-cost extension. Updated infant sample size from 30 to 40 to 30 to 56. Amended study statistician from Louise Linsell to Pollyanna Hardy.