FROSTTIE

Study Title:	FROSTTIE: A randomised controlled trial of FRenotomy and breastfeeding support Or breastfeeding Support without frenotomy to investigate continuation of breastfeeding for babies with Tongue-TIE
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Clinical Trials Unit:	NPEU CTU
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There are no conflicts of interest to declare.

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1. KEY TRIAL CONTACTS

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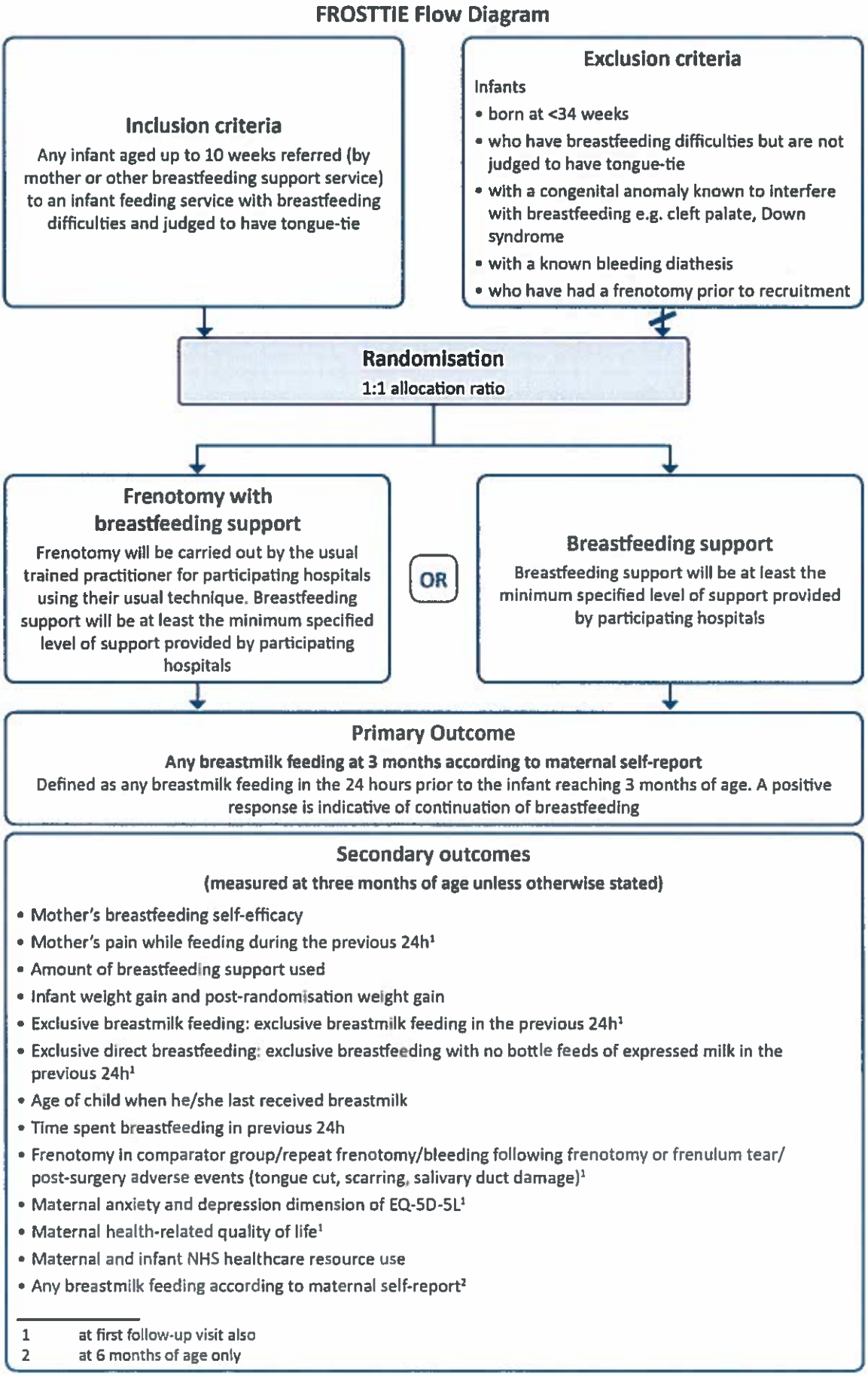
2. SYNOPSIS

Study Title	FROSTTIE: A randomised controlled trial of FRenotomy and breastfeeding support Or breastfeeding Support without frenotomy to investigate continuation of breastfeeding for babies with Tongue-TIE	
Internal ref. no. / short title	FROSTTIE	
Study Design	Multicentre randomised controlled trial	
Study Participants	Any baby aged up to ten weeks referred to an infant feeding service with breastfeeding difficulties and judged to have tongue-tie.	
Planned Sample Size	870	
Planned Study Period	Participant involvement for 36 months; with follow-up 2.5 years following end of intervention collecting routine health data.	
Aim	To investigate whether frenotomy is clinically and cost effective to promote continuation of breastfeeding at three months in infants with breastfeeding difficulties diagnosed with tongue-tie.	
	Objectives	**Outcome Measures**
Primary	To compare the rate of any breastfeeding at 3 months of age in infants with breastfeeding difficulties and diagnosed tongue-tie who undergo frenotomy and receive breastfeeding support versus those who receive breastfeeding support only.	Any breastmilk feeding at 3 months according to maternal self-report, defined as any breastmilk feeding in the 24 hours prior to the infant reaching three months of age. A positive response is indicative of continuation of breastfeeding.
Secondary	• To investigate the effect of frenotomy on various important other secondary outcomes measured at first follow-up visit and/or three months of age. • To investigate the impact of tongue-tie severity and mothers' prior beliefs on the primary outcome.	Measured at first follow-up visit and 3 months of age: • mother's pain while feeding during the previous 24 hours • exclusive breastmilk feeding • exclusive direct breastfeeding • frenotomy in comparator group • repeat frenotomy • bleeding (following frenotomy or frenulum tear) • post-procedure adverse events (tongue cut, scarring, salivary duct damage)

		• maternal anxiety and depression dimension of EQ-5D-5L • maternal health-related quality of life (EQ-5D-5L) Measured at 3 months of age: • mother's breastfeeding self-efficacy (Breastfeeding Self-Efficacy Scale – Short Form) • amount of breastfeeding support used, measured by total number of contacts with any breastfeeding supporter since the FROSTTIE procedure (whether face to face, or by telephone) • infant weight gain from birth • infant post-randomisation weight gain • age of child when s/he last received breastmilk • time spent breastfeeding in previous 24 hours • maternal health-related quality of life (EQ-5D-5L)
	• To examine, through an alongside economic evaluation, whether any additional benefits associated with frenotomy are justified by any additional health care resources needed to deliver the intervention	• maternal and infant NHS healthcare resource use
	• To investigate the effect of frenotomy on breastfeeding rates measured at six months.	Secondary outcome measured at 6 months: • any breastmilk feeding

3. TRIAL FLOW CHART



4. ABBREVIATIONS

BTAT	Bristol Tongue Assessment Tool
CI	Chief Investigator
CIG	Co-Investigator Group
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
HRA	Health Research Authority
LATCH	A breastfeeding assessment tool (Latch, Audible swallowing, Type of nipple, Comfort, Hold)
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPEU	National Perinatal Epidemiology Unit
PI	Principal Investigator
PIL	Parent Information Leaflet
PMG	Project Management Group
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
S/AE	Serious / Adverse Event
SF-MPQ	Short Form McGill Pain Questionnaire
SOP	Standard Operating Procedure
TSC	Trial Steering Committee

5. BACKGROUND AND RATIONALE

Tongue-tie can be diagnosed in 3–11% of babies (Edmunds et al. 2011), with the variation in reported prevalence thought to relate to the use of different diagnostic or severity criteria (Fox et al. 2016). However, less than 50% of babies with tongue-tie are reported to have breastfeeding difficulties, although this reported proportion is also highly variable, with some studies reporting almost universal difficulties, and others reporting very few feeding difficulties which relate to the tongue-tie itself, instead noting that incorrect positioning and attachment are the primary reasons behind the observed breastfeeding difficulties and not the tongue-tie itself (Edmunds et al. 2011). In a recent survey (Fox et al. 2016), it was noted that management of tongue-tie in infants with breastfeeding difficulties is therefore highly variable across the UK. This is coupled with highly variable provision of breastfeeding support (World Breastfeeding Trends Initiative 2016), which can range from minimal to expert and intensive, and using a variety of different models including peer supporter, midwife and health visitor.

A recent Cochrane review (O'Shea et al. 2017) has identified five prior RCTs of frenotomy including a total of only 302 infants. The trials are small and under-powered and/or include only very short-term or subjective outcomes, suggesting further robust evidence is needed. Hence there is considerable controversy regarding, not only the diagnosis and clinical significance, but also the management of tongue-tie. Current NICE guidance (NICE 2005) allows for the procedure, based on lack of safety concerns, but notes very limited evidence of efficacy. There is therefore a clear need for an assessment of the clinical and cost-effectiveness of frenotomy for babies diagnosed with tongue-tie in the form of an adequately powered, pragmatic randomised controlled trial; taking into account the diagnostic controversy and variation in practice.

We therefore propose a multicentre randomised controlled trial, with internal pilot, to investigate whether frenotomy with breastfeeding support is clinically and cost-effective to promote continuation of breastfeeding at three months of age in infants with breastfeeding difficulties and diagnosed tongue-tie, compared with breastfeeding support only. Any baby aged up to ten weeks referred (by mother or other breastfeeding support service) to an infant feeding service with breastfeeding difficulties and judged to have tongue-tie will be eligible. The results of the trial will be generalisable to any population with a similar profile to those participating in the trial due to the pragmatic nature of the trial recruitment and intervention strategies.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Time point(s) of evaluation of this outcome measure (if applicable)
Primary Objective To compare the rate of any breastfeeding at 3 months of age in infants with breastfeeding difficulties and diagnosed tongue-tie who undergo frenotomy and receive breastfeeding support versus those who receive breastfeeding support only.	Any breastmilk feeding at 3 months according to maternal self-report: defined as any breastmilk feeding in the 24 hours prior to the infant reaching three months of age (Dennis, Jackson et al. 2014, McFadden, Gavine et al. 2017). A positive response is indicative of continuation of breastfeeding.	3 months of age
Secondary Objectives To investigate the effect of frenotomy on various important other secondary outcomes measured at first follow-up visit and/or three months of age. To investigate the impact of tongue-tie severity and mothers' prior beliefs on the primary outcome.	**Mother's breastfeeding self-efficacy:** measured using the Breastfeeding Self-Efficacy Scale – Short Form **Mother's pain while feeding during the previous 24 hours*:** measured using visual analogue scale of the Short Form McGill Pain Questionnaire (SF-MPQ), modified into a Likert-type scale **Amount of breastfeeding support used:** measured by total number of contacts (whether face to face or by telephone) with any breastfeeding supporter since the FROSTTIE procedure **Infant weight gain:** measured as difference in weight for age z-scores between birth and three months of age **Infant post-randomisation weight gain:** measured as difference in weight for age z-scores between baseline and three months of age	First follow-up visit (outcomes indicated by *) 3 months of age (all secondary outcomes)

	Exclusive breastmilk feeding*: exclusive breastmilk feeding in the previous 24 hours **Exclusive direct breastfeeding*:** exclusive breastfeeding directly from the breast with no bottle feeds of expressed milk in the previous 24 hours **Age of child when s/he last received breastmilk:** age when child last received breastmilk, to determine when and whether switch to exclusive formula feeding has occurred **Time spent breastfeeding in previous 24 hours:** time in minutes/hours spent breastfeeding in previous 24 hours **Frenotomy in comparator group*:** measured by a specific question **Repeat frenotomy*:** measured by a specific question **Bleeding following frenotomy or frenulum tear*:** measured by a specific question **Post-procedure adverse events (tongue cut*, scarring, salivary duct damage*):** measured by specific questions **Maternal anxiety and depression dimension of EQ-5D-5L*** **Maternal health-related quality of life:** as elicited by the EQ-5D-5L*	
To examine, through an alongside economic evaluation, whether any additional benefits associated with frenotomy are justified by any additional health care resources needed to deliver the intervention	**Maternal and infant NHS healthcare resource use:** collected at 3 months of age on general practice visits and hospital admissions	

To investigate the effect of frenotomy on breastfeeding rates measured at six months.	**Any breastmilk feeding at 6 months** according to maternal self-report: defined as any breastmilk feeding in the 24 hours prior to the infant reaching six months of age	At 6 months of age

7. STUDY DESIGN

A multicentre randomised controlled trial of frenotomy with breastfeeding support versus breastfeeding support with no frenotomy to investigate continuation of breastfeeding.

Infants aged up to ten weeks referred to an infant feeding service with breastfeeding difficulties and judged to have tongue-tie will be randomised to frenotomy with breastfeeding support versus breastfeeding support with no frenotomy.

The trial aims to recruit 870 participants from 19 centres in the UK over 24 months (2 recruits per centre per month). Each participant will undergo: screening/baseline, randomisation, intervention, routine post-intervention follow-up visit, 3 and 6 month post-intervention follow-up.

Data on the primary and secondary outcomes will be collected by mother's self-report via SMS text or web-link to data capture platform, or extracted from hospital records by assessors blinded to treatment allocation, or by linkage to routine data, where possible, for longer-term outcomes.

A training programme will be developed for recruiting midwives at all centres, to include consent processes, explanation of need for rapid access to breastfeeding support following group allocation to ensure mothers have high quality breastfeeding support and to minimise recourse to private frenotomy in the comparator group, tongue assessment using the Bristol Tongue Assessment Tool (BTAT) score (Ingram, Johnson et al. 2015) as well as standard trial processes.

In order to minimise bias, staff conducting follow-up visits should not be the same staff member who performed the procedure. All trial staff, with the exception of those providing the frenotomy service, will be masked to trial allocation wherever possible. Trial staff will be considered as follows in order to maintain masking as far as possible:

- Infant feeding/frenotomy service staff: Will conduct the initial assessment of infant eligibility and provide parents with information about the trial. Will take informed consent from parents who wish their infant to be entered into the trial. Infants randomised to the intervention will have the frenotomy performed without the parents directly observing the procedure; infants randomised to breastfeeding support alone will be shielded from view as if they were undergoing the procedure. Parents will thus be masked to allocation group. All parents will be provided with a standard post-frenotomy observed feed and standard post-frenotomy advice.
- Breastfeeding support workers: Follow-up breastfeeding support outside the hospital frenotomy clinic should be provided by different staff from those conducting the initial assessment of infants, and from those in the frenotomy service to maintain masking as far as possible. Support workers will be advised to urgently re-refer infants participating in the trial who have ongoing feeding difficulties to the hospital infant feeding service for further assessment in order to minimise the chance of parents seeking frenotomy with a private provider. Staff in the infant feeding service will offer breastfeeding support to any mothers referred back with the aim of avoiding frenotomy or repeat frenotomy. However, babies with ongoing problems may be re-referred to the frenotomy service for a first or repeat frenotomy in the event that this is felt to be clinically indicated.

7.1. Internal pilot

The internal pilot will assess monthly recruitment, masking, loss to follow up and contamination. It will assess the following assumptions:

- Monthly recruitment of 2 infants per centre by month 6
- Centres take 2 months to reach stable recruitment
- All pilot centres actively recruiting by month 6
- Masking is effective
- Loss to follow-up overall is less than 5%
- Contamination between arms is no more than 5%
- The proportion of babies recruited at four weeks or over is less than 40%

Pre-defined stop-go criteria after 9 months, with 266 recruits predicted, will be:

- Recruitment is 75% or more (N ≥ 199) - continue directly with the main trial;
- Recruitment is 50-75% (133 ≤ N < 199) - recruit more centres and review in 6 months;
- Recruitment is < 50% (N < 133) - undertake an urgent detailed review of options with Trial Steering Committee to subsequently recommend to the funder.

All mothers of infants recruited during the pilot phase will be asked at the three-month follow-up whether they remained masked to their infant's treatment allocation. If parents remain masked, the study will continue with the masked design, recording blinding status.

8. PARTICIPANT IDENTIFICATION

8.1. Study participants

Infants aged up to 10 weeks referred to an infant feeding service (by a parent, midwife or other breastfeeding support service) with breastfeeding difficulties and judged to have tongue-tie.

Tongue-tie will be assessed using the BTAT; however all infants judged to have tongue-tie will be included irrespective of the formally assessed score.

Although not the study population, the mothers of eligible infants will be asked to consent for their babies and themselves to take part in the study as they will be providing outcome data, through maternal self-reporting, on their experiences amongst other measures.

8.2. Inclusion criteria

- Any infant aged less than 10 weeks referred (by parent or other breastfeeding support service) to an infant feeding service with breastfeeding difficulties and judged to have tongue-tie, whose parent has given informed consent for participation.

8.3. Exclusion criteria

Infants may not enter the study if ANY of the following apply:

- Infant is older than 10 weeks
- Infant has breastfeeding difficulties but is not judged to have tongue-tie
- Infant was born at less than 34 weeks' gestation
- Infant has a congenital anomaly known to interfere with breastfeeding e.g. cleft palate, Down syndrome
- Infant has a known bleeding diathesis
- Infant has had a frenotomy prior to recruitment

9. STUDY PROCEDURES

9.1. Recruitment

Potential participants will be identified by the infant feeding/frenotomy service staff from the population of infants with breastfeeding difficulties referred to hospital infant feeding services through volunteer breastfeeding supporters, other breastfeeding counsellors, midwives, or by self-referral by parents.

Parents will be provided with written and verbal information about the study. Any baby who is referred for tongue-tie will be screened for eligibility to take part.

9.2. Screening and eligibility assessment

As standard, following referral to hospital, infant feeding will be observed and tongue assessment conducted, and mothers will receive advice on positioning and attachment. To take account of the diagnostic controversy and varying opinions concerning clinical significance, any baby with breastfeeding difficulties diagnosed with tongue-tie is eligible for inclusion. The tongue-tie diagnosis will be made according to usual hospital practice which may include using any suitable tool. The degree of tongue-tie severity may vary, since there is no fully validated tool and no evidence associated with a specific cut-off in severity score. However, all babies whose parents consent for their participation in the trial will have an assessment of their tongue-tie made using the Bristol Tongue Assessment Tool (BTAT) (Ingram, Johnson et al. 2015), which will enable a subgroup analysis to examine the effect of frenotomy amongst babies who may be considered to have more and less severe tongue-tie.

9.3. Informed consent

A verbal explanation and written information, the Parent Information Leaflet (PIL), will be given to the parent(s). The parent(s) will be allowed as much time as they need to consider the information, and the opportunity to question staff to decide whether they consent for their baby to participate in the study. As the mother will be providing outcome data via self-reporting, they will also consent for themselves.

Written informed consent will then be obtained by means of the mother's dated signature and dated signature of the person who obtained the informed consent. The mother of the infant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

Written informed consent will also include optional consent for linkage of their baby's data to routine data sources to allow the potential for further follow-up beyond the funded trial, for example to routine health visitor data at 2.5 years.

9.4. Randomisation

The infants entered into the trial will be randomised 1:1 to either:

- frenotomy with standard breastfeeding support (intervention arm), or
- no frenotomy with standard breastfeeding support (comparator arm).

Multiples (twins or higher order multiples) will be randomised to the same arm. Stratified block randomisation (using variable block sizes) will be performed via a secure 24-hour web-based randomisation system (hosted by the NPEU CTU, University of Oxford) stratified by infant's age (<2 and ≥2 weeks) at randomisation, mother's parity (primiparous or multiparous) within centre. A telephone back-up system will be available 24 hours a day (365 days per year). Users of the system will have no insight into the next allocation.

A statistician independent of the trial 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. The implementation of the randomisation procedure will be monitored by the Senior Trials Programmer and independent statistician throughout the trial and reports will be provided to the Data Monitoring Committee.

9.5. Baseline assessments

Baseline information will be collected on sociodemographic and other characteristics, including:

- Infant birthweight
- Infant current weight
- Estimated date of delivery
- Current feeding practices (e.g. expressed breastfeeding, use of infant formula)
- Assessment of the degree of tongue-tie using the BTAT
- Mother's prior beliefs about frenotomy: Using a three-point Likert scale, the opinions of all mothers of infants recruited to the trial will be sought at the time of recruitment on their prior belief of the potential benefit of frenotomy
- EQ-5D-5L
- Mother's pain while feeding during the previous 24 hours: measured using visual analogue scale of the Short Form McGill Pain Questionnaire (SF-MPQ), modified into a Likert-type scale (scores ranging from 0 to 10) (Dennis, Jackson et al. 2014)
- Exclusive breastmilk feeding: exclusive breastmilk feeding in the previous 24 hours

- Exclusive direct breastfeeding: exclusive breastfeeding directly from the breast with no bottle feeds of expressed milk in the previous 24 hours
- Pre-trial entry breastfeeding support received

9.6. Subsequent visits/data collection

9.6.1. Intervention

The following will be undertaken and data collected from the clinician performing the procedure on the day of the intervention:

- Intervention undertaken according to randomisation schedule and technique used (see section 9.4)
- Bleeding following frenotomy or frenulum tear
- Post-procedure adverse events (tongue cut, salivary duct damage): measured by specific questions

9.6.2. Routine follow-up visit

The following data will be collected from the mother at the routine follow-up visit (approximately one week post-intervention according to hospital practice):

- Mother's pain while feeding during the previous 24 hours: measured using visual analogue scale of the Short Form McGill Pain Questionnaire (SF-MPQ), modified into a Likert-type scale (scores ranging from 0 to 10) (Dennis, Jackson et al. 2014)
- Exclusive breastmilk feeding in the previous 24 hours
- Exclusive breastfeeding directly from the breast with no bottle feeds of expressed milk in the previous 24 hours
- Request for frenotomy/repeat frenotomy (defined as any further procedure on tongue-tie)
- Bleeding following frenotomy or frenulum tear
- Post-procedure adverse events (tongue cut, salivary duct damage): measured by specific questions
- Maternal anxiety or depression as indicated by the anxiety and depression dimension of EQ-5D-5L
- Maternal health-related quality of life: as elicited by the EQ-5D-5L

9.6.3. 3 month follow-up

The following data will be collected using maternal self-report (by smart-phone, tablet, computer, postal questionnaire or telephone) when the infant is 3 months of age:

- Mother's breastfeeding self-efficacy: measured using the Breastfeeding Self-Efficacy Scale – Short Form (Dennis 2003)
- Mother's pain while feeding during the previous 24 hours: measured using visual analogue scale of the Short Form McGill Pain Questionnaire (SF-MPQ), modified into a Likert-type scale (scores ranging from 0 to 10) (Dennis, Jackson et al. 2014)

- Total number of contacts with any breastfeeding supporter since first referral and specific means of support used
- Infant weight
- Exclusive breastmilk feeding in the previous 24 hours
- Exclusive breastfeeding directly from the breast with no bottle feeds of expressed milk in the previous 24 hours
- Age when child last received breastmilk, to determine when and whether switch to exclusive formula feeding has occurred (McAndrew, Thompson et al. 2010)
- Time spent breastfeeding in previous 24 hours: time in minutes/hours
- Request for frenotomy/repeat frenotomy
- Bleeding following frenotomy or frenulum tear
- Post-procedure adverse events (tongue cut, scarring, salivary duct damage): measured by specific questions
- Maternal anxiety or depression as indicated by the anxiety and depression dimension of EQ-5D-5L Maternal health-related quality of life: as elicited by the EQ-5D-5L
- Maternal and infant NHS healthcare resource use: collected on general practice visits and hospital admissions

9.6.4. 6 month follow-up

The following data will be collected using maternal self-report (via web-link to data capture platform, telephone, email or post) when the infant is 6 months of age:

- Any breastmilk feeding at 6 months according to maternal self-report: defined as any breastmilk feeding in the 24 hours prior to the infant reaching six months of age

9.7. Discontinuation/withdrawal of participants from study

Parents will have the right to withdraw their infant from the study at any time.

Parents will be asked for permission for the study team to complete data collection and follow-up, though they may wish to withdraw consent for any aspect of the study including the use of data already obtained. The reason for withdrawal, where provided, will be recorded in the eCRF. If parents who decide to withdraw their child at any stage consent for their child's data to be used, the data will be included within the final analysis. Withdrawn participants will not be replaced as the sample size has been inflated to account for withdrawal/loss to follow-up.

9.8. Definition of End of Study

The end of the trial will be defined as the date when the trial database is locked. An end of trial declaration will be made to the approving REC.

10. INTERVENTIONS

Infants will be randomised to either:

- frenotomy with standard breastfeeding support (intervention arm), or
- no frenotomy with standard breastfeeding support (comparator arm).

Breastfeeding support will include as a minimum: an initial face-to-face assessment of breastfeeding, for example using the LATCH tool (Jensen, Wallace et al. 1994) or BFI assessment tool, and advice on positioning and attachment and at least one follow-up visit, together with drop-in clinic advice as required, but available on more than one day a week. Staff will be asked to check whether infants have received standard vitamin K prophylaxis, or whether there is any family history of haemophilia prior to the procedure.

10.1. Intervention arm

Infants who are eligible for the trial and whose parents consent for them to participate and who are randomised to frenotomy with breastfeeding support will undergo the procedure according to usual hospital practice. Frenotomy will be carried out by the usual trained practitioner for participating hospitals using their normal technique. Frenotomy is usually a quick procedure in which the tongue is lifted and the frenulum (the tissue between the underside of the tongue and the base of the mouth) is divided. Breastfeeding may be conducted immediately post-procedure, and the baby will undergo an immediate post-frenotomy observed feed. Parents will receive further advice on positioning and attachment together with standard post-frenotomy advice concerning bleeding and other post-frenotomy adverse events. Parents will be provided with details about how to access rapid breastfeeding support in the event of ongoing feeding difficulties and an appointment for at least one follow-up visit.

10.2. Comparator arm

Infants who are eligible for the trial and whose parents consent for them to participate and who are randomised to breastfeeding support only will not undergo frenotomy, but at the frenotomy clinic will undergo an immediate observed feed and will receive further advice on positioning and attachment together with standard post-frenotomy advice concerning bleeding and other post-frenotomy adverse events. Parents will be provided with details about how to access rapid breastfeeding support in the event of ongoing feeding difficulties and an appointment for at least one follow-up visit.

11. SAFETY REPORTING

An independent Data Monitoring Committee (DMC) will be established to review the study data and outcomes including safety reports of Serious Adverse Events (SAEs). The DMC will ensure the safety and wellbeing of the trial participants and, if appropriate, make recommendations to the TSC regarding continuance of the study or modification of the protocol. The TSC will have ultimate responsibility for deciding whether the trial should be stopped on safety grounds.

11.1. Adverse events

An adverse event (AE) is any untoward medical occurrence observed in a participant, which may or may not have a causal relationship with the trial intervention. Bleeding following frenotomy (unless excessive) or frenulum tear and post-procedure adverse events (tongue cut, scarring, salivary duct damage) are expected in this population and will be collected as part of standard follow-up and do not require reporting as AEs.

11.2. Serious adverse events

A serious adverse event (SAE) is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

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.

NOTE: Congenital anomalies may be identified in the participants of this trial during their participation in the trial but cannot be causally related to the intervention (since, although they may be diagnosed after the infant joins the trial, they will have occurred before the intervention takes place), and therefore for the purposes of this trial they will not be considered SAEs.

11.3. Foreseeable serious adverse events

The following are known, but rare, complications of frenotomy. If they occur, they are to be reported as SAEs:

- excessive bleeding from the incision site (a small amount of bleeding is expected)
- significant soft tissue injury such as submandibular orifice injury
- severe infection

There are also SAEs which may be expected in the trial population or as a result of their routine care. The following events therefore are foreseeable SAEs and will not be subject to SAE reporting procedures:

- admission or extension of hospital stay due to:
    - breastfeeding difficulties
    - poor milk supply in the mother
    - weight loss or poor weight gain in the baby
    - jaundice

11.4. Unforeseeable serious adverse events

SAEs which are not included in section 11.3 are regarded as unforeseeable. Unforeseeable SAEs which occur from randomisation until the first routine follow-up visit must be reported.

11.5. Reporting procedures for serious adverse events

Unforeseeable SAEs and the SAEs associated with frenotomy (section 11.3) must be reported immediately as soon as study staff become aware of the event. Study staff may use one of the following methods:

- Staff with access to the clinical database may report SAEs through this. Once the SAE form is complete site staff will be required to print off the clinical database SAE form and obtain the signature of the study clinician carrying out the causality assessment. The completed signed SAE form must be emailed or faxed to the NPEU CTU. NPEU CTU staff will be informed via email of any SAEs reported electronically.
- Emailing or faxing a completed paper SAE form to NPEU CTU. Paper forms, with instructions, will be made available with the trial documentation to enable anyone to report an SAE.
- Where the above routes are not possible, then the SAE may be reported to NPEU CTU by telephone and the SAE form will be completed by NPEU CTU staff and a copy shared with the site Principal Investigator (PI) for causality assessment.

If following the reporting of an SAE additional information becomes available, a new SAE form should be completed with the details and emailed/faxed to NPEU CTU.

SAEs will be reported from trial entry until the first routine follow-up visit (approximately one week post-intervention according to hospital practice).

The NPEU CTU will forward a copy of the SAE form to the Chief Investigator (CI) or their delegate as soon as possible on receipt. The CI will assess whether the SAE was as a result of trial related activities (related). If assessed to be related and unforeseeable the NPEU CTU will send the SAE report to the Sponsor and the DMC. In addition, all related unforeseeable SAEs should be submitted to the Research Ethics Committee (REC) that gave a favourable opinion of the study within 15 working days of the CI becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

12. STATISTICS AND ANALYSIS

12.1. Sample size

Frenotomy rates are very variable between hospitals (<1% to 6% of babies born) and evidence on which to base an estimate of effect size is very limited. The 2010 Infant Feeding Survey indicates that 68% of infants are breastfed at 6 weeks (McAndrew, Thompson et al. 2010). The current reported rate of any breastfeeding at 6-8 weeks is 44% (Public Health England 2016), as compared with 30% exclusive breastfeeding. Breastfeeding rates are likely to be substantially higher in the highly motivated population

eligible for this trial. Breastfeeding rates at 3 months in relatively small studies of UK babies who have undergone frenotomy have varied between 65% in Southampton (Berry, Griffiths et al. 2012) to 78% in London (Khoo, Dabbas et al. 2009). Similarly, in a Bristol trial (Emond, Ingram et al. 2014), breastfeeding rates at 8 weeks were 83% in the intervention arm and 80% in the control arm, noting that most of the control arm underwent frenotomy. Six of eight infants who did not undergo frenotomy were breastfed at 8 weeks (75%). In another Southampton trial (Hogan, Westcott et al. 2005), the breastfeeding rate at 4 months was 60% in both the immediate and delayed division groups. Audit data from the Royal Berkshire Hospital infant feeding service, which includes a frenotomy service, showed that the following proportions of infants referred to the service were exclusively breastfed at three months: 2011/12 66%, 2012/13 62%, 2013/14 61%, 2014/15 77%, 2015/16 69%.

It is assumed, as supported by public consultations, that a 10% increase in the rate of breastfeeding represents the minimal clinically important difference that should be detectable by the trial; and breastfeeding rates will remain high in this motivated population (breastfeeding rates at 3 months will be around 70% in those who receive the minimum level of breastfeeding support).

Thus assuming a breastfeeding rate of 70% in the control group and 80% in the intervention group, at 90% power with a 5% level of significance, this gives a sample size of 392 in each group, totalling 784. Allowing for 5% loss to follow-up, with a further 5% increase to account for between-group contamination would give a sample size of 870; approximately 37 infants per month over a 24 month recruitment period.

Based on an assumed 2% of infants having breastfeeding difficulties and judged to have tongue-tie, an average number of births of 3,000 per centre, and a conservative 50% of mothers consent for their infant to participate, this would require 19 participating units (representing almost 114,000 births over the study period), with an estimated 2,300 babies with breastfeeding difficulties thought to have a tongue-tie (96 babies per month). With conservative estimates that assume 1 in 2 babies will be assessed and their parents agree to participate and provide complete outcome data, sufficient numbers to achieve our goal within the 3 years of the study are expected.

12.2. Description of statistical methods

Analysis will be undertaken according to a pre-specified statistical analysis plan.

Demographic and clinical data will be summarised with counts and percentages for categorical variables, means (standard deviations) for normally distributed continuous variables and medians (with interquartile or simple ranges) for other continuous variables.

Infants will be analysed in the groups to which they were randomly assigned, comparing the outcome of all infants allocated to intervention with all those allocated to the comparator group, regardless of deviation from the protocol or treatment received (referred to as the Intention to Treat (ITT) population).

The primary analysis will be adjusted for stratification factors (centre, infant's age at randomisation and mother's parity).

Binary outcomes will be analysed using risk ratios, whilst continuous outcomes will be analysed using either a mean or median difference as appropriate. 95% CIs will be presented for analyses of the primary and secondary outcomes.

Sensitivity analyses will be conducted on the primary outcome to investigate the impact of missing data, contamination and unmasking.

Pre-specified subgroup analyses will be undertaken, examining the primary outcome in the following groups:

- Infants aged less than two weeks vs. two weeks or older at randomisation
- Infants with BTAT score 4 or less vs. 5-6 vs. 7 or more at randomisation
- Prior belief concerning frenotomy: likely to be beneficial vs. uncertain vs. unlikely.

12.3. Level of statistical significance

Two-sided statistical testing will be performed throughout. A 5% level of statistical significance will be used for analyses of all outcomes.

12.4. Early trial cessation

A recommendation may be made by the Data Monitoring Committee to the Trial Steering Committee to stop the trial early following review of interim analysis or evidence from other relevant studies becoming available. Guidelines for the early cessation of the trial will be agreed with the DMC and documented in the DMC Charter.

12.5. Procedures for reporting deviations from the original statistical analysis plan

All deviations from the original statistical analysis plan will be reported in the final report, as appropriate.

12.6. Economic evaluation

The economic evaluation will take the form of a cost-consequence analysis and will present outcomes and healthcare costs in a disaggregated manner for both mothers and their infants (Mauskopf, Paul et al. 1998). The perspective of the analysis will be of the NHS and the time-horizon will be a one-year time frame for infants and lifetime for mothers. However, we will also present a cost-utility analysis from the mother's perspective with a time-horizon up to 3 months.

Health outcomes at 3 months of age will include the primary outcome, the maternal anxiety and depression dimension of the EQ-5D-5L, overall health-related quality of life (EQ-5D-5L), and maternal and infant healthcare costs. Healthcare resource use categories using the online data capture platform will collect information on general practice visits and hospital admissions up to 3 months of age. These healthcare resource use categories will be weighted by appropriate unit costs obtained from national sources to estimate the costs in each trial arm (Curtis and Burns 2015, Department of Health 2015). For the within-trial analysis, maternal quality adjusted life days (QALDs) will be derived as the area under the

curve for the health profile created connecting health-related quality of life measures at one week post-intervention and then at 3 months follow-up. To estimate costs (or savings) in each arm of the trial beyond the trial end date, we will employ a validated published economic model (Pokhrel, Quigley et al. 2015). The model evaluates the potential cost savings attributable to increases in breastfeeding rates through different healthcare policies. We will use the observed treatment effect in the trial (breastfeeding rate difference at 3 months of age) and map such value into one of the policies explored in the economic model to extrapolate costs. For infants, we will extrapolate up to one-year follow-up healthcare costs (or savings) associated with gastrointestinal illness, lower respiratory tract infection and acute otitis media. For mothers, we will use the treatment effect to estimate the potential lifetime maternal healthcare costs (or savings) due to breast cancer. These categories of healthcare costs (at one year for infants and lifetime for mothers) will also be included in the cost-consequence analysis.

Mean health-related quality of life values, resource use and costs estimated using trial data will be accompanied with appropriate 95% confidence intervals. Uncertainty around extrapolated cost figures using the economic model will be dealt with using deterministic sensitivity analysis.

13. DATA MANAGEMENT

13.1. Access to data

Direct access to the study data, source data and medical records will be granted to authorised representatives from the NPEU CTU, Sponsor and host institution for the purposes of monitoring, audit, or inspection of the study to ensure regulatory compliance. Staff will have authenticated and restricted access to the clinical database ensuring they are only able to see data on participants recruited at their Trust. Access to the electronic data is strictly controlled using individual passwords for all staff accessing the electronic databases.

13.2. Data recording and record keeping

Data on the primary and secondary outcomes will be collected by mother's self-report using a mobile phone, tablet, computer or by telephone, or extracted from hospital records by assessors blinded to treatment allocation, or by linkage to routine data, where possible, for longer-term outcomes. Text and/or electronic notification reminders for completion will be sent as appropriate, with the option for telephone completion in the event of a delayed response to ensure a high response rate. The option for telephone completion will be available for mothers who do not have a smartphone, or who require translation, or who have other specific access needs which preclude the use of the online data collection platform.

Trial data will be collected using paper or electronic Case Report Forms (eCRFs) and automatically transferred for storage in the clinical database. The individual participant data will be identified by a study participant specific number only. A separate administrative database will be used to store the participant's name and any other identifying details. The two central databases will link the data by the participant's study number only, and are hosted by the NPEU CTU on behalf of the Sponsor. All data will be processed

in line with the NPEU CTU Data Management Standard Operating Procedures (SOPs). The Sponsor has delegated the responsibility for ensuring confidentiality of participant information to the NPEU CTU.

Archiving will follow the completion of the study and publication of results as detailed in NPEU SOPs and in line with NHS guidelines for a minimum 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. Electronic files will be stored on a restricted access (named individuals) server held in a secure location. In line with the NPEU CTU security policy, authorised access to the NPEU CTU is via an electronic tag entry system and individual rooms are kept locked when unoccupied. Authorised staff will process data via a secure network which requires individual login name and password. No data are stored on individual workstations. The data is backed up automatically overnight to an offsite storage area accessed by authorised personnel via electronic tag and key-pad systems.

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

14. QUALITY ASSURANCE PROCEDURES

14.1. Monitoring

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

The NPEU CTU will develop an appropriate central monitoring plan for the trial, based on the risk assessment. 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 the central monitoring triggers cause to do so.

14.2. Risk assessment

The trial will undergo a risk assessment prior to starting, which will be reviewed at regular intervals.

14.3. Project management

The study is sponsored by the University of Oxford. The trial will be run by the NPEU CTU, based at the University of Oxford, and the CI.

The trial 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, CTU Director, Senior Trials Manager, the Trial Statistician, the Quality Assurance manager and other project staff. The PMG will meet every month.

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

The trial will be overseen by the Trial Steering Committee (TSC) which will have ultimate responsibility for considering and, as appropriate, acting on the recommendations of the DMC. The TSC will include an independent chair, at least two other independent members, PPI representative(s), and the Chief Investigator. The TSC will review the progress of the trial and report on progress to the funder. Observers from the HTA programme will be invited to attend all TSC meetings.

The Data Monitoring Committee (DMC), independent of the applicants and the TSC, will review the progress of the trial and interim analysis at least annually, and provide advice on the conduct of the trial to the TSC and (via the TSC) to the NIHR HTA programme.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Declaration of Helsinki

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

15.2. Guidelines for Good Clinical Practice

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

15.3. Approvals

The protocol, informed consent form, PIL and any proposed advertising material will be submitted and approval will be obtained from an NHS Research Ethics Committee (REC), through the Health Research Authority (HRA) approval system. In addition, Trust Confirmation of Capacity and Capability will be obtained prior to any trial activity at that site.

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

15.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

15.5. Participant confidentiality

The trial staff will ensure that participant anonymity is maintained. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with data protection regulations, which require data to be anonymised as soon as it is practical to do so.

15.6. Expenses and benefits

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

15.7. Other ethical considerations

Parents will be asked to consent for inclusion of their infants into the trial on the basis that they will be masked to intervention allocation. Parents will therefore need to be adequately advised on how to respond in the event of post-frenotomy adverse events such as bleeding, as well as what to do in the event of ongoing feeding difficulties. In order that parents are able to rapidly seek advice in the event of post-frenotomy adverse events (in the group that undergo frenotomy) or rapidly obtain further advice in the event of ongoing feeding difficulties (both groups) with recourse to rescue frenotomy or repeat frenotomy if necessary, both groups will be provided with standard post-frenotomy advice. Only sites with rapid access via drop-in clinic or telephone advice to breastfeeding support will be included in the study, and all parents will be given an appointment for at least one follow-up visit. All research midwives taking consent from parents will be trained in how to advise parents as to their actions in the event of either adverse events or ongoing feeding problems.

In order to maintain masking, infants may be taken into a separate room, where the frenotomy will be undertaken or not. This may be upsetting to both mother and infant. However, the infant will be returned to the mother after a few minutes of separation. Mothers will be made aware of this given the option to remain with their baby but will be asked not to directly observe the trial intervention in order to maintain blinding.

16. FINANCE AND INSURANCE

16.1. Funding

This trial is funded by the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) programme (ref: 16/143/01). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

16.2. Insurance

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 that is provided.

16.3. Intellectual Property

Ownership of IP generated by employees of the University vests in the University. The protection and exploitation of any new IP is managed by the University's technology transfer office, Oxford University Innovations.

17. PUBLICATION POLICY

The success of the trial depends on a large number of midwives, neonatologists, obstetricians, paediatric surgeons, breastfeeding supporters and parents. Credit for the trial findings will be given to all who have collaborated and participated in the trial including all local co-ordinators and collaborators, members of the trial committees, the FROSTTIE Co-ordinating Centre and trial staff. Authorship at the head of the primary results paper will take the form "[name], [name] and [name] on behalf of the 'The FROSTTIE Collaborative Group'". The drafting of the paper will be the responsibility of a writing committee. Named authors will be listed in the following order: individual responsible for completing the first draft of the paper, lead analyst, all other members of the writing committee in alphabetical order, lead supervising author. All other contributors to the study will be listed at the end of the report, with their contribution to the study identified.

Those responsible for other publications reporting specific aspects of the study, such as the economic evaluation, may wish to utilise a different authorship model. Decisions about authorship of additional papers will be discussed and agreed by the trial investigators and the TSC.

Parents will be sent a summary of trial publications if they wish, which will contain references to full papers.

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19. APPENDIX A: SCHEDULE OF STUDY PROCEDURES

Procedures					
	Baseline	Intervention	Follow-up visit	3 months of age	6 months of age
	Day 0	Up to 7 days	7-14	variable	variable
Eligibility assessment	X				
Informed consent	X				
BTAT	X*	X*			
Randomisation		X			
Frenotomy[1]		X			
Baseline data collection	X*	X*			
Outcome data collection (eCRF)		X	X		
Follow-up completion (electronic or telephone)				X	X
Serious/Adverse event assessments		X	X		
Informed consent for optional 2.5 year follow-up data	X				

[1]For infants randomised to the intervention arm.

*To be undertaken once on either baseline or intervention visit (if separate days) according to centre preference.

20. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
	1	27/09/18		Initial version submitted to REC.
	2	06/12/18	Oliver Hewer	Amendments made in accordance with NIHR (funder) and REC recommendations. Additional minor corrections to ensure consistency throughout.
	3	25/03/19	Oliver Hewer	Amendments made to exclusion criteria and SAE reporting; and minor corrections to wording in sections 3, 7 and 10.