Section 1: Study Protocol WP1&2

Development and feasibility study of an evidence-informed manualised intervention to compare CUe- Based versus Scheduled feeding for preterm infants transitioning from tube to oral feeding in neonatal units. WP1&2

Trial/Study Acronym	CuBS WP1&2
Sponsor	University of Dundee – NHS Tayside
Sponsor R&D Number	20170B03
Funder	NIHR HTA
Chief Investigator	Dr Alison McFadden
REC Number	18/ES/0059 Ethics Approval granted 29/05/2018
Clinical Trials Unit	Tayside Clinical Trails Unit
ISRCTN/clinicaltrials.gov Number	ISRCTN13414304
Version Number and Date	Version 4 17/01/2019

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Section 1

Section 2

PROTOCOL APPROVAL

Development and feasibility study of an evidence-informed manualised intervention to compare CUe-Based versus Scheduled feeding for preterm infants transitioning from tube to oral feeding in neonatal units (CuBS)

Signatures

The undersigned confirm that the following protocol has been agreed and approved by the Sponsor and that the Chief Investigator agrees to conduct the trial/study/study in compliance with this approved protocol and will adhere to the principles of GCP, the Sponsor SOPs, and any other applicable regulatory requirements as may be amended from time to time.

Dr Alison McFadden		27/03/2018
Chief Investigator	Signature	Date
Prof Peter Donnan	Peter Donnan	28/03/2018
Individual Responsible for Statistical Review	Signature	Date

LIST OF ABBREVIATIONS

AE	Adverse Event
BCT	Behaviour Change Technique
BMS	Breastmilk Substitutes
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Scheme
CRF	Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HCP	Health Care Practitioners
ICF	Informed Consent Form
IF	Incidental Findings
ISF	Investigator Site File
MRC	Medical Research Council
NIHR HTA	National Institute for Health Research Health Technology Assessment Programme
NNU	Neonatal Unit
PI	Principal Investigator
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
SMF	Study Master File
SMG	Study Management Group
SSC	Study Steering Committee
WP	Work Package

SUMMARY/SYNOPSIS

Study Title	Development and feasibility study of an evidence-informed manualised intervention to compare CUe-Based versus Scheduled feeding for preterm infants transitioning from tube to oral feeding in neonatal units. CuBS	
Study Design	Multi-method feasibility study with four work packages (WP): WP1 Building the evidence-base WP2 Developing the intervention A protocol for WP3 and 4 will be submitted on completion of WP2.	
Study Population	Parents of babies in NNUs Health care practitioners (HCPs) working in neonatal units; Stakeholders- third sector organisations, HCPs, Professional Associations, and representatives from UK Neonatal Networks.	
Sample Size	WP 1: n=68 WP 2: n=30	
Planned Study Period	WP1 and 2: 10 months	
Clinical phase duration	None	
Follow up phase duration	None	
Primary	Objectives 1. Describe the characteristics, components, theoretical basis and outcomes of approaches to feeding preterm infants transitioning from tube to oral feeding including by feeding type (breastmilk, donor breastmilk, formula, combined) and method (breastfeeding, bottle feeding); 2. Identify operational policies, barriers and facilitators and staff and parents' education needs in NNUs implementing cue-based feeding; 3. Co-produce an evidence-informed, adaptable, manualised intervention, including staff and parent educational support for feeding preterm infants at the transition from tube to oral feeding in response to feeding cues and signs of infant stability;	Outcome Measures for WP 1 and 2 Staff and parents experiences of feeding preterm babies in neonatal units transitioning from tube to oral feeding in neonatal units
Secondary	Objectives None	Outcome Measures
Inclusion Criteria	Parents of babies in or recently discharged from neonatal units Health care practitioners (HCPs) working in neonatal units Stakeholders- third sector organisations, HCPs, Professional Associations, and representatives from UK Neonatal Networks.	

Exclusion Criteria	

1 INTRODUCTION

2 BACKGROUND & RATIONALE

The frequency of feeding and volume of milk intake of healthy term infants is generally dictated by the infant's appetite. Term infants exhibit feeding and satiation cues and adjust their volume of intake to compensate for differences in the nutrient density of breastmilk or breastmilk substitutes (BMS). In contrast, enteral feeds for preterm infants are usually given as prescribed volumes at scheduled intervals[1]. Some evidence exists, however, that preterm infants are able to self-regulate their intake [2]. Furthermore, while feeding cues may be more difficult to detect in preterm infants, they may be sufficiently evident for a parent or caregiver to recognise and respond to [3], thereby supporting safer and more successful feeding experiences. Caregivers and parents can use infants' physiological and behavioural channels of communication to inform their feeding decisions and actions. This may also set the scene for future feeding practices and success, and parent-infant interaction. Although studies have shown that cue-based ("responsive") feeding is feasible for preterm infants, the adoption of cue-based feeding has been constrained by the "schedule- and volume-driven culture" in many neonatal units [4].

Cue-based feeding for preterm infants

Alternatives to a scheduled interval feeding regimen for preterm infants have been described [5]. These aim to respond to infant feeding and satiation cues and are particularly relevant to infants who are in the transition phase from gastric tube feeding to oral feeding (either breast or bottle) [6]. At this stage (about 32 to 36 weeks' postmenstrual age), preterm infants are usually beginning to develop periods of sustained alert activity and a suck-swallow-breathe pattern [7] sufficient for oral feeding to commence.

Cue-based feeding is a co-regulated approach [5]. The enteral feeding process starts when the caregiver recognises infant cues that indicate readiness to feed and ends when the infant demonstrates satiation. The infant, therefore, determines the timing, duration, and volume of intake. At each stage during transition to oral feeding, through understanding and interpretation of their cues, infants are supported in such a way that they are able to achieve all they are capable of with regards to oral feeding. Cue-based feeding occurs alongside supplementary tube feeding with the understanding that, developmentally, many preterm babies are not yet ready to fully sustain themselves by oral feeding. In modifications of cue-based feeding, caregivers may pre-set a maximum permitted duration of inactivity or sleep between feeds or a minimum required volume of intake or modify feeding plans to take into account the reduced endurance levels of preterm infants.

Why is the research important in terms of improving the health of the public and/or to patients and the NHS?

The transition to oral feeding is a critical developmental stage for preterm infants. Cue-based feeding may be considered a part of an integrated approach to providing 'developmental care' where infants are seen as individuals and caregivers are guided by the needs and behaviours of the infant [8]. Allowing preterm infants to inform the timing and duration of enteral feeding may result in longer rest periods between some feeds, promote infant-determined sleep and wake patterns that reduce unnecessary energy expenditure, and increase growth rates [9]. It is also possible that allowing the infant to determine the pattern of enteral feeding will help in

the development of organised behaviour states and the earlier establishment of full oral feeding, a key criterion for hospital discharge for preterm infants [10]. Reducing length of hospital stay has a direct effect on hospital costs and may also decrease cot occupancy in neonatal units, thus reducing the need for inter-hospital transfer of women and infants [11]. Compared to a scheduled approach, cue-based feeding may support infant stability during oral feeds as infants cues will be responded to resulting in fewer episodes of physiological instability which could cause significant harm e.g. aspiration, desaturation and bradycardia events [12]. As feeding a baby is a primary activity over the first year of life and a major preoccupation of parents, it is anticipated that there may be other benefits for the family and caregivers of cue-based feeding, principally allowing parents to: feel more directly involved with their infant's care; better understand their infant's communication, and increasing parental confidence and ability to recognise and respond to their infant's needs during their hospital stay and beyond. Enhanced parental satisfaction is a key quality indicator in measuring the effectiveness of family-integrated care in neonatal services [13].

Potential adverse effects of cue-based feeding for preterm infants are recognised. These mainly relate to whether such a regimen can guarantee metabolic stability, particularly normoglycaemia, in this vulnerable group. Even at the point of discharge home from hospital, some preterm infants are known to be susceptible to hypoglycaemia if a scheduled enteral feed is omitted or delayed [14]. Concern exists that repeated or prolonged episodes of hypoglycaemia may impair longer term growth and development [15]. There may be more acute problems relating to gastro-intestinal immaturity, such as feeding intolerance and a higher risk of aspiration of gastric contents into the lungs, as well as concerns that allowing unrestrained volumes of enteral intake may increase the risk of gastro-oesophageal reflux or feed intolerance. However, there is a lack of evidence of these potential adverse effects, and indeed some problems may be exacerbated by not responding to the infant's cues [12]. Despite these concerns, and despite a lack of evidence of benefit, cue-based feeding is established in some neonatal units in other countries e.g. Sweden [16, 17] and the USA [18, 19], and is increasingly being used in neonatal units in the UK [20]. Cue-based feeding for preterm infants is now recommended as a method to increase the duration of breastfeeding in the United Nations Children's Fund (UNICEF) Baby-Friendly Hospital Initiative "Ten steps to successful breastfeeding" [20, 21].

However, overall, the evidence to support cue-based feeding is limited. A recent Cochrane review [22] concluded that there was low quality evidence that cue-based feeding compared to scheduled feeding leads to earlier transition to full oral feeding. The review authors noted that this evidence should be treated with caution due to a number of methodological weaknesses [22]. Furthermore, there is a lack of strong or consistent evidence of the effect of cue-based feeding compared to schedule feeding on important outcomes for preterm infants or their families [22]. Therefore there is a need for rigorous evaluation of cue-based feeding for preterm infants within the NHS setting, based on the most up-to-date and complete evidence, and taking into account stakeholder (including parent) views. The first step towards this is to assess if such an intervention trial is justifiable and feasible.

3 STUDY OBJECTIVES & OUTCOMES

The aim of the research is to develop a manualised intervention and to assess whether it is feasible to conduct a clinical and cost-effectiveness study of cue-based versus scheduled feeding for preterm infants in neonatal units.

TABLE 1: PRIMARY OBJECTIVES AND OUTCOME MEASURES

Primary Objective:	**Outcome Measure:**	**Timepoint of outcome measured**
Objectives 1. Describe the characteristics, components, theoretical basis and outcomes of approaches to feeding preterm infants transitioning from tube to oral feeding including by feeding type (breastmilk, donor breastmilk, formula, combined) and method (breastfeeding, bottle feeding); 2. Identify operational policies, barriers and facilitators and staff and parents' education needs in NNUs implementing cue-based feeding; 3. Co-produce an evidence-informed, adaptable, manualised intervention, including staff and parent educational support for feeding preterm infants at the transition from tube to oral feeding in response to feeding cues and signs of infant stability;	Outcome Measures	

Table 2: Secondary Objectives and Outcome Measures
None

4 STUDY DESIGN

4.1 INTERVENTION

The intervention is to be developed as part of this study.
The intervention will be an evidence-informed manualised intervention to promote feeding in response to infant cues (cue-based feeding) for infants transitioning from tube to oral feeding (breast or bottle feeding) in neonatal units. In this study, cue-based feeding is defined as feeding babies in response to their feeding and satiation cues, taking into account their stability and energy level [22]. The purpose of the intervention is to provide a step-by-step protocol for neonatal unit staff and parents on the introduction and maintenance of cue-based feeding for preterm infants who are ready to/making the transition from tube feeding to oral feeding, and to create positive feeding behaviours as infants transition from tube to oral feeding. The components of the intervention will be determined by the synthesis of the data in WP1 and stakeholder views. However, based on the characteristics of the trials included in Watson and McGuire [22], we anticipate that the intervention will encompass: how to recognise infants' readiness to feed cues; frequency of assessment of readiness to feed; understanding infants' cues of physiological stability or instability during a feed; how to recognise satiation cues and when to stop an oral feed; minimum and maximum time between feeds; how to assess need for and when to give 'top-up' feeds by tube (especially for babies feeding at the breast); stages of transition to full oral feeding; monitoring infant wellbeing, and mother/parent confidence and satisfaction with feeding.

Procedures

WP1:
Telephone interviews with a sample of 20 neonatal units (2 from each UK neonatal network purposively sampled to reflect diversity in size and level of unit and different population settings). We will speak to the infant feeding adviser or nurse manager in each unit.
Focus group discussions (in three UK NNUs - Coventry, Dundee and Exeter) with eight HCPs), one focus group for medical staff (n=4) and one for non-medical staff (n=4) including nurses and allied health professionals (with additional telephone interviews for those unable to attend the focus group, and for senior staff), and one focus group with 6-8 parents.
WP2
One consensus-building workshop with 30 stakeholders including parents and third sector organisations (e.g. Bliss, TAMBA, La Leche League), HCPs, Professional Associations (e.g. Neonatal Nurses Association, British Association of Perinatal Medicine) and representatives from UK Neonatal Networks, to agree the intervention components, method of manualisation, and approach to education/training for HCPs and parents

Public involvement in the study
The study comprises four approaches to Patient and Public Involvement (PPI):
a) a panel of 6 parents with relevant experience will meet 3 times during the research to advise on aspects such as recruitment, topic guide for qualitative interviews, co-development of the intervention, interpretation of the findings and dissemination to parents. The Parent's Panel will also be invited to review the manualised intervention, in particular the training components for staff and parents. We will work with Bliss to support and train members of the Parent' Panel;
b) 2 members of the Parents' Panel will also be members of the Stakeholder Advisory, who, along with a representative from TAMBA (Bliss will represented through a co-applicant, will represent the views of parents;
c) The Bliss representative co-applicant will facilitate the Parent's Panel and will ensure that the views of parents are represented throughout the study;
d) Workshops (WP2) will be attended by voluntary organisations representing parents to ensure that parent's perspectives remain central to the development of the intervention and the framework of options for a future trial

4.2 STUDY DESCRIPTION

This four-phase multi-method study (approval is sought for the first two phases) will develop and test the feasibility of conducting a study of the clinical- and cost- effectiveness of responsive feeding vs scheduled feeding for preterm infants in neonatal units. The study comprises four work packages (WP) based on the MRC principles for developing and evaluating complex interventions [23] and process evaluations [24]. Data will not be collected for babies receiving schedule feeding.

Work package one, *building the evidence base*, months 1-6, addresses objectives 1 and 2, by building the evidence to inform the content and methods of the manualised intervention. It comprises:

a) a systematic literature review, building on the Cochrane review of RCTs [22], to synthesise existing evidence on the components, characteristics, theoretical basis and associated behaviour change techniques (BCTs) [25] of interventions, infant and parent outcomes, and any economic evaluations. We will also conduct a policy review to include published guidelines for cue-based feeding, such as the Alberta guidelines [26], and SOFFI [18];
b) three informal visits to neonatal units with embedded cue-based feeding (Sweden – Falun, Uppsala; UK – Glasgow) to inform how to optimise the intervention. The case

studies will involve observational visits, discussions with key informants (e.g. senior nurse, paediatrician), and analysis of policies, guidelines and training materials;

c) telephone interviews with a sample of 20 neonatal units (1 from each neonatal network across Scotland, England, Northern Ireland and Wales, purposively sampled to reflect diversity in size and level of unit and different population settings). We will speak to the infant feeding adviser or nurse manager in each unit as the most appropriate respondents. The purpose is to describe the range of approaches to the transition from tube to oral feeding, the scope of data collection systems, staff training needs, and assess variation in practice to inform a future 'usual care' trial arm;
d) qualitative research in three UK NNUs (Coventry, Dundee and Exeter) selected for their diverse approaches to the transition from tube to oral feeding. In each NNU we plan focus group discussions with eight health care practitioners (HCPs), one focus group for medical staff (n=4) and one for non-medical staff (n=4) including nurses and allied health professionals (with additional telephone interviews for those unable to attend the FG, and for senior staff), and a FG with 6-8 parents. The aim is to provide in-depth data on parents' and HCPs' views and understanding of cue-based feeding to inform development of the intervention.

The outputs from WP1 are: draft literature review ready for submission for publication; report on different approaches to cue-based feeding in the case study sites, including BCTs and intervention content, and education materials in use; and a report of the likely barriers, facilitators and training needs for implementing cue-based feeding from the perspectives of NNU staff and parents.

Work package two, *co-production of the intervention*, months 7-10, addresses objective 3, through co-production of an evidence-informed, adaptable, manualised intervention. It comprises:

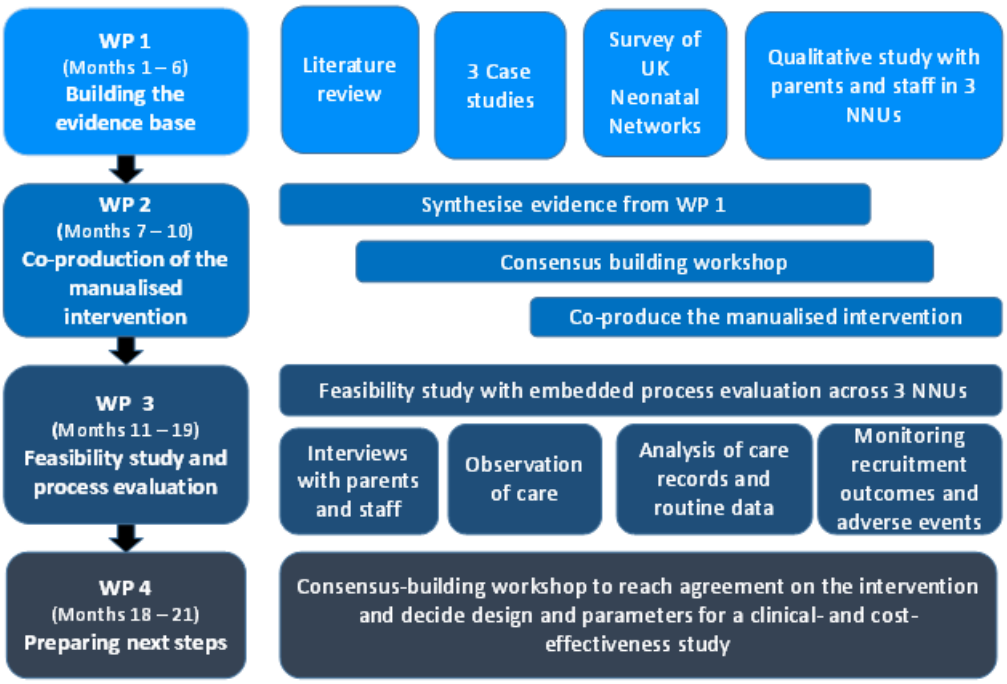
a) synthesis of the evidence from WP1 to create a matrix of options, activities and content to influence behaviour change techniques, formats and components of the intervention, underpinned by a logic model of evidence-based causal assumptions.

b) a consensus-building workshop with relevant stakeholders including parents and third sector organisations (e.g. Bliss, TAMBA, La Leche League), HCPs, Professional Associations (e.g. Neonatal Nurses Association, British Association of Perinatal Medicine) and representatives from UK Neonatal Networks, to agree the intervention components, method of manualisation, and approach to education/training for HCPs and parents;

c) co-production of the manualised intervention including BCTs, training packages and commissioning of new training materials i.e. a series of short films of infant cues. A core group of six (parents, HCPs, research team) will co-produce the manualised intervention.

The outputs from WP2 are the manualised intervention and a network of interested stakeholders to support the feasibility study (WP3), and dissemination.

4.3 STUDY FLOWCHART



4.4 STUDY MATRIX

Study Matrix

Procedure	Procedure 1	Procedure 2	Procedure	Procedure 4		
Work package 1: P1 months 3-6	Telephone interview	Focus group				
Work package 2:P3 month 9	Consensus-building workshop					

4.5 STUDY ASSESSMENTS

Not applicable for WP1 and 2

4.6 STUDY SAFETY ASSESSMENTS

Qualitative interviews and focus group discussions: the topics for the focus group discussions with parents in WP1 are not particularly sensitive, however parents with babies on neonatal units are in a vulnerable position and will have concerns about their babies' health and progress. If a parent becomes distressed during an interview/focus group discussion, he/she will be given the option to pause the interview for a break and resume later at a time convenient to the parent, or to end the interview. Parents who become distressed will be referred to the care team for additional support if the parent agrees to this. If the research nurse is concerned about the safety of a parent and/or baby, and even in the absence of the parent's agreement, he/she will discuss their concern confidentially with the Principal Investigator for the site.

4.7 TISSUE

Not applicable

4.8 INCIDENTAL FINDINGS

Any incidental findings (IF: previously undiagnosed condition) considered to be clinically significant will be reported to the participant's GP and/or consultant by the CI or Site PI, with the consent of the participant.

4.9 STUDY POPULATION

Parents of babies who are transitioning from tube to oral feeding and those who are about to be or have recently been discharged home fully orally feeding Health care professionals working in neonatal units (WP1)
Stakeholders including third sector organisations, HCPs, Professional Associations and representatives from UK Neonatal Networks (WP 2)

4.10 NUMBER OF PARTICIPANTS

The target sample sizes for the different work packages are listed below.
WP1: recruitment period 5 months

- 24 parents of babies who are transitioning from tube to oral feeding and those who are about to be or have recently been discharged home fully orally feeding (focus group discussions)
- 20 infant feeding co-ordinators/neonatal nurse managers (telephone interviews)
- 24 health care professions working in neonatal units in the 3 study sites (focus group discussions supplemented with telephone interview if necessary)

WP2: recruitment period 3 months

- 25 stakeholders (consensus-building workshop)

4.11 INCLUSION CRITERIA

WP1
Telephone interviews: neonatal unit staff member (e.g. matron/charge nurse or infant feeding co-ordinator) who has knowledge of the unit's approach to feeding babies who are transitioning from tube to oral feeding.

Focus group discussions with parent;
Parents aged over 18 who have recent experience (current or within previous 6 months) of their baby transitioning from tube to oral feeding in a neonatal unit, and who are sufficiently fluent in English language to participate in a focus group discussion.
Able to consent

Focus group discussions with staff
Member of the care team in a neonatal unit with experience of caring for babies transitioning from tube to oral feeding, and their parents.

4.12 EXCLUSION CRITERIA

There are no exclusion criteria for WP1 other than parents who do not give consent to participate in a focus group discussion.

Individuals will not be enrolled to the study if they are participating in the clinical phase of another interventional study or have done so within the last 30 days. Individuals who are participating in the follow-up phase of another interventional study, or who are enrolled in an

observational study, will be co-enrolled where the CIs of each study agree that it is appropriate.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

WP1

Participants for the telephone interviews will be identified via UK Neonatal Networks. Participants will be approached by relevant Neonatal Network Co-ordinator who will introduce the research team to potential participant. A participant information sheet will be sent to staff potential participants by appropriate staff member who has routine access to staff via e-mail. The staff potential participants will be will be asked to contact the research team directly to arrange a convenient time for this to take place. The appropriate staff co-ordinator will check whether the participant agrees to a telephone interview.

Participants for the parents' focus group discussions will be identified from parents of babies who are inpatients or recently discharged from the NNUs in the three study sites. Parents whose babies are inpatients will be approached by a member of the care team to explain the study and seek permission to refer them to the research nurse (if the research nurse is a member of the care team they will make direct contact). A letter of invitation to participate in the study and a PIS will be sent by the care team to parents of babies who are no longer inpatients. The research nurse will provide and discuss study information in the form of a participant information sheet for those parents who agree to consider participation in the study.

Participants for the staff focus group discussions will be approached by e-mail by the research nurse inviting them to participate in the study and providing a participant information sheet. Potential staff participants will be advised to contact the research team directly if they are interested in participating in the study. Parent and staff participants will have at least 24 hours to decide whether they wish to take part.

WP2

Stakeholders will be identified by the research team through the UK Neonatal Networks, Professional Associations and relevant civil society/charitable organisations. Co-ordinators of these organisations will be approached by the research team, providing study information and inviting them to send representatives to the workshops.

5.2 CONSENTING PARTICIPANTS

WP1

Telephone interviews

Participants who agree to take part in a telephone interview will be sent a PIS. At least one week later, a preliminary telephone call will provide an opportunity for a member of the research team to explain the study, answer any questions. The participant will sign the ICF and return to the study team prior to the telephone interview taking place. The ICF will include permission to audio-record the interview ICF will be recorded as at the beginning of the interview.

Parent and health professional focus group discussions. The research nurse will take writteninformed consent using the ICF prior to the focus group discussion and at least 24 hours after participant have given consent to participate. The ICF will include permission to audio-record the interview. The focus group discussion will take place in a venue that is convenient for the participants for example in a meeting room or similar on the neonatal unit.

WP2

Consent will be assumed by attendance at the workshopWhere a participant requests to speak with a physician from the study team the consent process will not be completed until the participant has spoken to the physician and had all their questions answered to their satisfaction.

For adults who lose capacity their previous wishes will remain legally binding and this will remain valid unless the protocol changes significantly. If this occurs and further consent is required from a participant who has lost capacity, the appropriate person will be asked for their consent. In all cases the CI or delegate will consult with carers and take note of any signs of objection or distress from the participant – the participant will be withdrawn if they raise objection. Where appropriate the participant will be withdrawn from any further clinical intervention and agreement will be sought from a carer to allow data collection.

The informed consent process will be conducted in compliance with TASC SOP07: Obtaining Informed Consent from Potential Participants in Clinical Research

5.3 SCREENING FOR ELIGIBILITY

The care team will select parents who meet the purposive sample criteria i.e. who have experience of a baby transitioning from tube to oral feeding in neonatal unit.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

5.4.1 Withdrawal procedures

Parents and health care professionals can withdraw from the study at any time. Where withdrawal is requested after a focus group discussion has taken place, a discussion will take place between the parent and the a member of the research team regarding whether the parent/HCP agrees to the information they contributed being included in the study or whether there are specific elements that they would like removed.

There will be no specific safety assessments required for WP1 and 2.

6 DATA COLLECTION & MANAGEMENT

6.1 DATA COLLECTION

WP component	Source of data	Time point	Collected by	Tools
WP1: survey of NNUs	Telephone interviews with HCPs Audio-recorded and transcribed	Months 3-4	Research team	Topic guide developed for the study
WP1 Focus groups with HCPs and parents	Focus group discussions Audio-recorded and transcribed	Months 4-6	Site research nurse	Topic guide developed for the study
WP2 Consensus-building workshop	Participatory workshops Notes taken by research team and other materials such as flip charts and post-it notes	Month 9	Research team	Materials developed by research team

6.2 DATA MANAGEMENT SYSTEM

Data management will be conducted in compliance with TASC SOPs on Data Management, TASC SOP53 Data Management Systems in Clinical Research.
The data management system (DMS) will be Excel, as approved by Sponsor.
The DMS will be based on the protocol and CRF for the study and individual requirements of the investigators. The CRF will collect only information that is required to meet the aims of the trial/study and to ensure the eligibility and safety of the participant. The trial/study database will be compliant with TASC SOP53 Data Management Systems in Clinical Research.
The database will be managed in line with all applicable principles of medical confidentiality and UK law on data protection, namely, the Data Protection Act 1998/General Data Protection Regulation 2018, which brought UK law into line with the EU Data Protection Directive. The Data Controller will be the University of Dundee and the Data Custodian will be the Chief Investigator.The CI may delegate CRF completion but is responsible for completeness, plausibility and consistency of the CRF. Any queries will be resolved by the CI or delegated member of the trial/study team.

Database lock will be conducted in compliance with TASC SOP32 Locking Clinical Study Databases.

7 STATISTICS AND DATA ANALYSIS

7.1 SAMPLE SIZE CALCULATION

The sample sizes for the different components of the study have been estimated based on the purpose of each element, to reflect the range and diversity of participants, the experience and expertise of the research team, and in discussion with the proposed study sites. Sample size calculation is not relevant to this feasibility study.

7.2 PROPOSED ANALYSES

The data for WP1 will comprise findings of the literature review, field notes of the case studies, and audio-recordings of the telephone interviews with Neonatal Unit respondents, the focus group discussions and telephone interviews with parents and staff. All research material will be anonymised and then transcribed by an external transcription company, and analysed thematically using the Framework Method [28] supported by text management software (NVivo). An analytical framework will be developed based on pre-specified constructs from the literature review (for example descriptions of important infant feeding cues and behaviours, and how to assess them) and the research objectives (barriers, strategies and educational needs). In this phase, each audio-recording will be listened to independently by two members of the research team and key points relevant to the analytical framework noted. Illuminating quotes will be transcribed. Any new themes in the data will be added to the analytical framework.
The synthesised data from WP1 will be used develop a matrix of options and components of the intervention in WP2. The data collected during the consensus –building workshop in WP2 will be analysed thematically and used to modify the intervention.

All data analysis will be carried out by the research team.

7.3 MISSING DATA

Not applicable

7.4 TRANSFER OF DATA

Data from the two external sites (Coventry and Exeter) will be collected by the research nurses. All data will be anonymised i.e. participant codes rather than names will be used. All data collected (audio-files and transcriptions of interviews and focus group discussions) will be held on password protected computers and uploaded via the cloud storage programme

Box which is password protected and held on the University of Dundee network. Only the research team will have access to the study Box folder.

8 STUDY MANAGEMENT AND OVERSIGHT ARRANGEMENTS

8.1 STUDY MANAGEMENT GROUP

One full-day research team meeting will be held in Dundee, in month 1 to set up the project to set-up the project, following which the team will have virtual meetings (by telephone or Skype) at least every alternate month, but more frequently as needed. There will be frequent communication by e-mail between the team members.

8.2 STUDY STEERING COMMITTEE

A Stakeholder Advisory Group will meet three times during the project. The first meeting in month two will be face-to-face (with international members joining by Skype) to agree the terms of reference and communication methods for the group. The first meeting will also involve agreement of the study protocol, advice for the conduct of the study including recruitment strategies, and a report on the progress during month one. The next two meetings will be by teleconference. A teleconference in month 8 will report on the findings of WP1, advise on the components and the methods of the intervention and agree the sites for the feasibility study in WP3. There will be additional communication with the Stakeholder Advisory Group by e-mail as required, for example the group will be invited to review the final report before submission to the funder. All project team members, NHS collaborators and members of the Stakeholder Advisory Group and Parents' Panel will be invited to attend the consensus-building workshop.

8.3 DATA MONITORING COMMITTEE

Not applicable

8.4 INSPECTION OF RECORDS

The CI, PIs and all institutions involved in the study will permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

9 GOOD CLINICAL PRACTICE

9.1 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the principles of good clinical practice (GCP).

In addition to Sponsorship approval, a favorable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the study.

9.2 CONFIDENTIALITY

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access to study staff only. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor or its designee. The CI and study staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

9.3 DATA PROTECTION

The CI and study staff involved with this study will comply with the requirements of the Data Protection Act 1998/General Data Protection Regulations 2018 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The CI and study staff will also adhere, if appropriate, to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate study staff.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

9.4 INSURANCE AND INDEMNITY

The University of Dundee and Tayside Health Board Co-Sponsoring the study.

Insurance – The University of Dundee will obtain and hold a policy of Public Liability Insurance for legal liabilities arising from the study.

Tayside Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme ("CNORIS") which covers the legal liability of Tayside in relation to the study.

Where the study involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity The Co-Sponsors do not provide study participants with indemnity in relation to participation in the Study but have insurance for legal liability as described above.

10 ANNUAL REPORTING REQUIREMENTS

Annual reporting will be conducted in compliance with TASC SOP 15: Preparing and Submitting Progress and Safety Reports in CTIMPs and Non-CTIMPs, as a condition of sponsorship and as a condition of a favourable opinion from a REC. An HRA Annual Progress Report for NCTIMPs will be prepared and submitted by the CI to REC, and copied to the Sponsor, on the anniversary date of the REC favourable opinion.

Any safety reports additional to SAE reports, for example, reports of a DMC, will be sent by the CI to REC, with a Safety Report Form, and to the Sponsor.

11 STUDY CONDUCT RESPONSIBILITIES

11.1 PROTOCOL AMENDMENTS, DEVIATIONS AND BREACHES

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other study docs will not be implemented without these approvals.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor and the funder. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

In the event that a serious breach of GCP or protocol is suspected, this will be reported to the Sponsor Governance Office immediately

11.2 STUDY RECORD RETENTION

Archiving of study documents will be for five years after the end of study.

11.3 END OF STUDY

The end of study is defined as the completion of the consensus-building workshop in work package 2. The Sponsor, CI and/or the SC have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

12 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

12.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

12.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

12.3 PEER REVIEW

The study was peer-reviewed as part of the NIHR HTA funding process

Prior to submission for funding, the grant application was peer-reviewed by the study team, the Associate Dean for Research and one independent member of staff in the School of Nursing and Health Sciences.

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Section 2: Study Protocol WP3&4

Development and feasibility study of an evidence-informed manualised intervention to compare CUe- Based versus Scheduled feeding for preterm infants transitioning from tube to oral feeding in neonatal units. WP3&4

Study Acronym	CuBS WP3&4
Sponsor	University of Dundee – NHS Tayside
Sponsor Ref Number	1-008-19
Funder	NIHR HTA
Chief Investigator	Professor Alison McFadden
REC Number	19 – NS- 0055 Ethics Approval granted 26 April 2019 (approval of substantial amendment AMO1 granted 4 June 2019)
ISRCTN	13414304
Version Number and Date	Version **3.0 28/05/2019**

This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme (16/144/05). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

PROTOCOL APPROVAL

Insert study title

Signatures

The undersigned confirm that the following protocol has been agreed and approved by the Sponsor and that the Chief Investigator agrees to conduct the trial/study/study in compliance with this approved protocol and will adhere to the principles of GCP, the Sponsor SOPs, and any other applicable regulatory requirements as may be amended from time to time.

Professor Alison McFadden	AMcFadden	16/04/2019
Chief Investigator	Signature	Date
Professor Peter Donnan	Peter Donnan	16/04/2019
Individual Responsible for Statistical Review	Signature	Date

LIST OF ABBREVIATIONS

AE	Adverse Event
BCT	Behaviour Change Technique
BMS	Breastmilk Substitutes
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Scheme
CRF	Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HCP	Health Care Practitioners
ICF	Informed Consent Form
IF	Incidental Findings
ISF	Investigator Site File
MRC	Medical Research Council
NIHR HTA	National Institute for Health Research Health Technology Assessment Programme
NNU	Neonatal Unit
PI	Principal Investigator
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
SMF	Study Master File
SMG	Study Management Group
SSC	Study Steering Committee
WP	Work Package

SUMMARY/SYNOPSIS

Study Title	Development and feasibility study of an evidence-informed manualised intervention to compare CUe-Based versus Scheduled feeding for preterm infants transitioning from tube to oral feeding in neonatal units. CuBS	
Study Design	Multi-method feasibility study with four work packages (WP). This protocol pertains to: WP3: feasibility study and process evaluation in 3 clinical sites (Coventry, Dundee and Exeter) WP4: preparing next steps	
Study Population	Preterm babies in NNUs and their parents Health care practitioners (HCPs) working in neonatal units; Stakeholders- third sector organisations, HCPs, Professional Associations, and representatives from UK Neonatal Networks.	
Sample Size	WP 3: n = 105 WP 4: n= 30	
Study Period	WP3 and 4: 11 months	
Clinical phase duration	9 months	
Follow up phase duration	None	
Primary	Objectives 1. Appraise willingness of parents and staff to implement and sustain the intervention; 2. Assess associated costs of implementing cue-based feeding in neonatal units; 3. Determine feasibility and acceptability of conducting a future randomised controlled trial (RCT), including views on important outcomes, of parents and staff; 4. Scope existing data recording systems and potential short- and long-term outcome measures e.g. feeding outcomes, length of time to transition to full oral feeding; length of stay in NNU; infant growth;	Outcome Measures 1a Views of parents of the acceptability, and experiences of the intervention 1b Willingness and capacity of staff to implement the intervention 1c Views of staff of the acceptability and experiences of the intervention 2: Additional staff time, length of time parents spend on ward; time to discharge 3a Parents' willingness to be randomised in a future trial 3b Parents' views of important outcomes for a future trial 3c Staff views of important outcomes for a future trial 3d Fidelity to the intervention 3e Harmful/unintended 3f Recruitment rates – number of babies eligible and number of parents consenting to participate 4a Routinely collected data available for potential short-and longer-term outcomes 4b Infant feeding data

	5. Determine key stakeholder views based on the evidence from our study (objectives 1-7) of whether a randomised controlled trial of this approach is feasible and what the components of a future study would look like.	5. Stakeholder views and preferences
Secondary	Objectives	Outcome Measures
Inclusion Criteria	*Preterm babies*: developmentally normal preterm infants, including multiple births, born before 37 weeks gestation, who are clinically stable and at least partially enterally fed, have an intragastric tube in place at the start of the study, and whose parent(s) consent to inclusion in the study. *Parents* who give consent to the inclusion of their babies in the study *Health care practitioners* (HCPs) working in neonatal units and who are involved in implementation of the intervention *Stakeholders*: third sector organisations, HCPs, Professional Associations, and representatives from UK Neonatal Networks.	
Exclusion Criteria	Babies born after 37 weeks gestation, infants who are not at least partially enterally fed, preterm infants who have transitioned to full oral feeding, infants with major congenital anomalies, gastrointestinal disorders (e.g. necrotizing enterocolitis), congenital infections, and major neurological conditions (e.g. cerebral palsy, seizures, Grades III-IV intracranial haemorrhage, periventricular leukomalacia), and infants whose parent(s) do not give consent for inclusion in the study.	

14 INTRODUCTION

15 BACKGROUND & RATIONALE

The frequency of feeding and volume of milk intake of healthy term infants is generally dictated by the infant's appetite. Term infants exhibit feeding and satiation cues and adjust their volume of intake to compensate for differences in the nutrient density of breastmilk or breastmilk substitutes (BMS). In contrast, enteral feeds for preterm infants are usually given as prescribed volumes at scheduled intervals[1]. Some evidence exists, however, that preterm infants are able to self-regulate their intake [2]. Furthermore, while feeding cues may be more difficult to detect in preterm infants, they may be sufficiently evident for a parent or caregiver to recognise and respond to [3], thereby supporting safer and more successful feeding experiences. Caregivers and parents can use infants' physiological and behavioural channels of communication to inform their feeding decisions and actions. This may also set the scene for future feeding practices and success, and parent-infant interaction. Although studies have shown that cue-based (“responsive”) feeding is feasible for preterm infants, the adoption of cue-based feeding has been constrained by the "schedule- and volume-driven culture" in many neonatal units [4].

Cue-based feeding for preterm infants

Alternatives to a scheduled interval feeding regimen for preterm infants have been described [5]. These aim to respond to infant feeding and satiation cues and are particularly relevant to infants who are in the transition phase from gastric tube feeding to oral feeding (either breast or bottle) [6]. At this stage (about 32 to 36 weeks' postmenstrual age), preterm infants are usually beginning to develop periods of sustained alert activity and a suck-swallow-breathe pattern [7] sufficient for oral feeding to commence.

Cue-based feeding is a co-regulated approach [5]. The enteral feeding process starts when the caregiver recognises infant cues that indicate readiness to feed and ends when the infant demonstrates satiation. The infant, therefore, determines the timing, duration, and volume of intake. At each stage during transition to oral feeding, through understanding and interpretation of their cues, infants are supported in such a way that they are able to achieve all they are capable of with regards to oral feeding. Cue-based feeding occurs alongside supplementary tube feeding with the understanding that, developmentally, many preterm babies are not yet ready to fully sustain themselves by oral feeding. In modifications of cue-based feeding, caregivers may pre-set a maximum permitted duration of inactivity or sleep between feeds or a minimum required volume of intake or modify feeding plans to take into account the reduced endurance levels of preterm infants.

Why is the research important in terms of improving the health of the public and/or to patients and the NHS?

The transition to oral feeding is a critical developmental stage for preterm infants. Cue-based feeding may be considered a part of an integrated approach to providing 'developmental care' where infants are seen as individuals and caregivers are guided by the needs and behaviours of the infant [8]. Allowing preterm infants to inform the timing and duration of enteral feeding may result in longer rest periods between some feeds, promote infant-determined sleep and wake patterns that reduce unnecessary energy expenditure, and increase growth rates [9]. It is also possible that allowing the infant to determine the pattern of enteral feeding will help in the development of organised behaviour states and the earlier establishment of full oral feeding, a key criterion for hospital discharge for preterm infants [10]. Reducing length of hospital stay has a direct effect on hospital costs and may also decrease cot occupancy in neonatal units, thus reducing the need for inter-hospital transfer of women and infants [11]. Compared to a scheduled approach, cue-based feeding may support infant stability during oral feeds as infants cues will be responded to resulting in fewer episodes of physiological

instability which could cause significant harm e.g. aspiration, desaturation and bradycardia events [12]. As feeding a baby is a primary activity over the first year of life and a major preoccupation of parents, it is anticipated that there may be other benefits for the family and caregivers of cue-based feeding, principally allowing parents to: feel more directly involved with their infant's care; better understand their infant's communication, and increasing parental confidence and ability to recognise and respond to their infant's needs during their hospital stay and beyond. Enhanced parental satisfaction is a key quality indicator in measuring the effectiveness of family-integrated care in neonatal services [13].

Potential adverse effects of cue-based feeding for preterm infants are recognised. These mainly relate to whether such a regimen can guarantee metabolic stability, particularly normoglycaemia, in this vulnerable group. Even at the point of discharge home from hospital, some preterm infants are known to be susceptible to hypoglycaemia if a scheduled enteral feed is omitted or delayed [14]. Concern exists that repeated or prolonged episodes of hypoglycaemia may impair longer term growth and development [15]. There may be more acute problems relating to gastro-intestinal immaturity, such as feeding intolerance and a higher risk of aspiration of gastric contents into the lungs, as well as concerns that allowing unrestrained volumes of enteral intake may increase the risk of gastro-oesophageal reflux or feed intolerance. However, there is a lack of evidence of these potential adverse effects, and indeed some problems may be exacerbated by not responding to the infant's cues [12]. Despite these concerns, and despite a lack of evidence of benefit, cue-based feeding is established in some neonatal units in other countries e.g. Sweden [16, 17] and the USA [18, 19], and is increasingly being used in neonatal units in the UK [20]. Cue-based feeding for preterm infants is now recommended as a method to increase the duration of breastfeeding in the United Nations Children's Fund (UNICEF) Baby-Friendly Hospital Initiative "Ten steps to successful breastfeeding" [20, 21].

However, overall, the evidence to support cue-based feeding is limited. A recent Cochrane review [22] concluded that there was low quality evidence that cue-based feeding compared to scheduled feeding leads to earlier transition to full oral feeding. The review authors noted that this evidence should be treated with caution due to a number of methodological weaknesses [22]. Furthermore, there is a lack of strong or consistent evidence of the effect of cue-based feeding compared to schedule feeding on important outcomes for preterm infants or their families [22]. Therefore there is a need for rigorous evaluation of cue-based feeding for preterm infants within the NHS setting, based on the most up-to-date and complete evidence, and taking into account stakeholder (including parent) views. The first step towards this is to assess if such an intervention trial is justifiable and feasible.

16 STUDY OBJECTIVES & OUTCOMES

Table 1: Primary Objectives and Outcome Measures

Primary Objective:	Outcome Measure:	Timepoint of outcome measured

1 Appraise willingness of parents and staff to implement and sustain the intervention;	1a Views of parents of the acceptability, and experiences of the intervention 1b Willingness and capacity of staff to implement the intervention 1c Views of staff of the acceptability and experiences of the intervention	During intervention implementation period
2. Assess associated costs of implementing cue-based feeding in neonatal units;	2: Additional staff time, length of time parents spend on ward; time to discharge	During intervention implementation period
3. Determine feasibility and acceptability of conducting a future randomised controlled trial (RCT), including views on important outcomes, of parents and staff	3a Parents' willingness to be randomised in a future trial 3b Parents' views of important outcomes for a future trial 3c Staff views of important outcomes for a future trial 3d Fidelity to the intervention 3e Harmful/unintended consequences 3f Recruitment rates – number of babies eligible and number of parents consenting to participate	During intervention implementation period
4. Scope existing data recording systems and potential short- and long-term outcome measures e.g. feeding outcomes, length of time to transition to full oral feeding; length of stay in NNU; infant growth;	4a Routinely collected data is available for potential short-and longer-term outcomes 4b Infant feeding data	During implementation of intervention a) daily during hospital stay b) two weeks following discharge
5. Determine key stakeholder views based on the evidence from our study (objectives 1-7) of whether a randomised controlled trial of this approach is feasible and what the components of a future study would look like.	5. Stakeholder views and preferences	Month 18

17 STUDY DESIGN

17.1 INTERVENTION

The intervention was developed in WP 1 and 2 of this study.
The intervention is an evidence-informed manualised intervention to promote feeding in response to infant cues (cue-based feeding) for infants transitioning from tube to oral feeding (breast or bottle feeding) in neonatal units. Cue-based feeding is defined as feeding babies in response to their feeding and satiation cues, taking into account their stability and energy level [22]. The purpose of the intervention is to provide a step-by-step protocol for neonatal unit staff and parents on the introduction and maintenance of cue-based feeding for preterm

infants who are ready to/making the transition from tube feeding to oral feeding, and to create positive feeding behaviours as infants transition from tube to oral feeding.
The components of the intervention are:

1. Assessment of infants' readiness to commence transitioning from tube to oral feeding

Babies will be assessed when in an alert state using defined criteria of

   a. Respiratory stability
   b. Airway safety – i.e. suck, swallow ,and cough or gag reflexes

2. Development of a transition to oral feeding plan that is family-centred, individualised, clearly communicated and appropriately documented. The plan will be reviewed daily by staff and parents together and based on continuous assessment of the baby's responses. Documentation should summarise infant engagement/disengagement cues, and strategies used to support feeding skills;

3. At the oral stage (i.e. from the first oral feed) communications by staff with parents will focus on quality of feeds rather than quantity and will facilitate positive interactions between parents and baby.

   a. Cues for initiating a feed are mouthing, infant stirring, rooting, hands-to-mouth
   b. Cues for stopping a feed are falling asleep/off the breast, stopping sucking, pulling away/head turning, physiological instability, change in colour, loss of tone, sudden change in alertness, no interest in sucking after a pause
   c. Minimum and maximum interval between feeds is one- to three-hourly
   d. No maximum duration of feed
   e. No set rate of transition
   f. The UNICEF Baby Friendly Initiative tool (a standard care tool) will be used to determine the amount of top-up for breastfeeding (none, half or full). The tool includes taking into consideration whether or not the mother will be available for the next feed.
   g. Feeding assessments will continue and be documented even when the mother/parents are not present so that they can see how often their babies are waking for feeds

4. Safety and monitoring will be according to usual care in the clinical setting which should be a standardised approach across NICU and transitional care
5. Feeding support techniques No coercive measure will be used (e.g. chin lift). Feeding support techniques should be used only as part of a prescribed programme following assessment for oral aversion. Bottle-fed babies should be held in elevated side lying position during feeding.
6. Education - the intervention wil include a 2-hour training package for staff and informational resources for parents.

WP4
One consensus-building workshop with 30 stakeholders including parents and third sector organisations (e.g. Bliss, TAMBA, La Leche League), HCPs, Professional Associations (e.g. Neonatal Nurses Association, British Association of Perinatal Medicine) and representatives

from UK Neonatal Networks, to agree the intervention components, method of manualisation, and approach to education/training for HCPs and parents

Public involvement in the study
The study comprises four approaches to Patient and Public Involvement (PPI):
a) A panel of 6 parents with relevant experience will meet 3 times during the research to advise on aspects such as recruitment, topic guide for qualitative interviews, co-development of the intervention, interpretation of the findings and dissemination to parents. The Parent's Panel will also be invited to review the manualised intervention, in particular the training components for staff and parents. We will work with Bliss to support and train members of the Parent' Panel;
b) 2 members of the Parents' Panel will also be members of the Stakeholder Advisory, who will represent the views of parents;
c) The Bliss representative co-applicant will facilitate the Parent's Panel and will ensure that the views of parents are represented throughout the study;
d) Workshop (WP4) will be attended by voluntary organisations representing parents to ensure that parent's perspectives remain central to the development of the intervention and the framework of options for a future trial

4.2 STUDY DESCRIPTION

This four-phase multi-method study (approval is sought for the third and fourth phases) will develop and test the feasibility of conducting a study of the clinical- and cost- effectiveness of cue-based feeding vs scheduled feeding for preterm infants in neonatal units. The study comprises four work packages (WP) based on the MRC principles for developing and evaluating complex interventions [23] and process evaluations [24]. Data will not be collected for babies receiving schedule feeding.

Work package three, *feasibility study*, months 11-19, addresses objectives 1-4.

We will conduct a feasibility study with an embedded process evaluation [24] to assess willingness of parents and staff to implement the intervention, explore the design of a future study, and determine the feasibility and acceptability of conducting a future RCT. We will implement the intervention for six months in three NNUs (Coventry, Dundee and Exeter).

We aim to recruit 20 babies and at least one parent per baby (for multiple births there may be more than one baby per parent) in each unit (total n=60). As this is a feasibility study, a sample size calculation is not required. Sixty infants should be sufficient to assess the feasibility of all aspects of the intervention. In each unit, parents of all infants, including multiple births, who are eligible to be included in the study will be approached by a member of the care team and invited to participate.

Following training of staff to implement the intervention, recruitment will continue over a six month period (with one further month as contingency in case of failure to reach the recruitment target within 6 months) or until consent for 20 babies has been reached. It is hoped that across the three units the sample will be sufficiently diverse, for example to assess the feasibility of the intervention for different feeding methods and types.

We will select a diverse purposive sample of 10 babies in each unit (total 30), and invite their parents to participate in an in-depth qualitative interview. Parents will be offered a £10 incentive for participating in the qualitative interview.

Records will be kept of the total number of infants in the neonatal units during the recruitment period and the proportion that are eligible, numbers of parents approached, numbers of parents who consent to inclusion, and if provided, the reason for non-consent, and the number retained in the study. This data will inform recruitment strategies for a future effectiveness trial.

In each unit we will also recruit 10-15 staff to include all grades and relevant disciplines. This may vary between the different units depending on the skill-mix of the staff but for example in each unit could include four neonatal nurses, four nursery nurses, one consultant neonatologist, two trainee medical staff, and one each of advanced nurse practitioner, infant feeding adviser, speech and language therapist and dietician.

Individual interviews with parents of the babies included in the study will allow in-depth exploration of their experiences and views of cue-based feeding. The interviews will seek to explore the acceptability of the intervention, whether it was implemented as intended, parental satisfaction with care and support for infant feeding, how parents would feel about a future randomised trial and their views on important outcomes. The in-depth interviews will be conducted with parent(s) of ten babies in each unit (study total n=30). We will aim for a purposive sample of parent(s) so that we include babies who are breastfed, formula fed, and or fed both. We will interview at least one parent for each baby (expect in the case of multiple births) but will include both parents together if they prefer. Interviews will last up to 60 minutes and will be audio-recorded with the participant's permission.

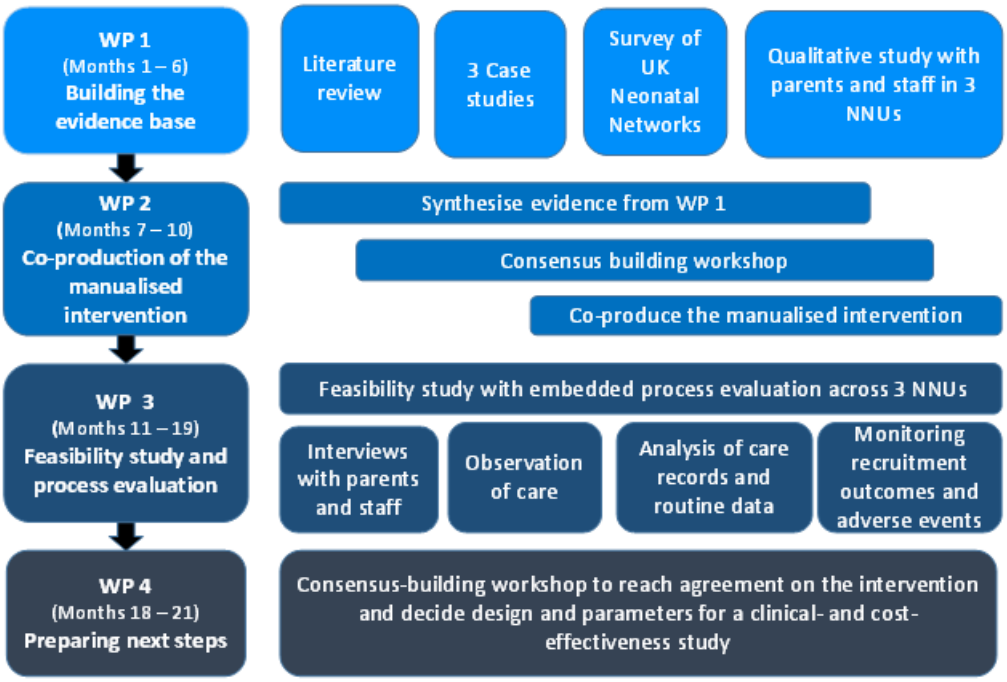
Informed by Normalisation Process Theory [25] and MRC guidance [24], interviews with staff will explore their views and experiences of the training provided, and of implementing cue-based feeding in the context of their unit. These data will be used to assess fidelity to the intervention, acceptability, tailoring/modification of the intervention to suit the local context, and their willingness to support a future randomised trial. Staff will also be asked about important outcomes for a future trial. Interviews will last up to 60 minutes and will be audio-recorded with the participant's permission.

We will conduct non-participant observation of **three hours on six** separate occasion (early, mid and late study) in each unit. The observation will be focussed on observing behaviours that are commensurate with the intervention such as staff reviewing feeding plans with parents, staff highlighting infant feeding cues with parents, babies being fed according to their cues. Observational data will be in the form of field notes following an observation guide with a focus on fidelity, interactions between staff and parents concerning feeding, Observations will be conducted by the research nurse in each unit.

Work package four, *preparing next steps,* months 18-21, objective 5 and dissemination.

This work package includes synthesis of the findings of all previous work packages (WP1-WP3), a stakeholder workshop to evaluate the evidence from WP1-3, explore preferences, reach agreement on the manualised intervention, and produce a framework for decision-making on the design, feasibility and acceptability of a future clinical and cost-effectiveness study of cue-based versus scheduled feeding for preterm infants. As far as possible, the attendees at the stakeholder workshop in this WP will include those who attended the consensus-building workshop in WP2. This is so that they are already engaged with, and understand the study which will provide more informed decisions and more efficient use of time. We may also add further research methodology experts to contribute to decision-making about a future trial.

4.3 STUDY FLOWCHART



17.2 STUDY MATRIX

	Screening	Daily during hospital stay	At discharge from hospital	2 weeks ater discharge	Once	**Six** times during clinical phase of study
Babies Feeding cues, type, frequency and method		x		x		
Babies Assessment of care records	x		x			
Parents Interview					x	
Staff Interview					x	
Observations of care						x

17.3 STUDY ASSESSMENTS

Babies: study assessments of feeding type, frequency and methods will be obtained from routine care records by the research nurse with parents' consent and by telephone call/**e-mai**l two weeks after discharge.
Observations will be made to ascertain fidelity to the intervention and any context-specific modifications by the research nurse with participants' consent guided by a checklist (Observation Schedule).

Parent(s) of 30 babies will be invited to take part in an individual face-to-face interview while their baby is on the neonatal unit. The interview, conducted by the research nurse or a member of the research team, in a suitable venue in the neonatal unit, will last up to one hour and will cover their experiences of feeding their baby during transition from tube to oral feeding, their views of cue-based feeding and the information provided for parents, how they would feel about being randomised in a future trial and their views of the important outcomes for a future trial. They will also be asked how long they have spent with their baby during the transition from tube to oral feeding. Parents will be offered a £10 shopping voucher to thank them for taking the time for the interview.
Staff; All relevant staff in the three sites will undertake a 2-hour training package to prepare them for implementing the intervention. The training package will be delivered first by a member of the research team, to the research nurse and members of staff who will then cascade the training to the remaining staff on the neonatal unit.
10-15 members of the multidisciplinary team will be invited to participate in an individual face-to-face interview. The interview, conducted by the research nurse or a member of the research team, in a suitable venue in the neonatal unit, will last up to one hour and will cover views of the acceptability and feasibility of the intervention, the training materials, and resources for parents, and their views of the acceptability and feasibility of conducting an RCT and their views of important outcomes for a future trial.
Non-participant observation guided by a checklist will take place **six times for three hours in each site.**

17.4 STUDY SAFETY ASSESSMENTS

The intervention safety assessments are:

1. Infants' readiness to commence transitioning from tube to oral feeding

Babies will be assessed when in an alert state using defined criteria of

   a. Respiratory stability
   b. Airway safety – i.e. suck, swallow ,and cough or gag reflexes

2. Development of a transition to oral feeding plan that is family-centred, individualised, clearly communicated and appropriately documented. The plan will be reviewed daily by staff and parents together and based on continuous assessment of the baby's responses. Documentation should summarise infant engagement/disengagement cues, and strategies used to support feeding skills;

3. At the oral stage (i.e. from the first oral feed) communications by staff with parents will focus on quality of feeds rather than quantity and will facilitate positive interactions between parents and baby.

   a. Cues for initiating a feed are mouthing, infant stirring, rooting, hands-to-mouth
   b. Cues for stopping a feed are falling asleep/off the breast, stopping sucking, pulling away/head turning, physiological instability, change in colour, loss of tone, sudden change in alertness, no interest in sucking after a pause
   c. Minimum and maximum interval between feeds is one- to three-hourly
   d. No maximum duration of feed
   e. No set rate of transition
   f. The UNICEF Baby Friendly Initiative tool will be used to determine the amount of top-up for breastfeeding (none, half or full). The tool includes taking into consideration whether or not the mother will be available for the next feed.

g. Feeding assessments will continue and be documented even when the mother/parents are not present so that they can see how often their babies are waking for feeds

4. Safety and monitoring will be according to usual care in the clinical setting which should be a standardised approach across NICU and transitional care

5. Feeding support techniques No coercive measure will be used (e.g. chin lift). Feeding support techniques should be used only as part of a prescribed programme following assessment for oral aversion. Bottle-fed babies should be held in elevated side lying position during feeding.

The study intervention assessments will be according to usual monitoring practice in the study sites and will include:
Feeding type, frequency and method will be recorded daily until the baby is discharged from hospital and then 2 weeks after discharge by a telephone call **or by e-mail depending on the parent's preference.**
Any adverse events will be recorded from the routine monitoring of preterm babies in the study sites.

Qualitative interviews with parents: the topics for the interviews with parents in WP3 are not particularly sensitive, however parents with babies on neonatal units are in a vulnerable position and will have concerns about their babies' health and progress. If a parent becomes distressed during an interview, they will be given the option to pause the interview for a break and resume later at a time convenient to the parent, or to end the interview. Parents who become distressed will be referred to the care team for additional support if the parent agrees to this. If the research nurse is concerned about the safety of a parent and/or baby, and even in the absence of the parent's agreement, they will discuss their concern confidentially with the Principal Investigator for the site.

17.5 STUDY POPULATION

Developmentally normal preterm babies who are transitioning from tube to oral feeding, (WP3).
Parents of babies who are included in the study (WP3)Health care professionals working in neonatal units (WP3).
Stakeholders including third sector organisations, HCPs, Professional Associations and representatives from UK Neonatal Networks (WP 4)

17.6 NUMBER OF PARTICIPANTS

The target sample sizes for the different work packages are listed below.
WP3: recruitment period 6 months

- 60 babies who are transitioning from tube to oral feeding, and their parents (a subset of 30 parents will be invited to participate in a qualitative interview)
- 30-45 health care practitioners working in neonatal units in the three study sites

WP4

- 30 stakeholders (workshop)

17.7 INCLUSION CRITERIA

Preterm babies: developmentally normal preterm infants, including multiple births, born before 37 weeks gestation, who are clinically stable and at least partially enterally fed, have an intragastric tube in place at the start of the study, and whose parent(s) consent to inclusion in the study.

Parents who give consent to the inclusion of their babies in the study
Health care practitioners (HCPs) working in neonatal units and who are involved in implementation of the intervention
Stakeholders: third sector organisations, HCPs, Professional Associations, and representatives from UK Neonatal Networks.

17.8 EXCLUSION CRITERIA

Babies born after 37 weeks gestation, infants who are not at least partially enterally fed, preterm infants who have transitioned to full oral feeding, infants with major congenital anomalies, gastrointestinal disorders (e.g. necrotizing enterocolitis), congenital infections, and major neurological conditions (e.g. cerebral palsy, seizures, Grades III-IV intracranial haemorrhage, periventricular leukomalacia).
Infants whose parent(s) do not give consent for inclusion in the study.
Infants whose parents are not able to give consent.

Individuals will not be enrolled to the study if they are participating in the clinical phase or have done so within the last 30 days or are participating in the follow-up phase of another interventional trial/study or who are enrolled in an observational study.

18 PARTICIPANT SELECTION AND ENROLMENT

18.1 IDENTIFYING PARTICIPANTS

Babies who are eligible to be included in the study and their parents will be identified by the care team. The member of the care team, will introduce the study and provide the participant information sheet. Parents who are interested in participating in the study will complete a reply slip which will be passed from the member of the care team to the research nurse. The research nurse will follow up with interested parties
The research nurse will discuss the study information in the participant information sheet for those parents who agree to consider participation in the study, including the feasibility study, the non-participant observation and the interviews. The research nurse will take written consent form parents for the elements of the study in which they agree to participate.

The research nurse will follow-up with parents who express a willingness to participate in an interview at least 24 hours after they have received the participant information sheet to confirm that they wish to take part in an interview and to arrange a date time convenient to the parent(s). For the non-participant observation, it will be explained to parents at the time they receive the participant information sheet, that this will take place only **6 times** during the 9-month clinical phase of the study, so will not apply to all parents. At least 24-hours before a planned non-participant observation session, the research nurse will visit parents on the neonatal unit who have expressed a willingness to participate, to confirm that they are still interested, and to take written informed consent.

Potential staff participants will be approached by email by someone who has regular access to staff. This person will introduce the study and attach the interview and non-participant observation staff participant information sheets. Staff who are interested will contact the research nurse directly by e-mail.
For the staff interviews, the research nurse will arrange to meet interested staff members to explain the information in the participant information sheet, to answer questions and to arrange a convenient date and time for the interview

For the non-participant observation of practice, the site research nurse will identify the day and time to conduct the observation when there is at least one baby enrolled in the study on the unit. At least 24-hours prior to a planned non-participant observation session the research

nurse will contact face-to-face or by e–mail, all staff who are rostered to be on duty during the observation to inform them that it is planned to take place and to provide the participant information sheet (PIS). Written informed consent will be taken immediately prior to the planned observation.

WP4
Stakeholders will be identified by the research team through the UK Neonatal Networks, Professional Associations and relevant civil society/charitable organisations. Co-ordinators of these organisations will be approached by the research team, providing study information and inviting them to send representatives to the workshops.

18.2 CONSENTING PARTICIPANTS

WP3

Parents of babies who are eligible to participate in the study: after receiving a reply slip, the research nurse will discuss the study and answer all questions. The research nurse will take written informed consent using the ICF at least 24 hours after the parents have been provided with the PIS. Consent will be taken on the neonatal unit. Consent will be given for the baby to be included in the study, for the research information to be collected from routine care records, for the follow-up telephone interview two weeks after discharge, and, for those parents who agree, consent to take part in the non-participant observation and/or the interview including permission to audio-record the interview.
The research nurse will arrange a date and time for the interview that is convenient to the parent(s). At the outset of the interview, the research nurse will confirm consent
At least 24-hours before a planned non-participant observation session, the research nurse will visit parents on the neonatal unit who have expressed a willingness to participate, to confirm consent.

Healthcare practitioners who contact the research nurse, will be invited to participate in an interview. The research nurse will take written informed consent using the ICF prior to the interview and at least 24 hours after being given the PIS. The ICF will include permission to audio-record the interview. The interviews, which will be audio-recorded with permission of participants will take place in a venue that is convenient for the participants for example in a meeting room or similar on the neonatal unit.

The research nurse will take written informed consent on the neonatal unit from relevant staff immediately prior to the observation commencing.

WP4

Consent will be assumed by attendance at the workshop.

Where a participant requests to speak with a physician from the study team the consent process will not be completed until the participant has spoken to the physician and had all their questions answered to their satisfaction.

For adults who lose capacity their previous wishes will remain legally binding and this will remain valid unless the protocol changes significantly. If this occurs and further consent is required from a participant who has lost capacity, the appropriate person will be asked for their consent. In all cases the CI or delegate will consult with carers and take note of any signs of objection or distress from the participant – the participant will be withdrawn if they raise objection. Where appropriate the participant will be withdrawn from any further clinical intervention and agreement will be sought from a carer to allow data collection.

The informed consent process will be conducted in compliance with TASC SOP07: Obtaining Informed Consent from Potential Participants in Clinical Research

18.3 SCREENING FOR ELIGIBILITY

The care team will identify babies who meet the inclusion criteria for the study

18.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

18.4.1 Withdrawal procedures

Babies whose condition changes such that they are no longer eligible for inclusion in the trial (for example complications that require enteral feeding to be stopped) will be withdrawn from the study.
Parents and health care practitioners can withdraw from the study at any time. Where withdrawal is requested after data has been collected relating to a baby or after an interview has taken place, a discussion will take place between the parent/HCP and a member of the research team regarding whether the parent/HCP agrees to the information about their baby or that they contributed being included in the study or whether there are specific elements that they would like removed.

19 DATA COLLECTION & MANAGEMENT

19.1 DATA COLLECTION

WP component	Source of data	Time point	Collected by	Tools
WP3 Feasibility study Feeding data	Care team or parents recording of infant feeding	Daily feeding records during transition from tube to oral feeding	Care team or parents	Case report form
WP3 Feasibility study Feeding data	Telephone call **or e-mail**	Two weeks after discharge	Site research nurse	Research nurse's notes of telephone call **or the e-mail response**
WP3 Feasibility study Baby daily weight, number of days to transition to full oral feeding, number of days in neonatal unit.	Routine care records and data systems	At discharge of each baby	Site research nurse	Case report form
WP3 Feasibility study	Interviews (audio-recorded) with parents	During intervention phase: months 11-19	Site research nurse	Topic guide
WP3 Feasibility study	Interviews (audio-recorded) with staff	During intervention phase: months 11-19	Site research nurse	Topic guide
WP3	Observation of care	During intervention	Site research nurse	Observation schedule

Feasibility study		phase: months 11-19		
WP3 Feasibility study	Recruitment log	During intervention phase: months 11-19	Site research nurse	Recruitment log
WP4 Consensus-building workshop	Participatory workshops Notes taken by research team and other materials such as flip charts and post-it notes	Month 18	Research team	Materials developed by research team

19.2 DATA MANAGEMENT SYSTEM

Data management will be conducted in compliance with TASC SOPs on Data Management, TASC SOP53 Data Management Systems in Clinical Research. The data management system (DMS) will be Excel, as approved by Sponsor

The DMS will be based on the protocol and CRF for the study and individual requirements of the investigators. The CRF will collect only information that is required to meet the aims of the trial/study and to ensure the eligibility and safety of the participant. The study database will be compliant with TASC SOP53 Data Management Systems in Clinical Research.
The database is managed in line with all applicable principles of medical confidentiality and data laws. The Data Controller will be the University of Dundee and the Data Custodian will be the Chief Investigator.

The CI may delegate CRF completion but is responsible for completeness, plausibility and consistency of the CRF. Any queries will be resolved by the CI or delegated member of the study team.

Database lock will be conducted in compliance with TASC SOP32 Locking Clinical Study Databases.

20 STATISTICS AND DATA ANALYSIS

20.1 SAMPLE SIZE CALCULATION

The sample sizes for the different components of the study have been estimated based on the purpose of each element, to reflect the range and diversity of participants, the experience and expertise of the research team, and in discussion with the proposed study sites. Sample size calculation is not relevant to this feasibility study.

20.2 PROPOSED ANALYSES

Outcomes of the feasibility study will be summarised as means and standard deviations for quantitative variables and percentages and denominator for categorical variables. The distributions of outcomes will also be explored. Intracluster correlations will be estimated and used in trial size calculations with cluster and stepped-wedge designs. These will be presented in total and by centre. Costs will be described in a similar way as other outcomes.

The anonymised qualitative interview data from WP3 will be transcribed verbatim by a third party and analysed thematically, along with the detailed field notes of the observations of

practice, using the seven-stage approach described by Gale et al. [26]: transcription, familiarisation, coding, developing a working analytical framework, applying the analytical framework, charting data into the framework matrix, and interpreting the data. Managing the analysis will be supported by text management software (NVivo). The analytical framework will be derived both deductively – in this work package the MRC Process Evaluation Framework [24] will be used – and inductively i.e. incorporating new themes that emerge from the data through open coding. This approach to analysis will enable comparison by themes across multiple accounts as well as retaining the context of individual experience. To enhance reliability of the coding, two researchers will independently code the first few transcripts before agreeing a set of codes to apply to all transcripts. The research team will meet regularly during analysis to discuss interpretation of research material. To enhance the credibility of the interpretation we will pay particular attention to negative or dissonant cases.

The synthesised data from WP3 will be used to develop a matrix of problems and options for components of the intervention and the design of a future trial. The data collected during the stakeholder workshop in WP4 will be analysed according to the ADePT process [27] and used to further develop the framework of options for the design, parameters, and important outcomes for a future clinical- and cost-effectiveness trial.

All data analysis will be carried out by the research team.

20.3 MISSING DATA

Not applicable to this study

20.4 TRANSFER OF DATA

Data from the three sites (Coventry, Dundee and Exeter) will be collected by the research nurses. All data will be anonymised i.e. participant codes rather than names will be used. All data collected (case report forms, audio-files and transcriptions of interviews) will be held on password protected computers and uploaded via the cloud storage programme Box which is password protected and held on the University of Dundee network (Dundee and Exeter) or using LabKey software (Coventry). Only the research team will have access to the study Box folder. Data entry will be performed by the study team at the University of Dundee.

21 STUDY MANAGEMENT AND OVERSIGHT ARRANGEMENTS

21.1 STUDY MANAGEMENT GROUP

The study will be co-ordinated by a Study Management Group (SMG), consisting of the grant holder Chief Investigator (CI), and research team

21.2 STUDY STEERING COMMITTEE

A Study Steering Committee (SC) has been established to oversee the conduct and progress of the study. The terms of reference of the SC are detailed in the SMF. Minutes of the SC will be maintained in the SMF.

21.3 DATA MONITORING COMMITTEE

It has been agreed by the sponsor and the funder that a data management committee is not required for this study.

21.4 INSPECTION OF RECORDS

The CI, PIs and all institutions involved in the study will permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

22 GOOD CLINICAL PRACTICE

22.1 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the principles of good clinical practice (GCP).

In addition to Sponsorship approval, a favorable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the study.

22.2 CONFIDENTIALITY AND DATA PROTECTION

The CI and study staff will comply with all applicable medical confidentiality and data protection principles and laws with regard to the collection, storage, processing and disclosure of personal data.

The CI and study staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or equivalent.

All study records and personal data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate trial staff only. Computers used to collate personal data will have limited access measures via user names and passwords.

Personal data concerning health will not be released except as necessary for research purposes including monitoring and auditing by the Sponsor, its designee or regulatory authorities providing that suitable and specific measures to safeguard the rights and interests of participants are in place.

The CI and trial staff will not disclose or use for any purpose other than performance of the trial, any personal data, record, or other unpublished, confidential information disclosed by those individuals for the purpose of the trial. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated personal data relating to participants will be restricted to the CI and appropriate delegated trial staff.

Where personal data requires to be transferred, an appropriate Data Transfer Agreement will be put in place.

Published results will not contain any personal data that could allow identification of individual participants.

22.3 INSURANCE AND INDEMNITY

The University of Dundee and Tayside Health Board are Co-Sponsoring the study.

Insurance – The University of Dundee will obtain and hold a policy of Public Liability Insurance for legal liabilities arising from the study.

Tayside Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme (“CNORIS”) which covers the legal liability of Tayside in relation to the study.

Where the study involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside’s membership of the CNORIS scheme.

Indemnity The Co-Sponsors do not provide study participants with indemnity in relation to participation in the Study but have insurance for legal liability as described above.

23 ADVERSE EVENTS

23.1 DEFINITIONS

Adverse Event (AE)	Any untoward medical occurrence in a clinical research participant which does not necessarily have a causal relationship with study participation
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life threatening • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • Or is otherwise considered serious

23.2 RECORDING AND REPORTING AE

All SAEs will be recorded on the AE Log in the CRF and will be assessed for severity by the CI or delegate. SAEs will be recorded from the time a parent consents to their baby joining the study until the participant's last study visit.

The Investigator will make a clinical judgment as to whether or not an AE is of sufficient severity to require the participant's removal from the study. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant should, if required, be offered an end of study assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable. SAEs will be followed up until 30 days after participant's last visit.

The CI or delegate will ask about the occurrence of SAEs and hospitalisations at every visit during the study. **SAEs which are both unexpected and related to study participation** will be submitted on an HRA NCTIMP Safety Report form to the REC by the CI, within 15 days of becoming aware of the SAE, and copied to the Sponsor Research Governance Office.

Worsening of the condition under study will not be classed as an AE, but will be defined as an outcome. Pre-specified outcome(s) will not be classed as an AE but as an outcome. Elective admissions and hospitalisations for treatment planned prior to randomisation, where appropriate, will not be considered as an AE. However SAEs occurring during such hospitalisations will be recorded.

24 ANNUAL REPORTING REQUIREMENTS

Annual reporting will be conducted in compliance with TASC SOP 15: Preparing and Submitting Progress and Safety Reports in CTIMPs and Non-CTIMPs, as a condition of sponsorship and as a condition of a favourable opinion from a REC. An HRA Annual Progress Report for

NCTIMPs will be prepared and submitted by the CI to REC, and copied to the Sponsor, on the anniversary date of the REC favourable opinion.

Any safety reports additional to SAE reports, for example, reports of a DMC, will be sent by the CI to REC, with a Safety Report Form, and to the Sponsor.

25 STUDY CONDUCT RESPONSIBILITIES

25.1 PROTOCOL AMENDMENTS, DEVIATIONS AND BREACHES

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other study docs will not be implemented without these approvals.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

In the event that a breach of GCP or protocol is suspected, this will be reported to the Sponsor Governance Office immediately

25.2 STUDY RECORD RETENTION

Archiving of study documents will be for five years after the end of study.

25.3 END OF STUDY

The end of study is defined as 2-week infant feeding data collection for all babies in the study The Sponsor, CI and/or the SC have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

26 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

26.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

26.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

26.3 PEER REVIEW

The study was peer-reviewed as part of the NIHR HTA funding process

Prior to submission for funding, the grant application was peer-reviewed by the study team, the Associate Dean for Research and one independent member of staff in the School of Nursing and Health Sciences.

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