CASSAVA

Optimal mode of delivery in preterm labour

Dear Colleague

You are being asked to comment on whether you would be willing to recruit participants to a proposed study called “CASSAVAplus . The purpose of this study (the research question) is to determine the most appropriate method of birth to offer women who will have a preterm delivery. This preterm delivery may be elective (planned) or may follow spontaneous preterm labour.

The research question was identified in the NICE Preterm labour and birth guideline. Section 1.1 in the protocol describes the existing literature on this subject. There are almost no randomised trials. Retrospective cohort data are conflicting, although some recent UK data suggests that caesarean section is associated with better neonatal outcomes but poorer maternal outcomes compared with vaginal delivery.

Despite this paucity of evidence, it is not clear whether women and clinicians would agree to participate in a randomised trial. We have devised the CASSAVAplus protocol and are asking women and clinicians if they think the trial is feasible.

Any trial has to have a hypothesis - the hypothesis for this trial is that there would be an absolute risk difference of 5% or more for the primary neonatal outcome (composite of alive at 6 months after birth or to home discharge without significant intraventricular haemorrhage or cystic periventricular leukomalacia) for those planning a vaginal birth compared with those planning birth by caesarean section. We think that this neonatal outcome is probably the most important one for women and clinicians, and a difference of 5% would be the minimum that would make one choice preferable to another.

We plan to collect a lot of secondary outcomes, including about maternal health, and other neonatal outcomes.

We are conscious that mode of delivery and neonatal outcomes are a very emotive subject, and that it might be “unfair” to keep any information we are collecting, and not use this to inform patient care. On the other hand, if we stop the trial too early, we won’t be able to be certain that one option truly is better than the other (or that they are equivalent). We therefore plan that this will be an “adaptive” trial, whereby we will take emerging information on which option is best, and use that to increase the proportion of women randomised to the better mode of delivery. There are conventional statistical methods of doing this which are commonly used in trials of cancer therapies, to make sure that as many patients have possible have the “best” treatment.

One of the challenges of this study is that we won’t be certain that women are going to deliver preterm (either as a result of preterm labour or as an elective procedure) until very shortly before preterm delivery occurs. There are challenges about asking participants for consent in this situation. We aim to identify women who are going to deliver preterm as early as possible, and let them know about the study. Such women might, for example, be at risk because of a previous preterm birth, or they may present with pregnancy induced hypertension. Many women will not, and we will have to recruit them when they present either in labour, or when elective preterm delivery is agreed. We acknowledge that this is a difficulty and we will use all the existing advice on how to manage this sensitively. Regardless, we will not randomise women to one method of delivery or another until it becomes clear that preterm delivery is likely to occur.

The interventions we will randomise women to are either a plan for a vaginal birth, or a plan for an elective caesarean section. (We will of course exclude women for whom one or other treatment is inappropriate). We think we will need to include around 2200 women, to address our primary hypothesis. We think this study can be done in the UK, recruiting over three years, even if only 25% of eligible women agree to participate.

We very much look forward to hearing your views on the study. Overleaf, we have provided the trial's inclusion and exclusion criteria together with a flow diagram (see Figure: 1). This will hopefully provide you with enough information to take part in the interview. However, we have also attached a protocol which you can dip into if you wish to access further information about the proposed trial.

INCLUSION CRITERIA FOR APPROACHING POTENTIAL PARTICIPANTS

Inclusion criteria (either A or B)

Women at risk of spontaneous preterm labour:

- Previous preterm birth before 34 weeks (spontaneous or induced)
- Cervical surgery (cone biopsy or cold coagulation)
- Short cervix or positive fFN prior to 24 weeks gestation
- Presenting with signs or symptoms of preterm labour (e.g. contractions, lower abdominal pain, mild PV bleeding, show)
- Presenting with preterm PROM

Women in whom a clinician decision has been made jointly by the clinician and the woman for elective preterm delivery between 22+0 and 36+6 weeks gestation

EXCLUSION CRITERIA FOR APPROACHING POTENTIAL PARTICIPANTS

Exclusion criteria

- Maternal or fetal indications for caesarean section

INCLUSION CRITERIA FOR RANDOMISATION

Inclusion criteria (either A or B)

Women 22+0 to 36+6 weeks gestation with signs and or symptoms of labour

Cephalic, flexed breech or extended breech presentation

Live baby in whom it is anticipated resuscitation will be attempted

Women 22+0 to 36+6 weeks gestation in whom elective preterm delivery will be performed in the next 72 hours.

- Cephalic, flexed breech or extended breech presentation
- Live baby in whom resuscitation will be attempted

EXCLUSION CRITERIA FOR RANDOMISATION

- Triplets and higher order multiples
- Diagnosed intrauterine death

Advanced labour such that caesarean section cannot be performed safely (at clinician's discretion)