# Non-CTIMP Study Protocol

## Feasibility and design of a trial to determine the optimal mode of delivery in women presenting in preterm labour or with planned preterm delivery: CASSAVA

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# LIST OF ABBREVIATIONS

| | |
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| **ACCORD** | Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board |
| **CI** | Chief Investigator |
| **CRF** | Case Report Form |
| **CS** | Caesarean Section |
| **GCP** | Good Clinical Practice |
| **GDPR** | General Data Protection Regulations |
| **ICH** | International Conference on Harmonisation |
| **NHS** | National Health Service |
| **PI** | Principal Investigator |
| **PICTR** | Patient Involvement in Clinical Trial Research |
| **QA** | Quality Assurance |
| **REC** | Research Ethics Committee |
| **SOP** | Standard Operating Procedure |
| **UK** | United Kingdom |

# INTRODUCTION

## 1.1 BACKGROUND

Preterm birth (birth before 37 weeks) is the major cause of neonatal mortality and morbidity in the United Kingdom (UK). Around 7% of UK babies are born preterm. Survival to age one year and rates of disability are inversely proportional to gestational length. Babies born at lower gestational ages do worse than those born at higher gestational ages. Importantly, although survival rates have increased with time, rates of disability remain unchanged (Costeloe, Hennessy et al. 2012, Moore, Hennessy et al. 2012).

There is uncertainty about the optimal method of delivery for preterm babies, as highlighted by NICE (Excellence 2015) and a Cochrane review (Alfirevic, Milan et al. 2013). Addressing this clinical uncertainty could significantly improve the Rates of intrapartum stillbirth, neonatal and long term mortality and morbidity which are higher in the 50,000 preterm babies born in the UK each year compared with term babies. It is plausible that planned delivery by caesarean Section (CS) could reduce either death or disability in preterm babies. Indeed, our recent retrospective study of 1575 UK babies born between 23 and 27 weeks gestation showed that, after adjusting for confounders, babies born vaginally had a higher odds (1.61 [95% CI 1.01 – 2.58]) of intraventricular haemorrhage (Gamaleldin, Harding et al. 2017). Another study has shown that neonatal mortality is lower babies born by CS (Riskin, Riskin-Mashiah et al. 2008). Conversely, CS is associated with higher National Health Service (NHS) costs and greater complications for the mother (Excellence 2011) and there is conflicting evidence of benefit for preterm babies (Werner, Savitz et al. 2012, Alfirevic, Milan et al. 2013, Werner, Han et al. 2013).

Despite the lack of evidence and uncertainty in the national guidance, it is not clear whether clinicians and pregnant women are in equipoise about the best mode of delivery for preterm pregnant women and babies, nor whether they would wish to participate in any future randomised trial. Randomised trials have been performed to address optimal mode of delivery for women with breech presentation [(Hannah, Hannah et al. 2000) and women with twin pregnancy (Barrett, Hannah et al. 2013), and these trials have (arguably) reduced uncertainty. However, there are few randomised trials to compare planned CS with vaginal delivery for women with a cephalic presentation at term (Dodd, Crowther et al. 2013), and none registered for preterm gestations.

## 1.2 RATIONALE FOR STUDY

This study is a commissioned call from the Health Technology Assessment (HTA) because the National Institute for Clinical Excellence (NICE) guideline development group on preterm labour and birth were (in November 2015) were unable to find evidence to address the question: “For women who present in suspected or diagnosed preterm labour (who have not planned antenatally to give birth by caesarean section (CS) and for whom there are no other known indications for CS birth), what is the clinical effectiveness of deciding to carry out a CS compared with deciding to allow vaginal birth?” (Excellence 2015).

The HTA have also prioritised the research question, but are uncertain where evidence is really needed and whether women and clinicians would support randomisation. The aim of this study is to identify with more precision the clinical uncertainties among clinicians and women, any additional information possible (e.g. from new publications), and find out whether women and staff (and if so, under what clinical circumstances) would be willing to participate in a randomised trial. Designing a randomised trial is integral to addressing these issues.

The majority of preterm births follow the premature initiation of spontaneous labour. There is clinical uncertainty and little evidence about the optimal mode of delivery in this scenario or for those with planned preterm delivery. A minority require caesarean section (CS) (e.g. those with fulminating pre-eclampsia), and they are not the focus of this study. For the remainder, some clinicians believe that delivery by CS is best, due to the hypothesised reduction in birth trauma and intrapartum hypoxia. Others believe that vaginal delivery confers advantages for the baby (reducing respiratory morbidity), the mother (avoiding operative complications) and the NHS (costs).

There is only one systematic review of randomised trials on this topic, which is inconclusive (Alfirevic, Milan et al. 2013). Recent large cohort studies have not resolved this uncertainty, with evidence of worse outcomes (Werner, Savitz et al. 2012, Werner, Han et al. 2013) better outcomes (Reddy, Zhang et al. 2012) (Gamaleldin, Harding et al. 2017) and no difference (Kuper, Sievert et al. 2017) in association with CS. Not only is there uncertainty about mode of delivery, there is also uncertainty about clinician and women’s willingness to participate in a randomised trial of method of delivery for preterm babies. In fact, the authors were unable to identify any research on women’s willingness to participate in such a trial: indeed the only evaluation of willingness to participate in a ‘method of delivery” trial is in twin pregnancy, where around 50% of women indicated they would be prepared to be randomised (McLeod, Barrett et al. 2004). A large trial was subsequently conducted, successfully addressing a major clinical

uncertainty (Barrett, Hannah et al. 2013). Importantly, in a study of term women with a previous CS, the majority were allocated by patient preference rather than randomisation to elective repeat CS or trial of vaginal delivery, suggesting reluctance to randomise or be randomised (Crowther, Dodd et al. 2012).

As we embark on the project, we will update the literature review for the NICE guideline (from November 2015) using the MeSH headings premature birth; delivery, obstetric OR caesarean delivery; labor, obstetric; in the time interval current date to five years previously. The purpose of this literature review is to determine the populations of preterm babies and the clinical scenarios where there is clinical uncertainty about the mode of delivery, and not to determine the feasibility of recruitment to a randomised trial.

We believe that this project will identify clinical uncertainties about the mode of preterm birth among clinicians and parents. It will also determine in which subgroups of women there is clinical uncertainty and who would be willing to undergo randomisation to either the intervention (caesarean section) or control (vaginal delivery). We will identify clinician willingness to recruit. We will also design (and provide approximate costs for) a randomised trial to address these clinical uncertainties in other words that it is the 'definitive' trial. Additionally, such a trial will only be worthwhile if it can be completed. If women (and clinicians) reject randomisation, the funds involved in commissioning a trial will be wasted.

If such a trial is feasible, and is commissioned, it could make an important impact on the outcome of babies being born preterm. A recent UK multicentre retrospective cohort study showed that the odds of severe intraventricular haemorrhage was 1.6 fold higher in babies of 23-32 weeks gestation born vaginally compared to those born by caesarean section (Gamaleldin, Harding et al. 2017). The potential impact of this on a UK population of babies being born between 23 and 32 weeks gestation can be calculated, based on around 2500 such UK births annually (Moser and Hilder 2008) a background prevalence of vaginal delivery of 40% (Gamaleldin, Harding et al. 2017), and a risk of around 25% of developing cerebral palsy for babies with severe intraventricular haemorrhage (Brouwer, Groenendaal et al. 2008). A very rough calculation suggests that if all babies between 23 and 32 weeks born by caesarean section, there would be 39 fewer cases of severe intraventricular haemorrhage and around ten fewer babies with cerebral palsy each year. These estimates should be viewed with extreme caution, given the assumptions made and the relatively wide confidence intervals. They also have to be set against the additional costs of caesarean section, and the adverse effects on maternal health (including the increased risk of stillbirth in a future pregnancy in association with caesarean section).

# 2 STUDY OBJECTIVES

## 2.1 OBJECTIVES

### 2.1.1 Primary Objective

This research aims to find out the groups of women and babies in preterm labour or with planned preterm delivery in whom is there clinical uncertainty about the optimal planned mode of birth and whether women and clinical staff would be willing to participate in a future randomised trial.

2.1.2. Secondary Objectives

To perform a survey with clinicians to establish CURRENT PRACTICE and OPINION in key clinical scenarios of women presenting in preterm labour (e.g. cephalic/breech, previous CS or not, indicated delivery for pre-eclampsia or not, twin pregnancy or not, 23, 26, 32 weeks gestation).

To CONVENE AN INTERACTIVE WORKING GROUP of clinicians, parents and other interested parties (including policy makers) to determine what kinds of trial/trials still need to be done, and what groups of women should be included. Formal consensus methodology will be used to resolve uncertainties.

To DESIGN A RANDOMISED TRIAL which addresses the agreed most important clinical uncertainties. In line with the HTA brief, we anticipate that the “control” in our randomised trial will be planned vaginal birth and the “intervention” will be planned CS, but this will be informed by the survey.

To mock up a SHORT TRIAL PROTOCOL to facilitate the qualitative study described below.

To perform a qualitative study among clinicians and women to determine the acceptability of randomization. We will conduct telephone interviews with clinicians, and focus groups with women who have had, or who are at risk of preterm birth.

Assuming that there are clinical uncertainties which can be addressed by a trial to which women and clinicians will support recruitment, we will finalise the design (and approximate costs) of a randomised trial of CS compared with vaginal delivery, to determine the optimal mode of delivery of women presenting in preterm labour

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# 3 ENDPOINTS

### 3.1.1 Primary Endpoint

Using surveys, focus groups, consensus workshops and interviews to identify and resolve clinical uncertainties about the willingness of clinicians and women to recruit to/participate in a trial about the best planned mode of birth for groups of women presenting in preterm labour or with planned preterm birth.

### 3.1.2 Secondary Endpoints

Survey results, working group report and consensus statement, protocol for randomised trial, and reports from qualitative studies.

# 4 STUDY DESIGN

The study design involves a survey of current practice and opinion, followed by an interactive consensus workshop and consensus study, followed by qualitative studies of women's and clinician views (focus groups, interviews), with each component informing the development of the next.

# 5 STUDY PLAN

## 5.1 Phase 1: Survey of current practice (Months 1-4)

We will perform a survey of clinicians regarding current practice and opinion offering examples of key clinical scenarios of women presenting in preterm labour or undergoing planned preterm delivery. The purpose of this survey is to determine the opinions of clinicians (consultant obstetricians, consultant neonatologists and midwives working in units with neonatal intensive care facilities) on the optimal mode of delivery. The survey will focus on scenarios where there is maximum clinical uncertainty and will be piloted to determine completion rates, ease of completion, and identify any questions which are unclear to respondents.

We will use a standardised format (likely an electronic format on a tool such as Bristol On-line survey), and present options in the form of tick boxes and/or ratings scales. We will be careful to vary our "agree" or "highest rating score" between caesarean section and vaginal delivery to avoid bias from "yeasayers" (Boynton and Greenhalgh 2004). We believe that a closed ended design is likely to be appropriate, but we will include a free text box for further

communication at the end of the questionnaire. If comments in the free text box suggest there are important controversies that we have not presented, we will consider issuing a further survey. A request for demographic information of the respondent (age band, clinical specialty, preterm birth specialist or not) will be included at the end of the survey.

The survey will be distributed through our professional networks of contacts. Contacts will include clinicians participating in existing preterm birth intervention studies currently led by co-applicants involved in this study. We will also invite participation through the NHS Preterm Birth Network and Royal College of Obstetrician and Gynaecologists (RCOG) Preterm Birth Clinical Study Group (CSG). We will also advertise the survey through the Royal College of Obstetricians, the Royal College of Midwives, the British Maternal and Fetal Medicine Society, the British Association of Perinatal Medicine, the Neonatal Society. At the end of the survey we will ask participating clinicians if they would be willing to be contacted to take part in an interview for Phase 3, and for their consent for us to collect and keep their contact details for this purpose. We have attached a draft advert and a cover letter in which we invite clinicians to participate in the survey.

We acknowledge that where surveys are distributed through external organisations it will be difficult to determine the proportion of people completing the survey. However, we will aim for completion from around 200 individuals with good representation from each group of clinicians (obstetricians, neonatologists, midwives): we anticipate that this large and diverse sample will overcome any potential bias due to clustering of responses from any particular professional group.

## 5.2 Phase 2: Interactive Consensus Workshop and Trial Design (Months 5-9)

Having performed a survey to establish current practice and equipoise in key clinical scenarios of women presenting in preterm labour, we will convene an interactive working of approximately 40 participants with a broad range of experience and expertise. This workshop will include the co-investigator team, multidisciplinary experts, clinicians, women, patient groups, and key stakeholders to determine what kind of trial/trials still need to be done, and what groups of women should be included to address outstanding research questions. The aim is to use Delphi methodology to refine the clinical uncertainties, to inform the design of a clinical trial.

### 5.2.1 Delphi Methodology:

A two-round Delphi consensus methodology will be used to reduce the survey list of clinical uncertainties into a short-list, prioritising those clinical scenarios which are both uncertain and important. The Delphi methodology enables all stakeholders to participate in a consensus process which assesses the extent of agreement (about priorities) and then resolves disagreement (Sinha, Smyth et al. 2011). All stakeholder groups including parents, healthcare professionals, researchers and healthcare regulators will be invited to participate.

Two rounds of the Delphi process will take place using a web-based survey application that has been developed by the University of Liverpool (DelphiManager) and adopted by the Comet Initiative (comet-initiative.org/delphimanager). Our survey will be hosted within an online portal and infrastructure designed by the University of Liverpool. Before entering the exercise, participants will be asked to register, provide demographic details, and commit to all rounds. After this has been reviewed a unique identifier will be allocated. The unique identifier will anonymise participant responses but also provide a means to send completion reminders. Participants will also be given the option of a paper (postal) questionnaire, if they do not have access to a computer.

**a) Pilot**

The Delphi questionnaire will be piloted to ensure the ease of completion by participants prior to recruitment. The Delphi survey will be piloted on the study committee and the PPI panel. This is to ensure that the outcome terminology is understood by stakeholders before allowing them to decide which outcome is important to them in the Delphi. Since those participating in the pilot are part of the study team, formal consent will not be taken.

b) **Round One**

Potential participants will receive an e-mail linking to the web-based questionnaire embedded within the study's website. (We will send a postal questionnaire to those who state that they do not have regular access to a computer). Initial questions will include the option to add additional scenarios for use in round two before proceeding to scoring. Even though it is likely these additional proposed scenarios would have been previously dropped from the longlist, this failsafe step will be able to identify any scenarios that may merit reconsideration.

Participants will score each clinical scenario listed using the Likert type scale, using a composite of “importance” and “clinical uncertainty” about the scenario in question. The scores will be summarised graphically using the DelphiManager.

**c) Round two**

The scenarios will be carried forward to round two. An anonymous summary of the responses will be fed back to participants according to each stakeholder group. Participants will be asked to re-score their preference to reach consensus. Any outcomes not deemed important by the pre-specified scale will be dropped.

**d) Final Consensus meeting**

An interactive consensus meeting will take place following the completion of the Delphi process to validate the final set of scenarios. The meeting will present scenarios retained and dropped by the Delphi process and discuss any scenarios in Delphi round 2 where "no consensus" was found. Only those stakeholders who completed both rounds of the Delphi study will be invited to participate. It is anticipated that 2-3 key participants from each stakeholder group will participate.

At this interactive meeting we will finalise the shortlist of scenarios that will inform the development of resources for the subsequent qualitative phases of the study. The aim is to use the prioritised scenarios to plan the single most important trial (which may have several subgroups of women [e.g. women in labour and women not in labour], and several stratification variables [e.g. twin and singleton women]). Any scenarios not possible to cover in a single trial will be discussed for future separate exploration.

### 5.2.2 Trial design

We anticipate that the randomised trial will use an efficient design and the PICO will be:

Participants: women in spontaneous preterm labour or with planned preterm delivery
Intervention: caesarean section
Comparator: vaginal delivery
Outcomes: to be determined.

The surveys of current opinion and practice, and the consensus process described above will identify key clinical uncertainties that could be addressed in a clinical trial. These clinical uncertainties will pinpoint subgroups of participants (such as women with breech presentation, or particular gestational ages, for example). The outcomes for the randomised controlled trial will include those that can best address the identified clinical uncertainties, and so determine which interventions will be clinically effective, safe, affordable, and acceptable to women. It will also include those indicated by COMET for preterm birth (van 't Hooft, Duffy et al. 2016). Our primary outcome (on which the trial will be powered) will be one which is considered important

by clinicians and parents, and is measurable with good reproducibility. A sample size calculation will be performed, and the approximate cost of the trial determined.

### 5.2.3 Mock up of short trial protocol.

Once the trial design is complete, the clinical team and the triallists in the panel will generate a short trial protocol. The qualitative team (helped by our PPI) will use the protocol to develop a descriptive vignette for use in the focus groups discussions.

## 5.3 Phase 3: Qualitative Design (Months 10-22)

Next we will perform a qualitative study among clinicians and women to determine if clinicians would be willing to recruit into the proposed trial and whether women would be willing to participate. An iterative, inductive approach will be used for the qualitative research in which data analysis will commence as soon as data collection begins. This will allow issues identified during the early phases of data collection to inform areas explored in later stages and possibly also sampling. The two components of the qualitative research – clinician interviews and focus groups with women – will take place in parallel, allowing them to be mutually informing.

### 5.3.1 Part 1: Clinician interviews

Recruitment and sampling

Clinicians who indicted at the end of the survey (see 5.1.2) that they would be willing to be contacted to take part in an interview will be sampled in light of: (a) their survey responses (e.g., so we draw upon the perspectives of those in favour of caesarean section and vaginal delivery, respectively); and, (b) so there is representation of the different kinds of clinical staff who would be involved in recruiting into the proposed trial (e.g. obstetricians, neonatologists, midwives, research midwives etc.) from different areas.

Individuals selected for an interview will be contacted by the qualitative researcher appointed to the study who will provide them with a participant information sheet for the interview study and a consent form and answer any questions they might have. Assuming the clinician still wishes to take part, the researcher will then arrange a convenient time to interview them on the phone.

If insufficient clinicians completing the survey give their permission to be contacted to take part in an interview, additional health professional recruitment will be undertaken by clinical co-investigators and collaborators on the study who will send out recruitment packs to obstetricians, neonatologists, midwives, research midwives within their networks, containing a participant information sheet, an opt-in form and a consent form. We may also 'snowball' from health professionals who have taken part in an interview by asking them to pass on recruitment packs to colleagues who they think would interested in taking part in an interview. Individuals receiving these recruitment packs will be asked to complete and return opt-in forms directly to the qualitative research team. Individuals who complete the opt-in form will be contacted by the research fellow who will answer any questions they have and arrange a convenient time to interview them on the phone.

Clinicians will be asked to complete and sign the consent form before their interview takes place; as part of the consent process, clinicians will be also be asked for their permission for their interview to be audio-recorded.

Data collection

Clinicians will be sent a brief summary (a short protocol) of the proposed trial design in advance of their interview and this will form the focus of the discussion in the interview. As well as seeking their views on whether (and why), they would be willing to recruit and randomize women, health professionals will be asked about the training, resourcing and other support they would need to deliver the trial were it to go ahead in the future. Health professional interviews will also explore the potentially distinctive challenges of recruiting minority ethnic women into the trial and what additional resourcing and support they feel they would need to optimize these women's participation.

Clinician interviews will be informed by a topic guide, which will help the discussion stay relevant to the study aims, while allowing flexibility for individuals to raise and discuss issues which they perceive as salient, including those potentially unforeseen at the study outset. The topic guide will be informed by literature reviews, inputs from the coinvestigator team, and revised in light of emerging findings (including, potentially, findings from the concurrent focus group study with women), in keeping with the inductive approach proposed for this study.

It is estimated that around 25 clinicians will need to be interviewed to garner a diversity of perspectives and achieve data saturation (that is, when no new findings emerge in new

data collection). However, if saturation is not achieved using this sample size, further interviews may be undertaken.

### 5.3.2 Part 2: Focus groups with women

Concurrent with the clinician interviews, we will conduct 6-8 focus group with women (5-8 individuals per group) who have had a pre-term birth (with representation of those who have had CS or vaginal delivery) and/or who are potentially at risk of preterm birth. Women will be identified from our PPI group, through advertisement by Tommy's and Bliss, and through advertisement via the International Stillbirth Alliance and the network of charities involved in the recent National Bereavement Care Pathway.

Women attending prematurity clinics at Edinburgh and London hospitals or who are identified from Tommy's databases, will be posted or given recruitment packs, containing a covering letter, a participant information sheet, an opt-in form and a consent form. Women may also be recruited through social media, including in collaboration with Bliss and Tommy's. Women will be asked to send their opt-in form directly to the qualitative research team. Women who opt-in to the study will be then be contacted by a member of the qualitative research team who will answer any questions they have and, assuming they still wish to take part, to arrange a time and location for them to take part in a focus group.

*Minority ethnic focus groups*

We will conduct three of the planned 6-8 focus groups with minority ethnic women to identify and explore potential barriers to trial participation from their perspective and how they think these might be overcome. We plan to approach the following minority ethnic groups (i) Edinburgh-based Pakistani Muslim women (ii) Edinburgh-based Polish women and (iiii) London-based Indian women. While Indian women will be able to speak and understand English to a sufficient level to take part in a focus group undertaken in English only, our previous research experience has taught us that it will be necessary to offer Edinburgh-based Pakistani women a focus group undertaken in a mixture of Urdu, Punjabi, and English and Edinburgh-based Polish women a focus group undertaken in a mixture of English and Polish.

We anticipate that some Polish, Pakistani and Indian women will opt-in to the research via recruitment undertaken in prematurity clinics and through Tommy's and Bliss databases and our other networks (see above). However to get sufficient numbers into each of the three dedicated groups and enable inclusion of what are stereotypically seen as 'hard to reach' individuals, additional community-based recruitment will be undertaken, if required. In line with learning from previous qualitative research undertaken by two of the co-investigators (JL and NH) and others (McLean and Campbell 2003, Sin 2004, Lawton, Ahmad et al. 2005), we will employ local Polish (Edinburgh-based) and Pakistani (Edinburgh-based) bi-lingual researchers. These individuals will recruit women via local community groups and by using known and trusted community members as the initial 'research brokers'. The bilingual researchers will hand out recruitment packs to women in community groups/settings and/or ask research brokers to distribute recruitment packs. Packs will contain an information sheet, an opt-in form and a consent form in English together with versions translated into Polish or Urdu (the written language used by Pakistani women living in Edinburgh), as appropriate.

Women who opt-in into the study will be contacted by a bi-lingual researcher to discuss the study further and to arrange a time and location for their focus group to take place. Pakistani and Polish women will be informed that their focus group will be co-facilitated by the bilingual researcher and hence that they will not be required to speak English in order to take part.

Before participating in a focus group women will be asked to review and complete a consent form. Each participant and the researcher will sign the form and a copy will be given to each woman to keep.

*Anonymity of participants:* At the beginning of each group, the researcher(s) will highlight the importance of the participants keeping each other's' comments and thoughts confidential and of not sharing these with anyone outside the group.

Data collection

The researcher(s) will provide women with a description of the proposed trial. This will be followed by an open discussion to explore women's views about the trial, the acceptability of randomization and what they think the main barriers and facilitators to recruitment will be. Women will also be asked about the kinds of information they think women would need in

order to make a decision about taking part in the trial. A topic guide will be used to orient discussion during the groups and the discussion group will be audio-recorded.

All focus group discussions will be transcribed. Focus groups (or parts of the discussion) undertaken in non-English languages will be translated into English, Confidentiality agreements will be signed by all individuals (e.g. employees of professional transcription companies) involved in the transcription/translation of focus groups discussions.

Reimbursement

Women will be reimbursed for out of pocket expenses and child care and/or given the opportunity to attend a focus group in a venue where they can bring their babies along to maximise attendance and be sensitive to their potential child care responsibilities. Women will be given a voucher for £30 to thank them for their participation.

# 6 STUDY POPULATION

## 6.1 NUMBER OF PARTICIPANTS

We plan to recruit in each phase:

**Phase 1: Survey.** We hope to survey around 200 clinicians on current opinion and practice and 200 members of the public

**Phase 2: Consensus** workshops and Delphi process will involve clinicians (including members of the co-investigator team), and other key stakeholders including women and their partners. We aim to ensure that 20-40 participants complete at least two rounds of the Delphi consensus exercise.

**Phase 3**: **Qualitative** interviews and focus groups: We will conduct interviews with clinicians (n=25) and focus groups with women (n=30-60) (i.e. 6-8 focus groups involving 5-8 women per group).

## 6.2 INCLUSION CRITERIA

Phase 1 surveys, we will include consultant obstetricians, neonatologists, and midwives working in hospitals with neonatal intensive care units (as these are the only hospitals that will

deliver the extreme preterm births, which are included in the scenarios). We will also include members of the public recruited via partner organisations and Public Patient Involvement (PPI) group, PICTR (Patient involvement in Clinical trials research). This is a group of i volunteers who are interested in supporting and commenting on research projects. The Centre for Reproductive Health (Edinburgh) Clinical Obstetric Trial team manages the PICTR group.

Phase 2 consensus workshop, we will recruit clinicians (obstetricians, anaesthetists, midwives, nurses and neonatologists and midwives) with 5 years of more experience or providing clinical care to women at risk of preterm labour or preterm infants born.

For the consensus workshops and Delphi process we will include women and their partners who fulfill the following criteria:

- age greater than 16 years
- willing to consent
- previous experience of the following
    i. Previous preterm labour or delivery
    ii. Women at risk of future preterm labour or delivery

Phase 3 Qualitative interviews we will recruit clinicians (obstetricians, anaesthetists, midwives, nurses and neonatologists and midwives) with 5 years of more experience or providing clinical care to women at risk of preterm labour or preterm infants born using volunteers from phase 1 and 2.

For the focus groups, we will recruit women only who fulfill the following criteria:

- age greater than 16 years
- willing to consent
- previous experience of the following
    i. Previous preterm labour or delivery
    ii. Women at risk of future preterm labour or delivery

## 6.3 EXCLUSION CRITERIA

Phase 1, the survey

- We will exclude clinicians working in units without neonatal intensive care facilities

NB: Women and their partners who have experienced adverse events as a result of the issues

above (e.g. neonatal death, stillbirth) will not be actively excluded from the consensus workshops or focus groups, but we will be mindful of the need to manage this sensitively. The members of the research team have significant experience of conducting mixed-methods research with parents who have experienced adverse events, including perinatal death.

# 7 CO-ENROLMENT

Co-enrolment will be allowed for this study as we are seeking the views and opinions of clinical staff and service users.

# 8 PARTICIPANT SELECTION AND ENROLMENT

## 8.1 IDENTIFYING PARTICIPANTS

### 8.1.1 Women and their partners

Four main strategies will be used to identify and approach women to participate in the interactive consensus workshop and in the focus groups.

(i) Some women will be invited to participate from antenatal clinics (including preterm birth clinics) and neonatal units at the NHS participating sites in Edinburgh, Bristol and London (UCL).

(ii) We will also recruit women and their partners through our charity partners Tommy and Bliss, the International Stillbirth Alliance, and the network of charities involved in the recent National Bereavement Care Pathway.

(iii) We will invite women who are already part of our PPI groups in Edinburgh, Bristol or London to participate.

(iv) Women from particular cultural groups: Polish (Edinburgh-based), Pakistani (Edinburgh-based) and Indian (London-based) will be recruited local community groups using via bi-lingual researchers where necessary. Known and trusted community members will be the initial 'research brokers'. The (bilingual) researcher will hand out recruitment packs to women in community groups/settings and/or ask research brokers to distribute recruitment packs. Packs will contain an information sheet, an opt-in form and a consent form.

Examples of recruitment strategies (invitation letter for NHS sites and for our PPI group, adverts placed by our charity partners and information sheets and opt in forms for the cultural groups) are attached.

Women will be asked to involve their partner in the interactive workshop, but not the focus group. We anticipate that recruitment via NHS sites described in (i) above will need R&D

approval from those sites. We do not anticipate that recruitment of women through strategies (ii) – (iv) will need R&D approvals, since it does not involve the NHS.

### 8.1.2 Clinical health care experts

We will invite clinicians to participate in the survey, interactive working group and Delphi, and the qualitative interviews through our networks: Royal Colleges (Midwives, Nurses, Obstetricians, Neonatologists), preterm birth network, RCOG clinical study groups (preterm birth, stillbirth, intrapartum care), and British Maternal and Fetal Medicine Society members). With purposive sampling, we will aim to include clinicians (labour ward leads, midwifery and neonatal nurse leads, and neonatologist leads) where possible including those with diverging clinician views about optimal mode of delivery. We do not intend to approach any through their NHS trust, and so we do not anticipate that R&D approval will be required for clinician participation. Exemplars of invitation letters are attached. We will approach clinicians who have participated in the survey to additionally participate in the consensus working group and the interviews, but these second two events will be optional.

Other stakeholders, including healthcare regulators responsible for pregnancy and childbirth including NHS England, the Care Quality Commission, and National Institute for Health and Care Excellence will be invited to participate in the focus groups.

# 9 CONSENTING PARTICIPANTS

## 9.1 WOMEN (AND WHERE RELEVANT THEIR PARTNERS)

Women (and where relevant their partners) will be approached as described in section 6.4. They will be provided with an information sheet about the study. Those who wish to participate will complete a consent form. Consent for the interactive workshop will be taken by the study administrator (or other research staff). Potential participants who wish further information will be referred to the lead for the interactive consensus workshop (Dr Dimitrios Siassakos) for further discussion.

Consent for the focus groups will be taken by the trained qualitative researcher conducting the focus groups. Those who wish further information will be referred to the lead for this part of the study, Professor Julia Lawton.

### 9.2 CLINICIANS

For the survey, clinicians will be approached by email – either directly (e.g. where we have consent from clinicians for contact for research related activities; where their email is publically available such as on NHS websites) or indirectly through Networks or societal email distribution lists. The email will describe the survey and its purpose, and include opt out options from further contact. The first email or advert will be followed by a second, follow-up email 2-7 days later, including further information and a link to the online survey for completion. A reminder email will be sent 6 weeks after initial approach. Consent will be presumed by survey completion. Potential participants who wish further information will be referred to Dr Sarah Stock (lead for the survey) for further discussion.

Clinicians will be provided with an information sheet describing either the consensus workshop or the interview (as appropriate). They will be asked to complete a consent form for the relevant part of the study. Most of this will be done by post. Potential participants who wish further information will be referred to the lead for the relevant part of the study (Dr Sarah Stock for the survey, Dr Dimitrios Siassakos, for the interactive consensus workshop or the qualitative researcher or Prof Julia Lawton for the interviews) for further discussion.

All participants will have at least 24 hours (might have to increase this for difficult ethics committees to a week) to consider whether they wish to participate.

## 10 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point. No attempt will be made to record reason for withdrawal. The participant will have the option of withdrawal from

I. all aspects of the study but continued use of data collected up to that point
II. all aspects of the study with removal of all previously collected data.

## 11 DATA COLLECTION

The data to be collected are the opinions of women (and their partners) and clinicians. These will include:

Phase 1 Survey results during the surveys we will collect no personal data (including IP addresses for the online surveys) unless the individual volunteers to provide contact information and requests to receive further information about phase 2 or 3 of the study. We will then request title, name, surname, address postcode, telephone and email contact details.

Phase 2 Discussion at the interactive consensus workshop (which will be audio-recorded (with consent) to aid future analysis) opinions will not be attributed to individuals. Audio recording will be held securely and transferred using a secure data transfer system i.e. Datasync. The data produced will be a ranking of scenarios (longlist and shortlist)

Phase 3 Data collected during the Focus groups and Interviews will be audio-recorded to aid future analysis. Audio recordings will transferred using the DataSync cloud service operated and hosted by the University of Edinburgh. Files on Datasync are only visible to others, if they are shared. Digital audio recordings of interviews will be uploaded to Datasync and an encrypted and time-limited link sent to a transcription company to enable the file to be downloaded. Transcripts of audio files will be returned to the researcher using password-encrypted word files. The transcription company will be asked to sign a confidentiality agreement, Only members of the research team will have access to the raw data or transcripts. At the point at which transcription takes place all information, which could potentially identify participants will be removed e.g. names, place names.

# 12 SOURCE DATA DOCUMENTATION

All data created for this study will be source there is no plan to access any pre-existing records or review medical notes. Participants will provide consent for the data obtained during the process.

Source data will be the surveys; electronic and paper. Audio recordings taken during the Delphi consensus, interviews and Focus groups will be transcribed and the transcriptions will be held as anonymised source data.

Further the output of the interactive working group will be a consensus summary, which will not attribute opinions to individuals.

The focus groups and interviews will be transcribed and analysed using a thematic approach. Nvivo software will be used to facilitate data coding and retrieval.

# 13 STATISTICS AND DATA ANALYSIS

## 13.1 SAMPLE SIZE CALCULATION

Our planned sample sizes are as follows:

- Clinician survey, n= 200
- Public survey, n= 200
- Interactive working group, n=40
- Focus groups with women, n=30-60
- Interviews with clinicians, n=25

There are no generally accepted guidelines for the optimal size to achieve a consensus in Delphi studies [44] however it is most important to obtain a sample with a broad range of experience and expertise. Approximately 40 participants will be recruited.

## 13.2 PROPOSED ANALYSES

The survey data will be used to determine current practice and public opinion. We will use a Likert scale 1-5 and analyse with appropriate non-parametric and/or parametric tests. Where more than 85% of individuals responding to the surveys agree on an answer to a clinical scenario, we will designate the scenario as having good agreement, and being accepted clinical practice. Where less than 50% agree on an answer, we will assume that there is significant uncertainty. Where 50-70% agree, we will designate the scenario as having moderate uncertainty. Where 70-85% agree, we will designate the scenario as having some uncertainty.

Data analysis for the Consensus. Delphi process will involve graphical summation of the scores indicating the whole groups' and individual participant groups' responses using the Delphi Manager. Participants will be asked to score each scenario using the Grading of Recommendations Assessment Development and Evaluations (GRADE) scale for Delphi processes (accessed online). Participants will be asked for example: 'How important is to include the following scenarios in a randomised trial of mode of delivery (caesarean/vaginal) for a preterm baby?' A pre-specified scale and criteria (Williamson, Altman et al. 2012)will be used for dropping and retaining items in the long-list created from the survey: scenarios with >70% participants scoring 7-9 and <30% scoring 1-3 would be included in subsequent rounds.

Data analysis for the qualitative research will be undertaken by highly experienced qualitative researchers with input from other members of the co-investigator team. Individual interviews will be read through repeatedly and cross-compared to identify issues and experiences which cut across different accounts (Strauss and Corbin 1990). Depending on emerging findings, interviews may also be analysed in clusters and cross compared according to the sites/NHS trusts to which clinicians belong, their clinical/professional roles, and questionnaire responses. A similar approach will be used for the focus groups discussions, with particular attention being paid to differences and similarities in the perspectives and views of women belonging to different cultural and religious groups and to those with prior experience of CS and vaginal delivery. In line with others' recommendations (Kitzinger 1994, Duggleby 2005, Wilkinson, Rees et al. 2007), careful attention will be also paid in the analysis to group interactions, including use of humour, as participants' (different) assumption can be revealed through the ways they challenge, question and support one another in the context of a group discussion (Kitzinger 1994). Team members will undertake separate analyses and write independent reports before meeting to discuss their interpretation of the data and reach agreement of key findings and themes which will then be used to inform development of a coding frame. Coded datasets will be subjected to further analyses to allow more nuanced interpretations of the data to be developed and identify illustrative quotations. Nvivo software will be used to support data coding and retrieval.

# 14 ADVERSE EVENTS

We do not anticipate any adverse outcomes from this study. However, we recognise that discussion of method of delivery might be upsetting for women and families (and indeed staff) who have experienced adverse events. Focus groups will be conducted by experienced researchers, who will be alert for any signs of distress, and who can refer individuals for further support of advice if required. The extended research team will be available for advice and support, and we are fortunate to have charities Bliss and TOMMY's as partners – these charities regularly provide information and support to women and partners who have experienced adverse events and have helplines that can support parents (and staff if necessary). We will signpost participants to these helplines and to other relevant health care professionals as relevant and necessary.

# 15 OVERSIGHT ARRANGEMENTS

## 15.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

## 15.2 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the co-sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs.

## 15.3 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

# 16 GOOD CLINICAL PRACTICE

## 16.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP). Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

## 16.2 INVESTIGATOR RESPONSIBILITIES

Investigators are responsible for the overall conduct of the study and compliance with the protocol and any protocol amendments in accordance with the principles of GCP. Responsibilities may be delegated to an appropriate member of study site staff.

### 16.2.1 Informed Consent

The Investigator or delegate is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involve.

We are assuming that those who respond to the survey consent to participate in it, but we will be clear with the respondents about how we will use the information.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided, where practical. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasized that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

### 16.2.2 Study Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

### 16.2.3 Data Recording

The Lead Investigator is responsible for ensuring the quality of the data recorded for each of the study aspects and sites.

### 16.2.4 Investigator Documentation

The Lead investigator for each aspect of the study will ensure that the required documentation is retained for the required period. All data will be archived centrally at the University of Edinburgh for the required period of time.

### 16.2.5 GCP Training

For this study all researchers are encouraged to undertake Good Clinical Practice (GCP) training, however, it is not a mandatory requirement. GCP training status for all investigators will be indicated in their respective CVs.

### 16.2.6 Confidentiality

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

### 16.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the General Data Protection Regulations (GDPR) 2018 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

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

Published results will not contain any personal data that could allow identification of individual participants. Anonymized data will be shared (if requested) with other researchers within the European Union as per the funders data sharing policy.

# 17 STUDY CONDUCT RESPONSIBILITIES

## 17.1 TEAM RESPONSIBILITIES

Jane Norman will have overall management of the project (and will Chief Investigator), assisted by Sonia Whyte, who will provide study management support.

**Phase 1:** The clinician and public surveys will be led by Sarah Stock.

**Phase 2:** The Delphi consensus exercise to finalise the research questions, will be led by Dimitrios Siassakos. John Norrie and Jane Norman will design the trial.

**Phase 3:** The qualitative research with women and clinicians in phase 3 will be led by Julia Lawton and Nina Hallowell. Jane Brewin (Tommy's) and Mehali Patel (Bliss) will help with identifying women from Tommy's and Bliss respectively to participate in focus groups. Jane Norman, Sarah Stock, Dimitrios Siassakos and David Odd will help identify women and health professionals to participate from their NHS sites.

Communication will be achieved through regular teleconferences (anticipated monthly), face to face meetings (likely half yearly) and other email etc. as required. A Trial Steering Committee (but not a data monitoring committee) will be set up in line with funder recommendations.

# 18 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to the funders and the sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

# 19 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, **will not be approved by the sponsors** and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this will be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log which will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of a member of the trial team becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

# 20 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

a. the safety or physical or mental integrity of the participants of the trial; or

b. the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

# 21 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

# 22 END OF STUDY

The end of study is defined as publication of the report to the study funder.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot.

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

# 23 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

Not applicable, for this study design.

# 24 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.

- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

# 25 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

The results of this study will form a report to HTA to allow them to decide whether to commission a future trial. However, we anticipate that the findings of this trial will also be suitable for journal publications. We also anticipate that the findings will be of interest to pregnant women and their families and we will disseminate the results through our charity partners (Tommy's and BLISS) who between them reach a very large audience of women, families and the general public who are interested in preterm birth.

# 26 AUTHORSHIP POLICY

Ownership of the data arising from this is set out in the collaborators' agreement and an authorship policy will be developed. On completion of the study, the study data will be analysed and tabulated, and a study report will be prepared in accordance with GCP guidelines.

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# 28 PROJECT FLOWCHART