Cord Pilot Trial

Immediate cord clamping versus deferred cord clamping for preterm birth before 32 weeks gestation: a pilot randomised trial

Final Version 6.2 dated, 8 September 2016

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Funder

NIHR Programme Grant for Applied Research

This protocol describes the **Immediate cord clamping versus deferred cord clamping for preterm birth before 32 weeks gestation: a pilot randomised trial** and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial. Problems relating to this trial should be referred, in the first instance, to the Chief Investigator.
This trial will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Amendment History

Amendment No. SA01			
Page	**Section**	**Previous wording**	**New wording**
Title	This change has been implemented throughout the document.	Preterm Cord Clamping Trial Immediate cord clamping with neonatal care at the roomside, versus deferred cord clamping with neonatal care at the bedside for preterm birth before 32 weeks gestation: a pilot randomised trial	Cord Pilot Trial Immediate cord clamping versus deferred cord clamping for preterm birth before 32 weeks gestation: a pilot randomised trial
Throughout the protocol		The wording has changed in the following sections Trial summary, Summary, Introduction (*Initial care at birth for very preterm infants: at the bedside or at the roomside)* Objectives, Pilot trial description, Pilot trial interventions Treatment of participants	At the collaborators meeting it became clear that some sites would want to offer care at the bedside to women with immediate clamping – as this is now part of their standard care. The protocol has been reworded to reflect this shift in practice.
Randomisation	3.4	Women who are eligible and have agreed to participate will be randomised using sealed consecutively numbered packs. Each maternity unit will keep a central log of all packs. On the front of the pack will be a check list of the inclusion and exclusion criteria, and space to record the date, time, woman's initials, her data of birth, and her expected data of delivery (or estimated gestation). Once this information is complete, the woman will be considered to be randomised, even if the pack is not opened. Inside the pack will be a card with the allocated intervention, two stickers (one each for the woman's	Women who are eligible and have agreed to participate will be randomised using sealed consecutively numbered opaque envelopes . Envelopes will be in a Cord Trial ringbinder, and removed in consecutive order by tearing at the punch holes. Each maternity unit will keep a central log of all envelopes. On the front of the envelope will be a reminder to check eligibility criteria, and space to record the date, time, woman's initials, her data of birth, and her estimated gestation. Once this information is complete, the woman will be considered to be randomised, even if the pack is not opened. Inside the envelope will be a card with the allocated intervention, two stickers (one each for the woman's and baby's notes) and a Birth Record to record details of the birth and initial care at birth .

		and baby's notes),a sticker for the consent form, and two booklets of data collection forms, one for the woman and one for the baby. Date and time of birth of the baby and time of cord clamping will be recorded on the front of the pack, and later transferred to the woman's booklet.	This Birth Record is then filed in the baby's hospital case notes.
Source data	3.11	Information required for randomisation will be recorded on the randomisation pack at trial entry (see 3.4 above).	Information required at randomisation will be recorded on the randomisation envelope at trial entry (see 3.4 above). To facilitate maintaining contact with the families, women will also be asked to provide contact details with other relevant relatives, for example grandparents.
Trial entry and recruitment	5.1		More clarification has been included

Substantial Amendment 03			
Page	**Section**	**Previous wording**	**New wording**
Trial Summary	Duration	Recruitment is for 12 months. Follow up for the women is for 12 months, and for the children until age two years (corrected for gestation at birth)	Recruitment to the initial feasibility phase of the pilot trial is for 12 months but will be extended after this phase until 31 December 2014. Follow up for the women is for 12 months, and for the children until age two years (corrected for gestation at birth)
Table 1	Child Age 2 years		Ages and Stages Questionnaire (ASQ) added to table for the 2 year follow up. PARCA_R and Bayley III assessment for families recruited from 01 March 2013 to 28 February 2014 only.
Summary		The sample size is 100-110 mother-infant pairs.	The target sample size for the initial feasibility phase is 100-110 mother-infant pairs in 8 sites.
Pilot Trial Description	3.3	The aim is to recruit at least 100-110 women in at least eight maternity units. Recruitment will be for 12 months. Follow up for the women is for 12 months, and follow up for the children is until age two years (corrected for gestation at birth).	The aim is to recruit at least 100-110 women for the initial feasibility phase in at least eight maternity units. Recruitment to the initial feasibility phase of the pilot trial will be for 12 months. After this initial phase recruitment will be extended until 31 December 2014. Follow up for the women is for 12 months, and follow up for the children is until age two years (corrected for gestation at birth).

Duration of Participation	3.7	Recruitment to the pilot trial will be for 12 months. Follow up for the women will be for 12 months, and for the children until they are two years old, corrected for gestation at birth. The end of the trial is defined as the "last child's neurodevelopment assessment".	Follow up for the women will be for 12 months, and for the children until they are two years old, corrected for gestation at birth. The end of the trial is defined as the "last child's 2 year Follow Up".
Source Data	3.11	Outcome data for the women will be the medical notes, and the pilot trial questionnaires. For the children, outcome data will come from the medical notes, the Parent Report of Children's Abilities – Revised (PARCA-R) and the Bayley Scales of Infant Development.	Outcome data for the women will be the medical notes, and the pilot trial questionnaires. For the children, outcome data will come from the medical notes, and the Ages and Stages Questionnaire (ASQ). For families recruited between 01 March 2013 – 28 February 2014, outcome data will also be collected from the Parent Report of Children's Abilities – Revised (PARCA-R) and the Bayley Scales of Infant Development.
Participant follow-up	5.3	Six weeks after the birth, women will also be asked to complete a brief questionnaire.	Within 2-3 months after the birth, women will also be asked to complete a brief questionnaire.
Participant follow-up	5.3	At the child's second birthday, corrected for gestation at birth, the family will be contacted to arrange a neurodevelopment assessment for the child. Four weeks before this assessment, the family will be sent the Parent Report of Children's Abilities – Revised (PARCA-R) by post, and asked to complete and return this before the assessment. The neurodevelopment assessment will use the Bayley Scales of Infant Development III, and will be conducted by a trained practitioner either at home or in the clinic, whichever is preferred by the family. The assessment usually takes between one and a half and two hours. If the child dies before their first birthday, the mother will remain in follow	At the child's second birthday, corrected for gestation at birth, the family will be contacted for the 2 year follow up. Families recruited into the trial between 01 March 2013 and 28 February 2014, will be contacted to arrange a neurodevelopment assessment for their child. Four weeks before the child's second birthday, corrected for gestation at birth, the family will be sent the Ages and Stages Questionnaire (ASQ) by post, and asked to complete and return this before the assessment. A stamped addressed envelope will be provided to return the questionnaire. The neurodevelopment assessment will use the Bayley Scales of Infant Development III, and will be conducted by a trained practitioner either at home or in the clinic, whichever is preferred by the family. The assessment usually takes between one and a half and two hours. Parents will also be offered the opportunity to complete the Parent Report of Children's Abilities – Revised (PARCA-R) at the neurodevelopmental assessment. This usually takes between 30-45 minutes to complete.

		up as long as she is in agreement with this.	Families recruited to the trial from 01 March 2014 onwards will be sent the Ages and Stages Questionnaire (ASQ) by post at around the child's second birthday, corrected for gestation at birth. A stamped addressed envelope will be provided to return the questionnaire.
Estimated Sample Size	7.1		In October 2013 it was agreed within the CORD Pilot Trial DMC and TSC meetings that recruitment to the pilot trial should be extended to run into the start of the main trial. This would allow clinicians in the current eight pilot study sites to avoid losing equipoise regarding the timing of umbilical cord clamping. Recruitment will be extended from 01 March 2014 until 31 December 2014, by which time a decision regarding the funding for the main trial should be definite.
References	15		Added reference: Squires, J., et al., Ages & Stages Questionnaire 3 User's Guide 2009, Paul Brookes Publishing Co: Baltimore, MD.

Substantial Amendment 04			
section	**Page**	**Previous wording**	**New wording**
Table of content	8		Appendix 2. Qualitative Substudy - Exploring women's and clinicians' views of the two consent pathways for the CORD Pilot Trial
Study Assessments	13		Added qualitative interviews for women and clinicians to study assessments table
1.2 Introduction: Why a trial is needed now	19	This protocol is for a pilot trial to assess the feasibility such a study	This protocol is for a pilot trial to assess the feasibility of such a study. This protocol also includes a qualitative interview substudy which aims to evaluate the experience of women who are invited to consent to participate in the Cord Pilot trial, as well as clinicians' experience of asking women for consent (Appendix 2 – substudy protocol).
3.11 Source data	22	the Parent Report of Children's Abilities – Revised (PARC-R) and	Text removed
5.1 Trial Procedures	23	The clinician will record in her hospital notes that consent was confirmed before randomising the womant.	The clinician will record in her hospital notes that consent was confirmed before randomising the woman.
5.3 Participant Follow up	24	Parents will also be offered the opportunity to complete the Parent Report of Children's Abilities – Revised (PARCA-R) at the	Text removed

		neurodevelopmental assessment. This usually takes between 30-45 minutes to complete.	

Substantial Amendment 05			
section	**Section**	**Previous wording**	**New wording**
Trial Summary	Duration	Recruitment to the initial feasibility phase of the pilot trial is for 12 months but will be extended after this phase until 31 December 2014.	Recruitment to the initial feasibility phase of the pilot trial is for 12 months but will be extended after this phase until 31 July 2015.
Pilot Trial Description	3.3	Recruitment to the initial feasibility phase of the pilot trial will be for 12 months. After this initial phase recruitment will be extended until 31 December 2014.	Recruitment to the initial feasibility phase of the pilot trial will be for 12 months. After this initial phase recruitment will be extended until 31 July 2015.
Randomisation	3.4		If the main UK Cord Trial is funded, an electronic randomisation system will be used instead of the envelope based randomisation system used in the Cord Pilot Trial. An electronic randomisation system is being piloted at some of the pilot sites. This is a web-based randomisation system, which can be accessed from a desktop computer, or remotely using a hand held device. The randomisation sequence for this electronic randomisation system is generated in the same way the sequence was developed for the envelope based randomisation system. Once a woman's eligibility has been checked, and the necessary data has been entered into the electronic randomisation system, the woman is randomised. Sites receive the allocated intervention directly from the web-based system. Stickers and birth record sheets are available in a separate randomisation folder. The birth record sheet can also be printed directly from the electronic randomisation system.
Source Date	3.11	Information required at randomisation will be recorded on the randomisation envelope at trial entry (see 3.4 above). Demographic details will be collected later from the medical notes. Compliance	Information required at randomisation will be recorded on the randomisation envelope, or electronic randomisation system, at trial entry (see 3.4 above). Demographic details will be collected later from the medical notes. Compliance with the allocated intervention will be based on timing of cord clamping and time of birth collected on the randomisation

		with the allocated intervention will be based on timing of cord clamping and time of birth collected on the randomisation pack	pack, or electronic randomisation system.
Estimated Sample Size	7.1	In October 2013 it was agreed within the CORD Pilot Trial DMC and TSC meetings that recruitment to the pilot trial should be extended to run into the start of the main trial. This would allow clinicians in the current eight pilot study sites to avoid losing equipoise regarding the timing of umbilical cord clamping. Recruitment will be extended from 01 March 2014 until 31 December 2014, by which time a decision regarding the funding for the main trial should be definite.	In October 2013 it was agreed within the CORD Pilot Trial DMC and TSC meetings that recruitment to the pilot trial should be extended to run into the start of the main UK Cord trial. This would allow clinicians in the current eight pilot study sites to avoid losing equipoise regarding the timing of umbilical cord clamping. Recruitment will be extended from 01 March 2014 until 31 July 2015. In January 2015 a decision will be made regarding the funding for the main UK Cord trial. If funded, this extension will allow a 6 month period for the main UK Cord trial to be set up, and will allow the pilot trial sites to continue recruiting into the start of the main trial. If the main trial is not funded, recruitment to the Cord Pilot Trial will end when the study team are informed of the funder's decision, and will not continue to the 31 July 2015.

Substantial Amendment 06			
section	**Section**	**Previous wording**	**New wording**
Trial Summary	Duration	Recruitment to the initial feasibility phase of the pilot trial is for 12 months but will be extended after this phase until 31 July 2015	Recruitment to the initial feasibility phase of the pilot trial is for 12 months but will be extended after this phase until 17 February 2015. Follow up for the women is for 12 months, and for the children until age two years (corrected for gestation at birth)
Trial Design	3.3	After this initial phase recruitment will be extended until 31 July 2015.	After this initial phase recruitment will be extended until 17 February 2015.
Trial Procedures	5.3	Four weeks before the child's second birthday, corrected for gestation at birth, the family will be sent the Ages and Stages Questionnaire (ASQ) by post, and asked to complete and return this before the assessment.	Two to four weeks before the child's second birthday, corrected for gestation at birth, the family will be sent the Ages and Stages Questionnaire (ASQ) by post, and asked to complete and return this before the assessment.
Trial Procedures	5.3		The trained practitioner will be trained in test administration and intrapretation by the study team prior to commencing data collection. The psychologist will videotape a random

			selection of 10% of assessments throughout the study period that will be observed by a trained examiner to assess intra-rater reliability.
Trial Procedures	5.3		Women's GPs will be contacted to check if women's contact details have changed, or if they have moved to a different practice. GPs will also be asked to check status of children in the trial before families are contacted for the 1 year and 2 year follow ups.

Substantial Amendment 08			
Section	**Section**	**Previous wording**	**New wording**
Key contacts		Angela Pushpa-Rajah	[Trial manager name]
Trial Summary	Duration	Recruitment to the initial feasibility phase of the pilot trial is for 12 months but will be extended after this phase until 31 July 2015.	Recruitment to the initial feasibility phase of the pilot trial is for 12 months but will be extended after this phase until 17 February 2015.
Trial design	3.3	After this initial phase recruitment will be extended until 31 July 2015.	After this initial phase recruitment will be extended until 17 February 2015.
Trial Procedures	5.3	Families recruited into the trial between 01 March 2013 and 28 February 2014, will be contacted to arrange a neurodevelopment assessment for their child. Four weeks before the child's second birthday, corrected for gestation at birth, the family will be sent the Ages and Stages Questionnaire (ASQ) by post, and asked to complete and return this before the assessment. A stamped addressed envelope will be provided to return the questionnaire. The neurodevelopment assessment will use the Bayley Scales of Infant Development III, and will be conducted by a trained practitioner either at home or in the clinic, whichever is preferred by the family. The assessment usually takes between one and a half and two hours.	Families recruited into the trial between 01 March 2013 and 28 February 2014, will be contacted to arrange a neurodevelopment assessment for their child. Two to four weeks before the child's second birthday, corrected for gestation at birth, the family will be sent the Ages and Stages Questionnaire (ASQ) by post, and asked to complete and return this before the assessment. A stamped addressed envelope will be provided to return the questionnaire. The neurodevelopment assessment will use the Bayley Scales of Infant Development III, and will be conducted by a researcher trained in conducting the Bayley III assessment. Visits will be either at home or a suitable alternative venue convenient for parents, whichever is preferred by the family. The assessment usually takes between one and a half and two hours. A random 10% of assessments will be video recorded and checked by a trained examiner to assess intra-rater reliability.
Trial Procedures	5.3		A proportion of these families may also be offered the Bayley if there is

			sufficient resources available.
Trial Procedures	5.3	If no telephone number is available a second reminder will be sent by post.	If no telephone number is available a second reminder will be sent by post, or the letter may be sent via email if the woman has given us her email address.
Trial Procedures	5.3		Women's GPs will be contacted to check if women's contact details have changed, or if they have moved to a different practice. GPs will also be asked to check status of children in the trial before families are contacted for the 1 year and 2 year follow ups. Every effort will be made to contact families for the 2 year follow up, however there may be some families that are uncontactable and lost to follow up. A health status questionnaire will be sent to the principal investigator to complete the basic neurodevelopmental scores for any children who are lost to follow up.

Substantial Amendment 09			
Section	**Section**	**Previous wording**	**New wording**
Key contacts	Trial Manager	Angela Pushpa-Rajah Telephone: 0115 8844936	Lindsay Armstrong-Buisseret Telephone: 0115 8844938
Participant follow-up	5.3	Families recruited to the trial from 01 March 2014 onwards will be sent the Ages and Stages Questionnaire (ASQ) by post approximately at around the child's second birthday, corrected for gestation at birth.	Families recruited to the trial from 01 March 2014 onwards will be sent the Ages and Stages Questionnaire (ASQ) for age 24 months by post approximately at around the child's second birthday, corrected for gestation at birth.
Participant follow-up	5.3	N/A – new paragraph 5	If it is not possible to contact a family when the child is approximately 24 months old e.g. due to not having correct contact details at the time, an ASQ appropriate for the child's age will be sent out. ASQ for age 27 months will be used when the child is approximately 27 months old (corrected for gestation at birth) and ASQ for age 30 months will be used when the child is approximately 30 months old (corrected for gestation at birth).
Participant follow-up	5.3	N/A – new sentence in paragraph 6	If the questionnaire is completed by phone, the ASQ appropriate for the child's age (corrected for gestation at

			birth) will be used.

Substantial Amendment 10			
Section	**Section**	**Previous wording**	**New wording**
Participant follow-up	5.3	N/A – new sentence in paragraph 6	If it has not been possible to contact the participant by phone, a letter will be sent by post or email to check whether the participant's telephone numbers have changed.
Participant follow-up	5.3	N/A – new paragraph 7	If a questionnaire has not been returned after two reminders, sites will give the questionnaire to the participant if they are still attending clinic visits. Participants will be asked to complete the questionnaire during the clinic visit and sites will return the completed questionnaires to NCTU.

Table of Contents

Glossary of Abbreviations

AW	Antenatal Ward
CRF	Case Record Form
DMC	Data Monitoring Committee
DS	Delivery Suite
GCP	Good Clinical Practice
NHS	National Health Service
R&D	Research and Development Department
SAE	Serious Adverse Event
TSC	Trial Steering Committee

Keywords

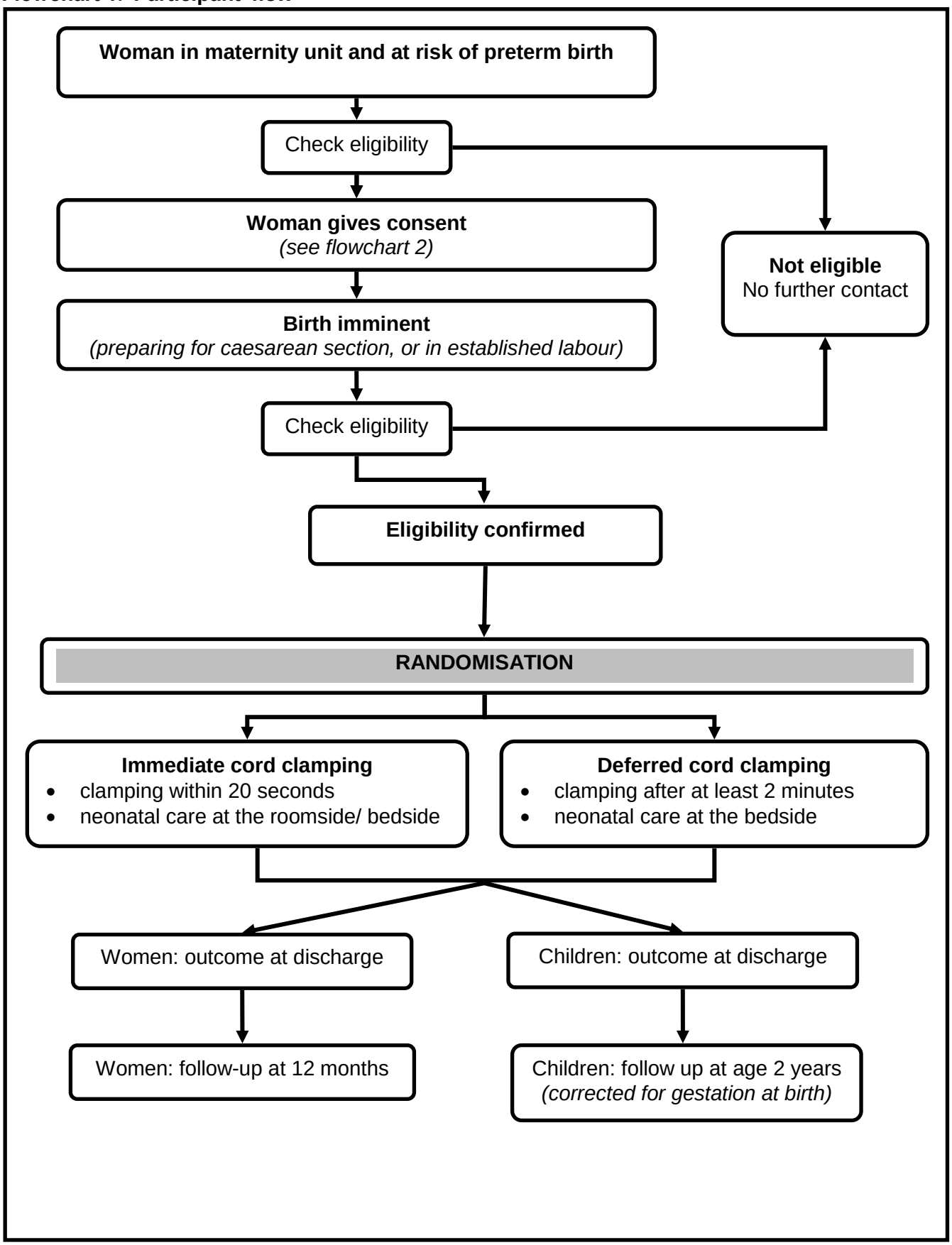
Cord clamping, placental transfusion, preterm birth, feasibility study, randomised trial, neurodevelopment

Trial Summary

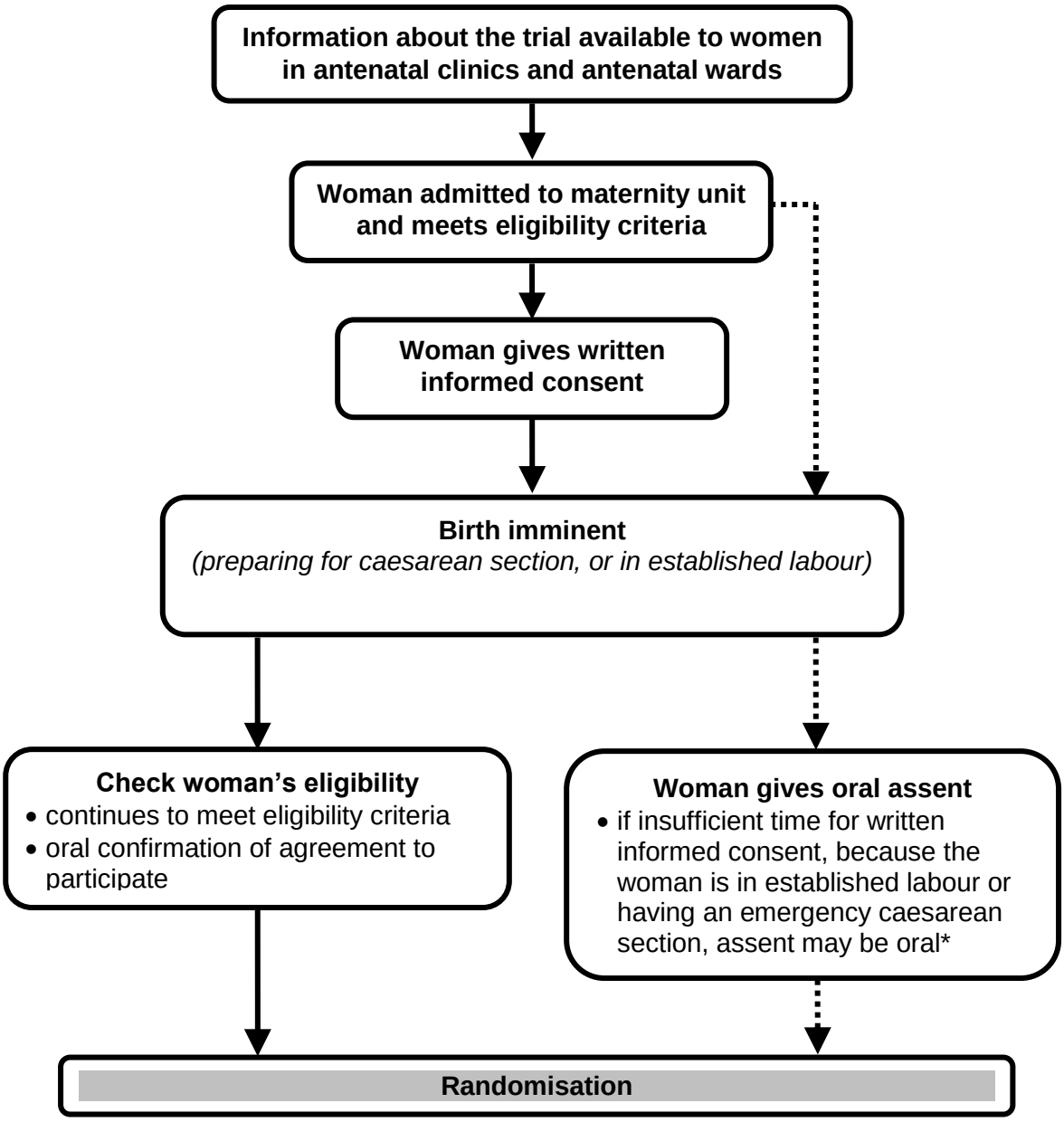
TITLE	Immediate cord clamping versus deferred cord clamping for preterm birth before 32 weeks gestation: a pilot randomised trial
DESIGN	Randomised trial
AIMS	To test the feasibility of conducting a large UK trial to assess the effect of timing of cord clamping for preterm birth before 32 weeks gestation on disability-free survival at two years of age.
OUTCOME MEASURES	For this feasibility pilot trial: 1. number of women recruited in each hospital 2. proportion of potentially eligible women recruited 3. reasons for non-recruitment (medical, parental, logistic, other) 4. spectrum of gestational age and neonatal outcome among recruits 5. compliance with the trial interventions, and reasons for non-compliance 6. completeness of data collection for main outcomes 7. views of women and their partners on recruitment, randomisation and the interventions 8. proportion lost to follow up after discharge from hospital, and reasons for loss to follow up
POPULATION	Women having a livebirth before 32 weeks gestation.
ELIGIBILITY	Women will be eligible for the study if they are expected to have a livebirth before 32 weeks gestation. Exclusion criteria are: • Monochorionic twins diagnosed by ultrasound • Triplets, or higher order, multiple pregnancy • Known congenital malformation
DURATION	Recruitment to the initial feasibility phase of the pilot trial is for 12 months but will be extended after this phase until 17 February 2015. Follow up for the women is for 12 months, and for the children until age two years (corrected for gestation at birth)

Reference diagrams

Flowchart 1. Participant flow



Flowchart 2. Guidance for consent



** Women will be approached to give oral assent in established labour or at emergency caesarean section only if the attending clinicians consider it appropriate Women will not be approached if there is insufficient time to give a brief oral summary of the trial, or they do not speak fluent English and no translator is available. How long will be required for oral assent will depend on factors such as how much the woman already knows about the study, and her knowledge and wishes about care during the third stage. If the woman does not give oral assent she will not be recruited.*

If oral assent for recruitment is given:

- *Women will be approached before discharge from hospital to give written consent to participation in follow up and access to their data*
- *Chief Investigator notified within 15 days, and monitoring by Trial Steering Committee*

Table 1. Study assessments

Assessments	Screening +/- consent	Delivery Suite	Discharge of woman	6 weeks after birth	Discharge of baby	12 months after birth	Child age 2 years (corrected)
Woman eligibility screening	AW or DS						
Woman consent	AW or DS						
Woman randomisation		X					
Intervention to woman/baby		X					
Outcomes for women							
Blood loss at birth			X				
Time of delivery of placenta			X				
Need for blood transfusion			X				
Hospital Anxiety and Depression Scale (HADS)				X		X	
Satisfaction with care at birth				X		X	
Woman's views about trial participation				X			
Outcomes for infants							
Time to first feed					X		
Any breast feeding					X		
Age breastfeeding/breast milk expressing stopped						X	
Death					X	X	X
Temperature on admission to SCBU					X		
Length of stay on SCBU					X		
Required phototherapy for jaundice					X		
Required exchange transfusion for jaundice					X		
Blood transfusion					X		
Intraventricular haemorrhage (grade 3-4)					X		
Periventricular leukomalacia					X		
Respiratory distress syndrome					X		
Chronic lung disease					X	X	
Necrotizing enterocolitis					X		
Ages and Stages Questionnaire (ASQ)							X
Bayley Scales of infant development III*							X

AW = Antenatal ward DS = Delivery suite

* For families recruited from 01 March 2013 to 28 February 2014 only

Summary

Preterm birth is the most important single determinant of adverse outcome in terms of: survival; quality of life; psychosocial and emotional impact on the family; and costs for health services. In the UK one in every 70 babies is born before 32 weeks (very preterm). These infants often need help with breathing, feeding, and other life support. Those who survive may spend months in hospital, and suffer ill health or disability in childhood. Even modest improvement for these children and their families would be important.

When a preterm infant is born, the cord is usually clamped immediately. Deferring cord clamping will allow blood flow between the placenta and baby to continue for a few minutes after birth. The net flow is known as 'placental transfusion'. For preterm babies, placental transfusion may amount to up to one third of the baby's potential blood volume, and may continue for 2-5 minutes. This period of continued blood flow may help the baby during the transition from fetal to neonatal circulation. The additional blood volume may help protect against some of the complications of being born too soon. The systematic review suggests deferring cord clamping may be beneficial, but more evidence is needed about effects on substantive measures of morbidity, mortality and disability-free survival.

At birth, neonatal care and stabilisation takes place on a resuscitaire. Traditionally, this is at the side of the room, or in an adjacent room. If cord clamping is deferred, this should not mean that neonatal care is deferred. For this study, we have developed strategies for providing neonatal care and stabilisation of the baby at the bedside. This allows the mother and her partner to share the first few moments of their baby's life, a more family-centred approach than taking the baby to the side of the room immediately at birth.

A large randomised trial to compare the effects of a policy of immediate cord clamping rather than deferred clamping for very preterm birth on survival and neurodevelopment of the child at age two years is needed. This protocol is for a pilot trial to assess the feasibility of conducting such a trial in the UK. Outcomes for the pilot trial are measures of feasibility of recruitment and retention. The target sample size for the initial feasibility phase is 100-110 mother-infant pairs in 8 sites.

1 INTRODUCTION

1.1 Background

In the UK infant mortality (deaths in the first year of life) for babies born very preterm (before 32 weeks gestation) is 144/1000 live births, compared to 1.8/1000 for those born at term (38 to 41 weeks)[1]. Very preterm birth accounts for 1.4% of live births in the UK, but 51% of infant deaths[1]. For infants born before 28 weeks, duration of hospital stay is 85 times longer than for term births, and hospital inpatient costs are £15,000 higher; for those born at 28 to 31 weeks, it is 16 times and £12,000 respectively[2].

Morbidity amongst children born very preterm who survive is also high compared to those born at term. Of very preterm infants who survive, 5%-10% develop cerebral palsy and those without severe disability have a twofold or greater increased risk for developmental, cognitive, and behavioural difficulties[3, 4]. Of babies born before 28 weeks, a quarter of survivors have neurosensory disability, such as cerebral palsy, severe developmental delay, blindness or deafness.[5] Surviving children have higher levels of dysfunction in a range of measures of cognition, behaviour and functioning[5], impairments which persist into adolescence and early adulthood[6, 7]. Teenagers and young adults born very preterm also report poorer physical abilities and more chronic ill health and functional limitation than their peers born at term, although self-reporting of health-related quality of life is similar[8, 9]. Prematurity and its sequelae have an enormous negative psychosocial and emotional impact on parents and families[5, 10]. Even modest improvement in outcome would be of substantial benefit; to the children, their families, and the NHS.

Placental transfusion

Placental transfusion is the transfer of blood between the placenta and the baby at birth. For term births, this blood flow is usually complete by two minutes, but may continue for up to five minutes. The mean volume of placental transfusion for term births is 100 ml, which is around 29 ml/kg birth weight and 36% of neonatal blood volume at birth[11]. For preterm births, placental transfusion may take longer[12], and is incomplete if the cord is clamped within 30-90 seconds[13]. This seems logical, as at term two-thirds of the feto-placental circulation is in the infant, whilst below 30 weeks gestation a greater proportion is in the placenta[14]. Also, the umbilical vein is smaller than at term, and uterine contraction less efficient. Cord clamping before placental transfusion is complete may restrict neonatal blood volume and red cell mass, and interrupt transition from the fetal to neonatal circulation.

As the baby is born, umbilical circulation slows and pulmonary vascular resistance falls, rapidly increasing pulmonary blood flow. This is the beginning of transition from the fetal to the neonatal circulation. For infants born too early, the mechanisms for these circulatory changes may not be fully developed and so may take longer. Continued flow in the umbilical vein and arteries at birth may be part of the physiological mechanisms assisting the baby as it makes the transition from fetal to neonatal circulation. Restricting this flow by immediate cord clamping may restrict the baby's ability to deal with this transition. If there is insufficient circulating blood volume to fill the expanding pulmonary vasculature, an infant may compensate by reducing flow to the peripheral circulation and/or to organs such as the kidney. Whilst most healthy babies at term may adapt without major consequences, for those born preterm or with their cardio-respiratory circulation already impaired there may be substantive consequences.

Cord milking (pinching the cord close to the mother and running the fingers towards the baby, usually several times) has been suggested for preterm births as a means to increase neonatal blood volume without deferring cord clamping[15]. Cord milking over-rides the infant's physiological control of its own blood volume and blood pressure, however, and disrupts umbilical blood flow.

Over 20 years ago it was first suggested that restricting placental transfusion by immediate clamping for preterm babies might increase the risk of intraventricular haemorrhage[16]. Possible

mechanisms for this increase were suggested to be hypovolaemia, and/or increased fluctuation in blood pressure following the abrupt transition to a neonatal circulation.

Systematic review: immediate versus deferred cord clamping

The recently Cochrane Review of timing of cord clamping for preterm births [17] includes 15 trials, with 738 infants, recruited between 24 and 36 weeks gestation. In these trials immediate cord clamping ranged from 5-20 seconds, although several studies did not state the duration. Deferred clamping ranged from 31-120 seconds for births before 34 weeks, one study recruiting between 34 weeks and 36 weeks gestation used 180 seconds. The few studies that reported a rationale for how long to defer clamping said it had been a balance between allowing placental transfusion, and what was perceived as an acceptable delay in transferring the baby to the resuscitaire and providing neonatal care. One small trial (40 mother-infant pairs) compared cord milking with immediate cord clamping [15].

Many outcomes are reported by only a few studies, so there is potential for reporting bias. No trials reported outcome for the mother.

Thirteen studies (668 infants) reported infant death (largely death before discharge from hospital). Of those allocated deferred cord clamping 10/319 (3.1%) died compared with 17/349 (4.9%) allocated less placental transfusion (risk ratio (RR) 0.63, 95% confidence interval (CI) 0.31 to 1.28). No trials reported outcome at age two to three years. One small trial[18] reported neurodevelopment at seven months (corrected for gestation at birth). Of 72 children recruited, five (6.9%) had died and nine (12.5%) were lost to follow-up. There were no significant differences between the groups in Bayley II Mental Development Index and Psychomotor Developmental Index for the 58 children assessed.

Severe intraventricular haemorrhage (grade three and four) was reported in six trials (305 infants) with no clear difference between babies allocated deferred rather than immediate clamping (5/154 versus 7/151: RR 0.68, 95% CI 0.23 to1.96). Ten trials (539 infants) reported IVH (all grades) and deferred clamping was associated with a lower risk ratio (RR 0.59, 95% CI 0.41 to 0.85). Only two studies (71 infants) reported periventricular leukomalacia, insufficient evidence for any reliable conclusions.

Three trials (143 infants) reported mean temperature on admission to special care unit; there was no clear difference between the groups (mean difference 0.14, 95% CI -0.03, to 0.31). Respiratory distress syndrome was reported by three studies (115 babies), with no clear difference between the two groups (RR 1.16, 95% CI 0.89 to 1.50). Five trials (265 infants) reported ventilation (RR 0.97, 95% CI 0.71 to 1.31). Need for oxygen at 28 days after birth was reported by two trials (76 infants), with no clear difference between the groups (RR 0.48, 95% CI 0.15 to 1.59). Need for oxygen at 36 weeks' gestational age was reported by five trials (209 infants), again with no clear difference between the groups (RR 0.69, 95% CI 0.42 to 1.13). Chronic lung disease was not reported in any studies.

There was no clear difference in need for transfusion for low blood pressure (4 trials, 130 infants, RR 0.52, 95% CI 0.24 to 1.11, random effects). In the seven studies (392 infants) reporting blood transfusion for anaemia, the risk was lower for those allocated deferred clamping: 44/186 (24%) versus 5/206 (36%). RR 0.61 (95% CI 0.46 to 0.81).

There was no clear difference between the groups in treatment for patent ductus arteriosus (5 trials, 223 infants, RR 1.04, 95% CI 0.60 to 1.81). Necrotising enterocolitis was reported in five trials with a lower risk ratio associated with deferred clamping (241 infants, RR 0.62, 95% CI 0.43 to 0.90).

Peak bilirubin concentration was higher for infants allocated deferred clamping (7 trials, 320 infants, mean difference 15.01 mmol/l, 95% CI 5.62 to 24.40). There was no clear difference in phototherapy for jaundice in the three studies reporting this outcome (180 infants, RR 1.21, 95% CI 0.94 to 1.55). Exchange transfusion was not reported by any of the trials.

The review concludes that "*to reliably compare strategies for influencing placental transfusion we need large high-quality trials, with sufficient power to reliably assess clinically relevant differences in important outcomes*".

Initial care at birth for very preterm infants: at the bedside or at the roomside
Initial neonatal care and stabilisation takes place on a resuscitaire. Traditionally, this is at the side of the room, or in an adjacent room. Disadvantages of these locations are that they necessitate immediate cord clamping, and that often the woman and her partner are not able to see or touch their baby at birth[19, 20]**.** If cord clamping is deferred this should not mean that neonatal care is deferred. Strategies for providing neonatal care and stabilisation of the baby at the bedside have now been developed. Parents views following initial care at the bedside have been universally positive[21]. Evaluation of the views of clinicians is also positive, although there are initial issues around training, practical arrangements for preparing and moving the equipment, and making space at the bedside[21]. The experience of providing initial neonatal care at the bedside has been so positive that it is now part of standard care in some hospitals

Deferring cord clamping should not delay neonatal care, rather neonatal care can be available at the bedside. Providing neonatal care for very premature infants at the bedside would allow the woman and her partner to share the first moments of their child's life[22, 23], if they wish to, and it is potentially a more family-centred approach. Family-centred care in neonatal units, with improved communication and involvement of parents in their baby's care, appears to benefit babies, is welcomed by parents[10] and is an NHS priority[24]. Providing neonatal care at the bedside has parallels with family presence during resuscitation of adults and children; which is preferred by families and appears to be beneficial[25-29].

Current practice for timing of cord clamping at very preterm births
In the UK, 57% of obstetricians report clamping the cord within 20 seconds for very preterm births [30]**.** Just 15% of midwives and 5% of obstetricians report that they routinely record when the cord was clamped in the medical notes. Guidelines for care during the third stage of labour make various recommendations, and it is often not clear how these should be applied to very preterm births. For example, the National Institute for Health and Clinical Excellence (NICE) recommends that active management of the third stage of labour for term births should include "*early cord clamping"*[31]. The World Health Organisation (WHO) recommendations for prevention of postpartum haemorrhage apply to all births. WHO recommends "*the cord should not be clamped earlier than is necessary for applying cord traction in the active management of the third stage of labour. For the sake of clarity, it is estimated that this will normally take around 3 minutes. Early clamping may be required if the baby is asphyxiated and requires immediate resuscitation"[32]*. This guideline also notes the low evidence base for these recommendations. In 2011, the Royal College of Obstetricians and Gynaecologists recommended "*the cord should not be clamped earlier than is necessary, based on a clinical assessment of the situation. Delayed cord clamping (more than 30 seconds) may benefit the neonate in reducing anaemia, and particularly the preterm neonate by allowing time for transfusion of placental blood to the newborn infant*". The Resuscitation Council recommendations for newborn life support state "*Cord clamping should be delayed for at least 1 minute in babies who do not require resuscitation. Evidence is insufficient to recommend a time for clamping in those who require resuscitation[33, 34]*. Most very premature babies will require resuscitation.

1.2 Why a trial is needed now

Preterm birth is the most important single determinant of adverse infant outcome in terms of: survival; quality of life; psychosocial and emotional impact on the family; and costs for health services. Current evidence is that for very preterm births timing of cord clamping, and other strategies to influence placental transfusion, may influence some measures of morbidity before discharge from hospital. But the trials are small and overall there is high risk of bias. The effects on more substantive outcomes and long term neurodevelopment remain uncertain. Assessing

alternative strategies for timing of cord clamping has been identified as a research priority by service users[35], researchers[36-39] obstetricians[30], midwives[30], neonatologists[40], NICE[31, 41], and the Royal College of Obstetricians and Gynaecologists[22]. Providing immediate neonatal care at the bedside is potentially a more family centred approach than providing immediate neonatal care at the side of the room.

Our primary hypothesis is that for children born before 32 weeks gestation immediate cord clamping is associated with higher death or neurosensory disability at two years of age (corrected for gestation at birth) than deferred cord clamping. A trial to test this hypothesis would need to be large and multicentre. This protocol is for a pilot trial to assess the feasibility of such a study.

This protocol also includes a qualitative interview substudy which aims to evaluate the experience of women who are invited to consent to participate in the Cord Pilot trial, as well as clinicians' experience of asking women for consent (Appendix 2 – substudy protocol).

2 PILOT TRIAL OBJECTIVES AND PURPOSE

2.1 Objectives

The objective of the main trial will be to compare the effects of immediate cord clamping versus deferred cord clamping for very preterm births on outcome for the women and children. This pilot trial is to assess the feasibility of conducting such a trial in the UK by:

1. estimating the number of potential recruits in each centre
2. measuring recruitment rate
3. listing reasons for non-recruitment (medical, parental, logistic, other)
4. measuring the spectrum of gestational age and neonatal outcome among recruits
5. measuring compliance with the trial interventions, and assessing factors in non-compliance
6. measuring the completeness of data collection for main outcomes
7. recording views of parents on the randomisation and treatment procedures
8. measuring losses to follow up after discharge from hospital.

3 TRIAL DESIGN

3.1 Main trial outcomes

The primary outcome for the main trial will be death or neurosensory disability at age two years (corrected for gestation at birth).

Secondary outcomes for the baby will include: death, blood transfusion, intraventricular haemorrhage (grade 3-4), periventricular leukomalacia, hypothermia, respiratory distress syndrome, ventilation, necrotizing enterocolitis, treatment for hyperbilirubinemia, duration of hospital stay, neurosensory delay at age 2 years (corrected for gestation at birth).

Secondary outcomes for the mother will include postpartum haemorrhage, depression, and breast feeding/expressing. Outcomes for the parents will include qualitative psychosocial outcomes (e.g. perceptions of the child's illness and care, parenting stress, parent-baby bond) and views about participation in the trial.

3.2 Pilot trial outcomes

For this pilot trial to assess feasibility of the main trial, outcomes will be:
1. number of women recruited in each hospital
2. proportion of potentially eligible women recruited
3. reasons for non-recruitment (medical, parental, logistic, other)
4. spectrum of gestational age and neonatal outcome among recruits
5. compliance with the trial interventions, and reasons for non-compliance

6. completeness of data collection for main trial outcomes (see above)
7. views of women and their partners on recruitment, randomisation and the interventions
8. proportion lost to follow up after discharge from hospital, and reasons for loss to follow up

3.3 Pilot trial description

This pilot trial will be a pragmatic randomised trial comparing a policy of immediate clamping of the umbilical cord with a policy of deferred clamping. For deferred cord clamping, care for the baby will be provided at the bedside. For immediate clamping care will be either at the bedside or at the side of the room, at the discretion of the attending clinicians. In both cases the baby will receive the same care at birth, just in different places. The aim is to recruit at least 100-110 women for the initial feasibility phase in at least eight maternity units. Recruitment to the initial feasibility phase of the pilot trial will be for 12 months. After this initial phase recruitment will be extended until 17 February 2015. Follow up for the women is for 12 months, and follow up for the children is until age two years (corrected for gestation at birth).

3.4 Randomisation

Women will be randomly allocated in a 1:1 ratio to the two intervention groups. Sequence generation will be using computer generated random permutated balanced blocks of randomly varying size, created by the Nottingham Clinical Trials Unit in accordance with their standard operating procedure. Randomisation will be stratified by hospital.

Women who are eligible and have agreed to participate will be randomised using sealed consecutively numbered opaque envelopes . Envelopes will be in a Cord Trial ringbinder, and removed in consecutive order by tearing at the punch holes. Each maternity unit will keep a central log of all envelopes. On the front of the envelope will be a reminder to check eligibility criteria, and space to record the date, time, woman's initials, her data of birth, and her estimated gestation. Once this information is complete, the woman will be considered to be randomised, even if the pack is not opened.

Inside the envelope will be a card with the allocated intervention, two stickers (one each for the woman's and baby's notes) and a Birth Record to record details of the birth and initial care at birth . This Birth Record is then filed in the baby's hospital case notes.

If the main UK Cord Trial is funded, an electronic randomisation system will be used instead of the envelope based randomisation system used in the Cord Pilot Trial. An electronic randomisation system is being piloted at some of the pilot sites.

This is a secure web-based randomisation system maintained by Nottingham Clinical Trials Unit, which can be accessed from a desktop computer, or remotely using a hand held device. The randomisation sequence for this electronic randomisation system is generated in the same way the sequence was developed for the envelope based randomisation system.

Once a woman's eligibility has been checked, and the necessary data have been entered into the electronic randomisation system, the woman is randomised. Sites receive the allocated intervention directly from the web-based system. Details of the randomisation are emailed to the lead research nurse and PI at site, as well as the trial manager and programming team at the Nottingham Clinical Trials Unit. Stickers and birth record sheets are available in a separate randomisation folder. The birth record sheet can also be printed directly from the electronic randomisation system.

3.5 Minimisation of bias

Allocation to the treatment group will be concealed until after the woman has been entered into the trial. This will minimise selection bias. Stratification by centre will minimise the potential for chance imbalance at trial entry.

Blinding of the intervention is not possible for this study. Neurodevelopment assessment of the child at age two years, corrected for their gestation at birth, will be blind to the treatment group. Potential for bias in the assessment of outcome will be minimised by the use of objective outcomes.

3.6 Pilot trial interventions

There is no consensus about the definition of immediate or deferred cord clamping, or about the optimal timing of cord clamping for very preterm birth. We have chosen our interventions based on current practice in the UK[30], the interventions reported in the trials included in the Cochrane review[37], consultation with neonatologists, and our work measuring the volume and duration of placental transfusion[11]:

The interventions are:

- immediate cord clamping: clamping the cord within 20 seconds.
- deferred cord clamping: clamping the cord after at least two minutes.

For deferred cord clamping, care for the baby will be provided at the bedside. For immediate clamping care will be either at the bedside or at the side of the room, at the discretion of the attending clinicians. In both cases the baby will receive the same care at birth, just in different places. For both allocated groups, whilst the cord is intact the baby should not be lifted above the level of the mothers' abdomen.

Neonatal care will be the same for the two allocated groups, based on local unit policy and consistent with newborn life support guidelines[33, 34]. Standard equipment will be used for both groups according to local practice, this is likely to include plastic sheets or bags (depending on gestation and local practice), towels and any other equipment such as hats, warming mattress or overhead heaters, and saturation monitors.

For neonatal care at the bedside, babies will be placed onto a firm surface next to the mother's bed or to the operating theatre table, with easy access to necessary equipment. This will be achieved either by moving the conventional resuscitaire alongside the woman's bed (Schoonakker, personal communication) or by using a small specialised mobile trolley (for example the BASICS trolley[42]). For neonatal care at the side of the room, care and stabilization will be according to usual practice in that unit.

All other aspects of care will be at the discretion of the attending clinicians, including administration of a prophylactic uterotonic drug.

3.7 Duration of participation

Follow up for the women will be for 12 months, and for the children until they are two years old, corrected for gestation at birth. The end of the trial is defined as the "last child's 2 year Follow Up".

3.8 Stop-go criteria for proceeding to the main trial

These will be:

- recruitment is at least 50% of target at 12 months. But, if recruitment is below 80% of target, there will need to be clear and achievable strategies for overcoming identified barriers thereby improving recruitment
- at least 80% of women in each group receiving the intervention to which they had been allocated or, if compliance is initially poor, this level of compliance is achieved during the final 6 months of recruitment
- median difference between the two groups in timing of cord clamping is at least 45 seconds

3.9 Compliance with interventions

Time of birth and time of cord clamping will be recorded for both treatment arms. If the cord is not clamped according to the allocated intervention, the reason will be recorded. Neonatal care at the place of birth will be documented. Reasons for non-compliance will be discussed with local clinicians and every effort made to remove obstacles to good compliance.

Compliance will be assessed by an independent observer for a randomly selected sample of participants.

3.10 Maintenance of randomisation codes and procedures for breaking code

In this trial it will not be possible for the participants or the labour ward staff to be blind to which intervention has been allocated. A procedure for breaking the code is therefore not necessary.

Every effort will be made to ensure neurodevelopment assessment of the child is blind to the allocation. The assessor will not have access to this information, and parents will be asked not to reveal it.

3.11 Source data

Information required at randomisation will be recorded on the randomisation envelope, or electronic randomisation system, at trial entry (see 3.4 above). Demographic details will be collected later from the medical notes. Compliance with the allocated intervention will be based on timing of cord clamping and time of birth collected on the birth record sheet.

Outcome data for the women will be the medical notes, and the pilot trial questionnaires. For the children, outcome data will come from the medical notes and the Ages and Stages Questionnaire (ASQ)[43]. For families recruited between 01 March 2013 – 28 February 2014, outcome data will also be collected from the Bayley Scales of Infant Development [44].

To allow contact for the follow up assessment contact details for the women and children will be sent to the central co-ordinating team at the Nottingham Clinical Trials Unit. To facilitate maintaining contact with the families, women will also be asked to provide contact details with other relevant relatives, for example grandparents. NHS numbers will also be supplied, so that they can be used for 'flagging' with the NHS Information Centre (see below). This will allow identification of deaths and movement out of the NHS before the family is contacted for follow-up. All identifiable data will be held securely and separately from the trial data. Access will be restricted. All trial data will be anonymised by use of unique participant trial numbers. The chief investigator, Professor Lelia Duley, is the custodian of the data. Participants have the right to revoke their authorisation for the use of personal information.

4 SELECTION AND WITHDRAWAL OF TRIAL PARTICIPANTS

4.1 Inclusion criteria

Women will be eligible for the study if they are expected to have a livebirth before 32 weeks gestation, regardless of mode of birth or whether cephalic or breech presentation.

4.2 Exclusion criteria

Exclusion criteria are:

- Monochorionic twins (from an ultrasound scan) or clinical evidence of twin-twin transfusion syndrome
- Triplets or higher order multiple pregnancy
- Known congenital malformation

4.3 Participants who withdraw

Women who give informed consent but decide later that, for whatever reason, they do not wish to be entered into the trial will not be randomised. Women who give informed consent, but do not give birth before 32 weeks will not be randomised.

Withdrawal between randomisation and birth is unlikely, as these events should be close together. If this does happen, care will be according to their preference or the preference of their attending clinician. Women will be analysed in their allocated group as "intention to treat" regardless of whether they received the intervention.

Women cannot withdraw from the trial intervention after the birth, as the intervention will be complete. Women who withdraw after discharge from hospital will not be contacted further. If a woman does withdraw, the date and reason for withdrawal (if available) will be recorded. Data for women who withdraw will be included in the analysis, unless they request that their data are not used.

If a family is lost to follow up, all reasonable attempts will be made to contact them in order to complete the trial assessments.

4.4 Managing and replacing participants who withdraw from the trial early

We anticipate minimal withdrawals from the trial, and this will be one of the outcomes assessed in this feasibility pilot. Women who withdraw will not be replaced.

5 TRIAL PROCEDURES

5.1 Trial entry and recruitment

General information about the trial, including posters and a summary information leaflet, will be available at all antenatal clinics, and on antenatal wards. Other strategies to help raise awareness of the trial, such as a short video for use in antenatal clinics and short talks with a question and answer session, will be developed and evaluated as part of this pilot study. To avoid causing unnecessary anxiety, this information will make clear that women would only be approached about the study if they were considered likely to give birth before 32 weeks gestation, and that this occurs for only around 1 in 70 births. If a woman requests not to be approached to participate, this wish will be respected and recorded in the medical notes. Women who ask for more information may be offered the parents' information leaflet

Women who are in hospital, in a day care unit, or a high risk antenatal clinic, and are expected to give birth before 32 weeks gestation, will be given the parents' information sheet. They will have the opportunity to discuss this with their family and to ask any questions they might have. Clinical staff, including midwives, obstetricians and neonatologists, will be informed about the trial, so they are able to discuss it with potentially eligible women and their partners.

Whenever possible, women will have at least 12 hours to consider participation. If they are willing to participate they will have eligibility criteria checked, and be asked to provide written informed consent. If the woman does not wish to participate, she will not be required to give a reason. Clinical care for the woman and her baby will not be influenced by whether or not she agrees to participate. A log will be kept of potentially eligible women not approached to give consent, women who decline participation, and any other reasons for non-participation (if available).

When a woman who has given consent is in established labour, or being prepared for caesarean section, the attending clinician will check eligibility again (flowchart 1). If she remains eligible, the woman will be asked if she is still willing to participate. The clinician will record in her hospital notes that consent was confirmed before randomising the woman. This randomisation close to the time of birth will help ensure women who are randomised do give birth before 32 weeks gestation.

Nevertheless, if women are randomised but give birth after 32 weeks gestation they will remain in the analysis, which will be by intention-to-treat.

Preterm birth can sometimes be rapid and unexpected. For a few women, birth may be so rapid that there is not sufficient time to discuss the study in detail and secure written informed consent. As this group of women and their babies are high risk for poor outcome, it is of particular importance that they are offered the opportunity to participate in the trial, rather than being excluded. As outlined above, all women will have had access to information about the trial whilst attending antenatal clinics. If there is not sufficient time to discuss the study and obtain written informed consent, women will be approached to give oral assent only if the attending clinicians consider it appropriate. This process is in line with Clinical Governance Advice for valid consent for research while in labour research from the Royal College of Obstetricians and Gynaecologists[45]. After giving a brief summary of the study, with the opportunity to ask any questions, the woman will be asked if she is willing to be recruited. If she says yes, she will be randomised. If she does not give oral assent she will not be recruited. How long will be required for oral assent will depend on factors such as how much the woman already knows about the study, and her knowledge and wishes about care during the third stage. If the woman is recruited, she will be approached before discharge from hospital to give written informed consent for access to her medical records, and for participation in the trial follow up (flowchart 2). This strategy for recruitment is endorsed by the National Childbirth Trust and Bliss, the special care baby charity. Representatives of both these organisation are co-investigators on the trial and have contributed to development of this protocol, including the procedures for consent, oral assent and recruitment.

5.2 Treatment of participants

Once in the trial, women will either have the cord clamped within 20 seconds or the cord will be clamped after at least 2 minutes. The time of birth and the time of cord clamping will be recorded using the same clock. For deferred cord clamping, care for the baby will be provided at the bedside. For immediate clamping care will be either at the bedside or at the side of the room, at the discretion of the attending clinicians.

Whilst the cord is intact the baby can be at the level of the placenta, effectively on the bed between the woman's legs if she has had a normal birth and is semi-recumbent. If the woman gave birth on all fours she should be encouraged to adopt a semi-recumbent position and the baby placed between her legs. For a vaginal instrumental birth the baby should be no higher than the woman's abdomen. For a Caesarean section, the baby should be no higher than the anterior thigh. All other aspects of care will be at the discretion of local clinicians, including strategies for keeping the baby warm at birth.

If neonatal care is at the bedside, women will be able to see and usually touch their baby, if they wish. For Caesarean section with epidural anaesthesia, women will be offered the opportunity to see their baby, if they wish (this may be possible either by leaving a gap in the surgical drapes or by use of a mirror). Training for all the clinicians in providing care at the bedside will include encouraging them talk to the parents, to support them and to explain what is happening.

If the allocated intervention is not given, the reason will be recorded. For example, the attending clinician may decide not to comply with the allocated intervention, and women have the right to request at any time that the timing of cord clamping is changed. Women and their babies remain in the trial regardless of whether or not they received the allocated intervention.

Training for clinicians will be provided for both interventions. Compliance with the allocated intervention will be checked on a random sample at each centre, by independent observation. Information about other aspects of care during the third stage of labour that might influence placental transfusion, such as position of the baby whilst cord intact and timing of administration of the uterotonic drug, will also be collected.

5.3 Participant follow-up

The follow up assessments are summarised in table 1. At discharge from hospital, outcome data for the women and babies will be collected from the medical notes. Within 2-3 months after the birth, women will also be asked to complete a brief questionnaire. If their baby is still in hospital, they may be given this questionnaire by the research nurse. Otherwise it will be posted to them with a stamped addressed envelope.

When the child is one year old, a birthday card will be sent along with a questionnaire about the woman's own health. A stamped addressed envelope will be provided to return questionnaires. If the child dies before their first birthday, the mother will remain in follow up as long as she is in agreement with this. At the child's second birthday, corrected for gestation at birth, the family will be contacted for the 2 year follow up.

Families recruited into the trial between 01 March 2013 and 28 February 2014, will be contacted to arrange a neurodevelopment assessment for their child. Two to four weeks before the child's second birthday, corrected for gestation at birth, the family will be sent the Ages and Stages Questionnaire (ASQ) by post, and asked to complete and return this before the assessment. A stamped addressed envelope will be provided to return the questionnaire. The neurodevelopment assessment will use the Bayley Scales of Infant Development III, and will be conducted by a researcher trained in conducting the Bayley III assessment. Visits will be either at home or a suitable alternative venue convenient for parents, whichever is preferred by the family. The assessment usually takes between one and a half and two hours. A random 10% of assessments will be video recorded and checked by a trained examiner to assess intra-rater reliability.

Families recruited to the trial from 01 March 2014 onwards will be sent the Ages and Stages Questionnaire (ASQ) for age 24 months by post approximately at around the child's second birthday, corrected for gestation at birth. A stamped addressed envelope will be provided to return the questionnaire.

If it is not possible to contact a family when the child is approximately 24 months old e.g. due to not having correct contact details at the time, an ASQ appropriate for the child's age will be sent out. ASQ for age 27 months will be used when the child is approximately 27 months old (corrected for gestation at birth) and ASQ for age 30 months will be used when the child is approximately 30 months old (corrected for gestation at birth).

For all questionnaires, a reminder will be sent after two weeks. If there is no response after a further two weeks the family will be contacted by phone to find out whether they received the questionnaires, and to offer the opportunity of completing the questionnaire by phone. If the questionnaire is completed by phone, the ASQ appropriate for the child's age (corrected for gestation at birth) will be used. If no telephone number is available a second reminder will be sent by post, or the letter may be sent via email if the woman has given us her email address. If it has not been possible to contact the participant by phone, a letter will be sent by post or email to check whether the participant's telephone numbers have changed.

If a questionnaire has not been returned after two reminders, sites will give the questionnaire to the participant if they are still attending clinic visits. Participants will be asked to complete the questionnaire during the clinic visit and sites will return completed questionnaires to NCTU.

A proportion of the families recruited to the trial from 01 March 2014 onwards may also be offered the Bayley III assessment if sufficient resources are available.

Flagging with the NHS Information Centre

All women and their babies recruited in the trial will be 'flagged' after discharge through the Medical Research Information Service, at the NHS Information Centre. Information from the NHS Information Centre may be used to help contact participants, and to check their health status. This

will avoid causing unnecessary distress to the family, as it will avert inappropriate contact if the baby dies after discharge from hospital. It will also reduce losses to follow up.

Women's GPs will be contacted to check if women's contact details have changed, or if they have moved to a different practice. GPs will also be asked to check status of children in the trial before families are contacted for the 1 year and 2 year follow ups.

Every effort will be made to contact families for the 2 year follow up, however there may be some families that are uncontactable and lost to follow up. A health status questionnaire will be sent to the principal investigator to complete the basic neurodevelopmental scores for any children who are lost to follow up.

6 ADVERSE EVENTS

In this study the key participants are babies born very preterm, who are high risk for adverse outcome due to being born too soon. The study is comparing two different policies for care at birth, to assess their comparative effects. Adverse events that could be influenced by the trial interventions are therefore outcomes for the study. Data on these events will be recorded on the case report forms.

6.1 Serious adverse events

Although neonatal or infant death is one of the outcomes for this study, death before discharge from hospital will be considered as a serious adverse event (SAE). Any unexpected and serious adverse event, for either the mother or the baby, considered to be potentially related to the study interventions will also be reported as a SAE. Any SAE that is not a death will be followed until there is resolution or the event is considered stable.

All SAEs will be reported to the Chief Investigator within one working day . The Chief Investigator will submit, every six months for the duration of recruitment to the trial or on request, a safety report to the Data Monitoring Committee which will include all reported SAEs.

7 STATISTICS AND DATA ANALYSIS

7.1 Estimated sample size

For this feasibility pilot study, we plan to include eight large maternity hospitals and recruit for one year. There are a total of 43,600 livebirths per year at these eight hospitals (average annual livebirths per unit 5-6,000). In the UK, 1.4% of livebirths are before 32 weeks gestation; we therefore expect 610 potentially eligible births and anticipate recruitment of between 100 and 110 women (16-18% accrual). If more than eight hospitals wish to participate, we will include them on the agreement we do not have site-specific funding to support their participation. Inclusion of such sites would give further evidence of feasibility of conducting the study within the Comprehensive Local Research Network.

In October 2013 it was agreed within the CORD Pilot Trial DMC and TSC meetings that recruitment to the pilot trial should be extended to run into the start of the main UK Cord trial. This would allow clinicians in the current eight pilot study sites to avoid losing equipoise regarding the timing of umbilical cord clamping. Recruitment will be extended from 01 March 2014 until 31 July 2015. In January 2015 a decision will be made regarding the funding for the main UK Cord trial. If funded, this extension will allow a 6 month period for the main UK Cord trial to be set up, and will allow the pilot trial sites to continue recruiting until the start of the main trial. If the main trial is not funded, recruitment to the Cord Pilot Trial will end when the study team are informed of the funder's decision, and will not continue to the 31 July 2015.

For this study there should be no loss to follow up before discharge from hospital. For the questionnaire at six weeks we anticipate minimal loss to follow up (2%), as many infants will still be in hospital, and so parents will be asked to complete the questionnaire when they visit. At twelve months we anticipate 10% loss to follow up, and at two years 15%. Strategies to minimise losses to follow up will include regular contact with the family, for example thanking them for participation, birthday cards, and updating newsletters.

7.2 Analysis plan

Demographic and other baseline data at trial entry will be summarised using descriptive statistics (number and percentage, mean and standard deviation, median and inter quartile range (IQR)) as appropriate, by allocated group. All analyses will be according to the allocated group, i.e. by intention-to-treat.

Main trial outcomes: As this is a feasibility pilot trial there will be no formal test for efficacy. Nevertheless, data on the primary and secondary outcomes proposed for the main trial will be presented along with any missing data (number, percentage). Any unexpected SAEs reported will be described.

Pilot trial outcomes: The number of potentially eligible women at each centre will be reported, with the number recruited and reasons for non-recruitment (medical, parental, logistic, other, not known). Women recruited following oral assent will be described, along with the proportion who subsequently consented to participation in follow up and access to their data. The spectrum of gestational age at recruitment (range, median and IQR), and neonatal outcome for infants recruited will be described (number, percentage).

Compliance with the trial interventions will be summarised based on: number (percentage) who received the allocated intervention; median (IQR) for the difference in time of cord clamping between the allocated groups; position of the baby whilst the cord was intact per protocol (number and percentage). Reasons for any non-compliance with the allocated intervention will be listed (number, percentage). Neonatal care provided at birth will be described, along with whether at the bedside or at the side of the room (number, percentage). As outlined above, missing data for the main trial outcomes will be described (number, percentage).

Analysis of the views of women and their partners of participation in the trial will use methods described in detail elsewhere [46]. Factors that might influence parents experiences will be pre-specified as primary variables (death of the baby, allocated group) and secondary variables (maternal age at recruitment, gestation at recruitment less than 30 weeks, whether oral assent consent was used, severe post partum haemorrhage, postnatal depression, length of stay in special care baby unit longer than six weeks, and need for a reminder to complete the questionnaire).

The proportion of women and children lost to follow up after discharge from hospital will be reported at six weeks, one year and two years, along with reasons for the loss to follow up (if known).

No formal interim analysis is planned for this pilot study. Data will be monitored for safety only, in strict confidence, by the independent Data Monitoring Committee who will report to the Trial Steering Committee. The trial may be stopped due to a change in opinion of the research ethics committee; safety concerns of the Trial Steering Committee; or concerns about the trial conduct at the discretion of the sponsor.

Further details of the analysis will be supplied in a Statistical Analysis Plan to be finalised before database lock.

8 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor as requested for trial-related monitoring and audit.

9 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The trial will be conducted in compliance with the current revision of the Declaration of Helsinki (last amendment October 2008), with relevant regulations, and with MRC Guidelines for Good Clinical Practice in Clinical Trials (1998) which is based on ICH guidelines for GCP (CPMP/ICH/135/95) July 1996.

Compliance with the trial protocol will be ensured by a number of procedures:

9.1 Site start-up and training

Before trial recruitment begins, a meeting for the Principal Investigators, neonatologists and research midwives will be organised with workshops to discuss protocol issues, the trial interventions and related clinical issues, data collections issues, and trial procedures.

Each hospital will have a trial start-up visit, including training in the trial procedures, before the first woman is recruited. Sites will have at least one follow up visit within the first six months of recruitment, to ensure adherence to the protocol and to identify any specific site issues. Midwife trial days will be held for the research midwives involved in the trial to ensure that they are fully aware of issues such as consent, compliance with the protocol, data collection, and changing regulations.

Six months after recruitment begins, a second meeting for the Principal Investigators, neonatologists and research midwives will be organised to assess progress towards the pilot trial objectives, to discuss any problems that have been encountered, and to share experiences between sites.

9.2 Data collection and processing

Data will be collected using specific Cord Pilot Trial data collections forms. Processing of trial data and monitoring for consistency, validity and quality will be done as data accumulate by the Nottingham Clinical Trials Unit. Screening will include computerised checks for out-of range data, and cross-checks for conflicting data within and between data collections forms. Missing data and data queries will be referred promptly back to the recruiting site for clarification.

9.3 Monitoring

Trial monitoring will be by central statistical monitoring combined with site visits. Central statistical monitoring will be used to monitor patterns of recruitment at sites, reasons for non-recruitment of potentially eligible women, characteristics of women recruited, gestation at recruitment, time of recruitment, etc. It will also be used to assess compliance with the protocol, which may include checking measures of eligibility and compliance with the trial interventions.

Based on assessment of data processing and central statistical monitoring, the Chief Investigator and Trial Statistician will decide if any further action needs to be taken.

When site visits are performed, a random sample of participants will have their data monitored at source (Source Document Verification). Any major discrepancies or concerns at a site visit would trigger a more extensive audit of trial data at that site.

9.4 Archiving

Data and all appropriate study documentation will be stored for a minimum of 10 years after completion of the trial, including the follow-up period. The trial master file and trial documents held by the Chief Investigator on behalf of the sponsor will be archived in secure archive facilities at

Nottingham University Hospitals NHS Trust. This archive will include all trial databases and associated meta-data encryption codes.

10 TRIAL MANAGEMENT

Day-to-day management of the trial will be the responsibility of the Trial Management Group. The Trial Management Group will report to the independent Trial Steering Committee. An independent Data Monitoring Committee will monitor safety of participants, and will report to the Trial Steering Committee. Trial co-ordination will be through the Nottingham Clinical Trials Unit (NCTU).

10.1 Trial Management Group

The Trial Management Group (TMG) will include the Chief Investigator, Study Clinical Neonatologist, NCTU Senior Trial Manager, Study Trial Manager, Trial Statistician, and other project staff. This group, based at the NCTU, will meet regularly, at least every four weeks.

10.2 Trial Steering Committee

The independent Trial Steering Committee (TSC) will provide oversight of the trial. It will meet (in person or by telephone conference) prior to commencement of the trial, and then at regular intervals until completion (at least annually). Specific tasks of the TSC are:

- to approve the trial protocol
- to approve necessary changes to the protocol based on considerations of feasibility and practicability
- to receive reports from the Data Monitoring Committee
- to resolve problems brought to it by the co-ordinating centre and TMG
- to ensure publication of the trial results
- to advise on whether the main trial would be feasible

10.3 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established. As discussed above no interim analysis is planned for this pilot trial, and so the role of the DMC for this feasibility study is to assess safety only. The DMC will receive safety reports every six months, or more frequently if requested. They will report their assessment to the chair of the TSC.

Collaborators, and all others associated with the trial, may write through the trial office to the DMC, to draw attention to any concern they may have about the trial interventions, or any other relevant issues.

10.4 Principal investigators

Each participating hospital will identify a Principle Investigator. The Principle Investigator (or his/her nominee) will be the local co-ordinator for that site, whose responsibilities will be to:

- be familiar with the trial protocol
- liaise with the Trial Co-ordinating Centre at the NCTU
- ensure that all site staff involved in the care of potentially eligible women are informed about the trial and have received requisite training
- ensure that the processes for recruiting eligible women, including easy availability of parent information, are in place; monitor their effectiveness and discuss reasons for non-recruitment with relevant staff
- notify the Trial Co-ordinating Centre of any serious adverse events
- make data available for verification, audit and inspection, as necessary
- ensure that confidentiality of all information about trial participants is fully respected

11 ETHICS

11.1 Approvals

The Chief Investigator will obtain approval from the Research Ethics Committee, which will be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the SSA approval letter before accepting participants into the trial.

All subsequent amendments to the protocol and associated documents will be submitted for approval prior to their implementation. The Chief Investigator will provide reports to the ethics committee at the intervals stipulated in the ethics committee guidelines.

Source documents shall be filed at the local site and may include but are not limited to consent forms, current medical records and CRFs. Only trial staff listed on the delegation log shall have access to the trial documentation other than the regulatory requirements listed above.

11.2 Participant confidentiality

Confidentiality of all participant information will be maintained throughout the trial. Each participant will be assigned a unique trial identification number, allocated at randomisation. This number will be used for data collection forms, other trial documents, and the trial database. Trial documents and the trial database will also use participants initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mm/yyyy).

Data collection forms will be treated as confidential documents, and held securely. The Principal Investigator at each site will make a separate confidential record of the participant's name, date of birth, local hospital number, NHS number, and participant trial number, to permit identification of all participants enrolled in the trial. To facilitate follow up, the address and telephone number for all participants will be sent to the Trial Co-ordinating Centre at the NCTU after they are discharged. This information will be stored securely and separately to the anonymised trial data. Access to all data will be restricted to those personnel approved by the Chief or local Principal Investigator, and recorded on a delegation log.

12 DATA HANDLING AND RECORD KEEPING

All trial data will be entered on a trial specific database with participants identified only by the unique trial number, date of birth, and initials. The database will be developed and maintained by the trial coordinating centre at the NCTU. Access to the database will be restricted and secure. As discussed above, data quality and compliance with the protocol will be assessed throughout the trial by central statistical monitoring and site visits.

For the follow up phase, identifiable information about participants will be held in a separate database to the trial anonymised data. Access to this information will be restricted to those involved in the follow up phase, as authorised by the Chief Investigator.

13 FINANCING AND INDEMNITY

This pilot trial is funded through the NIHR Programme Grant for Applied Research: Improving quality of care and outcome at very preterm birth (RP-PG-0609-10107).

Nottingham University hospitals NHS Trust will act as the main sponsor for this trial. Delegated responsibilities will be assigned to the NHS trusts taking part in this trial. Standard NHS Indemnity applies.

14 PUBLICATION POLICY

14.1 Reporting, dissemination and notification of the results

Trial results will be published in a peer reviewed journal. Reporting will be in compliance with CONSORT [47, 48] recommendations. Results will be made available to participants through a newsletter (unless they state they do not wish to receive this), and will also be publicised though NCT and BLISS (co-investigators for the trial) and where possible in the local press and media.

14.2 Policy for publication and authorship

The pilot trial results will be published by named members of the trial team, on behalf of the Cord Pilot Trial Collaborative Group. Members of the collaborative group will be listed in the publication, based on contributorship. Any secondary publication may be published by named individuals, but with appropriate acknowledgement of the collaborative group.

15 REFERENCES

1. Moser, K., et al., *Introducing new data on gestation-specific infant mortality among babies born in 2005 in England and Wales.* Health Stat Q, 2007(35): p. 13-27.
2. Petrou, S., et al., *The impact of preterm birth on hospital inpatient admissions and costs during the first 5 years of life.* Pediatrics, 2003. **112**(6 Pt 1): p. 1290-7.
3. Zeitlin, J., et al., *Differences in rates and short-term outcome of live births before 32 weeks of gestation in Europe in 2003: results from the MOSAIC cohort.* Pediatrics, 2008. **121**(4): p. e936-44.
4. Bhutta, A.T., et al., *Cognitive and Behavioral Outcomes of School-Aged Children Who Were Born Preterm: A Meta-analysis.* JAMA, 2002. **288**(6): p. 728-737.
5. Saigal, S. and L.W. Doyle, *An overview of mortality and sequelae of preterm birth from infancy to adulthood.* Lancet, 2008. **371**(9608): p. 261-9.
6. Aarnoudse-Moens, C.S., et al., *Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children.* Pediatrics, 2009. **124**(2): p. 717-28.
7. Anderson, P. and L.W. Doyle, *Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s.* JAMA, 2003. **289**(24): p. 3264-72.
8. Saigal, S., et al., *Comparison of current health, functional limitations, and health care use of young adults who were born with extremely low birth weight and normal birth weight.* Pediatrics, 2007. **119**(3): p. e562-73.
9. Saigal, S., et al., *Self-perceived health-related quality of life of former extremely low birth weight infants at young adulthood.* Pediatrics, 2006. **118**(3): p. 1140-8.
10. POPPY Steering Group, *Family-centred care in neonatal units. A summary of research results and recommendations from the POPPY project*. 2009, London: NCT.
11. Farrar, D., et al., *Measuring placental transfusion for term births: weighing babies with cord intact.* Bjog, 2011. **118**(1): p. 70-5.
12. Saigal, S., et al., *Placental transfusion and hyperbilirubinemia in the premature.* Pediatrics, 1972. **49**(3): p. 406-19.
13. Aladangady, N., et al., *Infants' blood volume in a controlled trial of placental transfusion at preterm delivery.* Pediatrics, 2006. **117**(1): p. 93-8.
14. Dawes, G.S., *Foetal and Neonatal Physiology: A Comparative Study of the Changes at Birth. Chapter 13*. 1968, Chicago: Year Book Medical Publishers.
15. Hosono, S., et al., *Umbilical cord milking reduces the need for red cell transfusions and improves neonatal adaptation in infants born at less than 29 weeks' gestation: a randomised controlled trial.* Arch Dis Child Fetal Neonatal Ed, 2008. **93**(1): p. F14-9.
16. Hofmeyr, G.J., et al., *Periventricular/intraventricular haemorrhage and umbilical cord clamping. Findings and hypothesis.* S Afr Med J, 1988. **73**(2): p. 104-6.
17. Rabe, H., et al., *Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes.* Cochrane Database of Systematic Reviews, in press.

18. Mercer, J.S., et al., *Seven-month developmental outcomes of very low birth weight infants enrolled in a randomized controlled trial of delayed versus immediate cord clamping.* J Perinatol, 2010. **30**(1): p. 11-6.
19. Arnold, L., et al., *Parents' first moments with their very preterm babies: a qualitative study.* BMJ Open, 2013. **3**(4).
20. Sawyer, A., et al., *Parents' experiences and satisfaction with care during the birth of their very preterm baby: a qualitative study.* Bjog, 2013. **120**(5): p. 637-43.
21. Thomas, M., et al., *Service evaluation of a new specialised mobile trolley for providing care at the women's bedside at the birth of for sick and preterm infants.* in preparation.
22. RCOG Scientific Advisory Committee, *Clamping of the umbilical cord and placental transfusion*. 2009, Royal College of Obstetricians and Gynaecologists.
23. Wyllie, J. and S. Niermeyer, *The role of resuscitation drugs and placental transfusion in the delivery room management of newborn infants.* Semin Fetal Neonatal Med, 2008. **13**(6): p. 416-23.
24. Department of Health, *Toolkit for high quality neonatal services*. 2009: Department of Health.
25. Boie, E.T., et al., *Do parents want to be present during invasive procedures performed on their children in the emergency department? A survey of 400 parents.* Ann Emerg Med, 1999. **34**(1): p. 70-4.
26. Robinson, S.M., et al., *Psychological effect of witnessed resuscitation on bereaved relatives.* Lancet, 1998. **352**(9128): p. 614-7.
27. Moons, P. and T.M. Norekval, *European nursing organizations stand up for family presence during cardiopulmonary resuscitation: a joint position statement.* Prog Cardiovasc Nurs, 2008. **23**(3): p. 136-9.
28. Critchell, C.D. and P.E. Marik, *Should family members be present during cardiopulmonary resuscitation? A review of the literature.* Am J Hosp Palliat Care, 2007. **24**(4): p. 311-7.
29. Resuscitation Council, *Should relatives witness resuscitation?* 1996: Resuscitation Council (UK).
30. Farrar, D., et al., *Care during the third stage of labour: a postal survey of UK midwives and obstetricians.* BMC Pregnancy Childbirth, 2010. **10**: p. 23.
31. *Intrapartum care: care of healthy women and their babies during childbirth*. NICE clinical guideline; no. 55. 2007, London: National Institute for Health and Clinical Excellence.
32. WHO, *WHO Recommendations for the Prevention of Postpartum Haemorrhage.* . 2006, Geneva: World Health Organization.
33. Perlman, J.M., et al., *Part 11: Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations.* Circulation, 2010. **122**(16 Suppl 2): p. S516-38.
34. Richmond, S. and J. Wyllie, *European Resuscitation Council Guidelines for Resuscitation 2010 Section 7. Resuscitation of babies at birth.* Resuscitation, 2010. **81**(10): p. 1389-99.
35. Gyte, G., *NCT evidence based briefing. Third stage labour. Part 2: Active management of third stage.* New Digest, 2006(October): p. 22-28.
36. Hutton, E.K. and E.S. Hassan, *Late vs early clamping of the umbilical cord in full-term neonates: systematic review and meta-analysis of controlled trials.* JAMA, 2007. **297**(11): p. 1241-52.
37. Rabe, H., G. Reynolds, and J. Diaz-Rossello, *Early versus delayed umbilical cord clamping in preterm infants.* Cochrane Database Syst Rev, 2004(4): p. CD003248.
38. Rabe, H., G. Reynolds, and J. Diaz-Rossello, *A systematic review and meta-analysis of a brief delay in clamping the umbilical cord of preterm infants.* Neonatology, 2008. **93**(2): p. 138-44.
39. Reynolds, G.J., *Beyond sweetness and warmth: transition of the preterm infant.* Arch Dis Child Fetal Neonatal Ed, 2008. **93**(1): p. F2-3.
40. Duley, L., et al., *Survey of the Extended Neonatal Network to assess views on timing of cord clamping and placental transfusion. Report prepared for the Extended Neonatal Network.* 2009.
41. *Caesarean Section.* . NICE clinical guideline 132. 2011, London: National Institute for Health and Clinical Excellence.

42. Weeks, A.D., M. Peake, and W. Yoxall, *The Bedside Assessment, Stabilisation and Initial Cardiorespiratory Support (BASICS) trolley: enabling neonatal resuscitation with an intact cord.* , in *RCOG World Congress*. 2013: Liverpool.
43. Squires, J., et al., *Ages & Stages Questionnaire 3 User's Guide* 2009, Paul Brookes Publishing Co: Baltimore, MD.
44. Bayley, N., *Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III)*. 2005: Pearson Assessment.
45. RCOG, *Obtaining valid consent for research while in labour*. Clinical Governance Advice Vol. No. 6a. 2010.
46. Smyth, R.M., et al., *Women's experiences of participating in the Magpie Trial: a postal survey in the United Kingdom.* Birth, 2009. **36**(3): p. 220-9.
47. Moher, D., et al., *CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials.* BMJ, 2010. **340**: p. c869.
48. Schulz, K.F., D.G. Altman, and D. Moher, *CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials.* BMJ, 2010. **340**: p. c332.

Appendix 1. Principal Investigator Declaration

Principal Investigator Declaration

I confirm I have read and understood this protocol (version 6.2, dated 8 September 2016) and I agree to conduct the study in accordance with the protocol.

Principal Investigator: (name) _____

Centre name: _____

Signature: _____

Date: _____

Appendix 2: Qualitative Substudy - Exploring women's and clinicians' views of the two consent pathways for the CORD Pilot Trial

The aims of this qualitative substudy are to:
1) Explore women's experiences and views of giving either oral assent (two stage pathway) or written consent (one stage pathway) to participate in the Cord Pilot Trial.
2) Explore clinicians' experiences and views of offering oral assent and written consent in the Cord Pilot Trial.
3) Explore and compare adequacy of the two consent pathways in the Cord Pilot Trial.

Methods

A qualitative study using semi-structured interviews. Women who were recruited into the Cord Pilot Trial and the clinicians responsible for enrolment, will be interviewed about: (i) their overall experience and views of the consent process, (ii) the acceptability of the consent process, and (iii) the adequacy of the consent process.

This interview study for women and clinicians will be coordinated from the Nottingham Clinical Trials Unit (NCTU). The interviews will be conducted by Professor Susan Ayers, Professor of Maternal and Child Health, and her team in the School of Health Sciences, at City University, London.

Participants

a) Women
Women who participated in the Cord Pilot Trial will be eligible. Women whose babies died will be included, so the sample represents the experience of this group of women. Women will be recruited across a range of time frames, from before their baby is discharged home up to one year after the birth.

Sample size: We anticipate between 20 and 30 interviews will be required to achieve data saturation. As of 30 April 2014, 152 women had been recruited into the trial, of whom 37 (24%) were recruited via the oral assent pathway. Based on average monthly recruitment of 14, we anticipate 166 will have been recruited by the end of May 2014, with 39 recruited via the oral assent pathway. Our previous experience contacting parents who have had a very preterm birth was that 30% responded to a letter of invitation[20]. With this response rate we expect 50 women would be willing to be interviewed. However, even assuming a 20% response rate, 33 women would be willing to be interviewed. As recruitment began in April 2013, this will allow interviews to be conducted over a wide time frame.

b) Clinicians
Clinical staff (obstetricians, midwives, neonatalologists and research nurses) who invited participation to the Cord Pilot Trial will be eligible. This will include those who offered either pathway, or just one of the pathways. Clinicians will be included regardless of whether women accepted their invitation to participate in the Cord Pilot Trial.

Sample size Based on our previous experience of interviewing clinicians and parents about their experiences of very preterm birth, we anticipate interviews with clinicians will be shorter (between 10 and 20 minutes) and data saturation will be achieved with 15-20 participants.

Interview schedules
A semi-structured interview schedule will be used. The semi-structured format will allow women and clinicians to have flexibility in their answers and identify areas not covered by the interviewer.

For women the topics include: experience and views of the recruitment/consent process; acceptability of the consent process; adequacy of the consent process; potential improvements in the recruitment/consent process. At the end of the interview they will be asked about their level of education and marital status

For clinicians the topics include: experience and views of the two consent pathways, acceptability of each pathway, adequacy of each pathway, and potential improvements in the consent process. At the start of the interview, they will be asked their job title and length in that role.

Interview training

The interviewer will be trained and supervised by Professor Susan Ayers who has extensive experience of research interviews with postnatal women, including interviews with women who have had a very preterm birth and whose infants died.

Recruitment and interviews

a) *Women*

If the baby has been discharged home, a recruitment pack (with letter of invitation, the information sheet, a reply form, and a self-addressed envelope) will be posted to the woman. If the baby is still on the neonatal unit, the Nottingham Clinical Trial Unit will send the recruitment pack to the local research staff and ask them to give this to the women. Women will be asked to return the reply form to indicate their consent to participate in the research. They will then be contacted to organise the interview. Women can choose the location of the interview, either at home or in a quiet room at the hospital. In some cases, interviews may also be done by telephone.

If women do not respond, a reminder letter will be sent after 2 weeks. If the baby died, a reminder letter will not be sent.

Once a woman has agreed to an interview, the research team at City University will be sent a summary of her obstetric and neonatal data by the Trial Co-ordinating Centre at the Nottingham Clinical Trials Unit. This is so that the researcher is aware of the events the woman and baby experienced whilst in hospital. The summary will include gestation at birth, multiple pregnancy, mode of birth, date of birth, neonatal complications, neonatal death, date of discharge from the neonatal unit.

All obstetric and neonatal data will be sent to the research team at City University, identified by the unique Cord Pilot Trial ID number. No confidential identifiable information, such as names, will be sent with this data, to ensure the data remains non-identifiable. In a separate file, the women's names will be linked to the Cord Pilot Trial unique IDs numbers.

Before the interview the study will be explained and women will be given the opportunity to ask further questions. The woman's consent to participate in the interview will be confirmed by the researcher at the start of the interview with an opportunity to ask any further questions. Interviews are likely to last 30-60 minutes, and will be recorded then transcribed with all identifying information removed.

After the interview, women will receive a letter thanking them for taking part and explaining that they will receive a summary of the results of the study. If they do not want to receive this information they can opt out by notifying the Nottingham Clinical Trials Unit.

b) *Clinicians*

Clinicians and researchers who have offered consent will be identified by the Principal Investigator at each site. The Principal Investigators have agreed to gather a representative list of clinicians from their unit, who in principle, agree to participate in this interview study. The PI will send this list of clinicians, and their email addresses, to the Nottingham Clinical Trials Unit. An invitation email will then be sent to the clinicians, inviting them to participate in the interview study. The information

leaflet will be included as an attachment to the email. If clinicians would like to take part, they can reply to the invitation email, notifying the Nottingham Clinical Trials Unit of their interest in participating in an interview. A convenient place, date and time for this interview will then be arranged with the clinician.

Interviews will take place in a quiet room in the hospital. In some cases, interviews may also be done by telephone. Interviews are likely to last 10-20 minutes, and will be recorded and then transcribed with all identifying information removed.

After the interview, clinicians will receive a letter thanking them for taking part and explaining that they will receive a summary of the results of the study. If they do not want to receive this information they can opt out by notifying the Nottingham Clinical Trials Unit.

Analysis

Data will be analysed using systematic thematic analysis to identify main themes emerging from the interviews. Specialist software (NVivo) will be used to ensure systematic coding. Once saturation is achieved and new codes no longer arise, a detailed coding schedule will be developed and all interviews recoded on the basis of this schedule. Reliability will be ensured through checks both within codes and between coders.

Main themes will be written up as a report for publication with anonymous quotes taken from the interviews. A summary of these results will be sent to participants.