This document provides a description of a hypothetical individual patient randomised trial which may be conducted in the future. The decision about whether this trial will be taken forward will be informed by feedback from health professionals, including yourself, as well as a consultation exercise with women. **This extended description of the proposed trial is intended for reference only, we do not expect you to read this document in its entirety prior to the interview. The key information on which the interview topics are focussed are contained in the two page summary document which you have also been sent.** During the interview you will be asked whether you think health professionals would be willing to recruit to this trial (and if not, why not) and also what resourcing training and support you think health professionals would need at their sites to deliver the trial if it is taken forward.

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Summary
This protocol describes an individual patient randomised trial comparing planned caesarean section with planned vaginal birth (CASSAVAplus). This design of this trial has been informed by patient and clinician surveys, followed by a Delphi process, to determine the most important questions on mode of preterm birth which should be answered in a clinical trial. The treatment is the "plan" for a specific intervention: analysis will be by intention to treat for planned intervention. Our primary outcome is a neonatal primary outcome, because we believe this is the outcome pregnant women are most concerned about. We will also collect information on women's outcomes, as clearly this is also important for women, families and caregivers on deciding the best mode of delivery for them.

CASSAVAplus is an "individual participant" randomised trial, where participants (pregnant women) are allocated either to the treatments of planned vaginal delivery or planned caesarean section. We acknowledge that some women who plan a vaginal delivery will birth by caesarean section, and vice versa but outcomes will be analysed on an intention to treat basis. For example outcomes women who plan a vaginal delivery will be analysed in that group, regardless of the actual mode of birth. The trial is adaptive, so that, as evidence accumulates, more women are allocated to the "best" treatment. If enough evidence accumulates to be certain that one treatment is better than the other, the trial will be halted, analysed and reported.

BACKGROUND

Preterm birth (birth before 37 weeks gestation) is the single biggest cause of neonatal mortality and morbidity in the UK. Around 7% of babies are born preterm in the UK. Survival to one year of life and rates of disability are inversely proportional to length of gestation – in other words, 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 have remained unchanged[1, 2].

Options for mode of preterm birth

The options for birthing preterm are vaginal delivery or caesarean section. The decision making for clinicians and pregnant women (the 'treatment intervention') is which mode of preterm birth they should plan. It is acknowledged that there will be some cross over following the plan - for example some women who are randomised to planned caesarean section may deliver vaginally before caesarean section can be performed. Additionally some women who plan a vaginal birth may have labour complications (eg significant fetal distress) which mandate caesarean section. Regardless of the plan made, a significant proportion of preterm births are by caesarean section. For example, a review of 1575 consecutive infants

born between 23+0 and 31+6 weeks gestation showed that 57% were born by caesarean section[8]. This is a much higher proportion than for all UK births, where the rate of caesarean section is less than 30%.

Uncertainty about best way to birth preterm for mother and baby

The majority of preterm births follow the premature initiation of spontaneous labour. There is clinical uncertainty about the optimal mode of delivery in this scenario. A minority of women require caesarean section (e.g. those with fulminating pre-eclampsia), and they are not the focus of this study. For the remainder, there is significant clinical uncertainty: some clinicians believe that delivery by caesarean section 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 are similar uncertainties about the best mode of planned preterm delivery. Addressing these clinical uncertainties could significantly improve the health of the public and patients. Rates of intrapartum stillbirth, neonatal and long term mortality and morbidity are higher in the 50,000 preterm babies born in the UK each year compared with term babies.

In addition to these clinical uncertainties, there is very little evidence on the best mode of delivery. There is only one systematic review of randomised trials on this topic: in this systematic review only four studies (involving only 116 women) were considered to be sufficiently robust to be able contribute data to the analysis[3]. There were very little data of relevance to the three main (primary) outcomes for the **baby** considered in the review. For the **mother**, women in the vaginal delivery group had lower rates of puerperal pyrexia (RR 2.98, 95% CI 1.18 to 7.53; three trials, 89 women) and other maternal infection (RR 2.63, 95% CI 1.02 to 6.78; three trials, 103 women). The authors concluded: “There is not enough evidence to evaluate the use of a policy of planned immediate caesarean delivery for preterm babies. Further studies are needed in this area.”

The Cochrane systematic review was updated by the Guideline Development Group for the NICE Preterm Labour and Birth Guideline (2015)[4], which found no new randomised trials. In preparation for this application, we updated this search in October 2017, using the MeSH headings premature birth AND delivery, obstetric AND randomised trial; premature birth AND caesarean delivery AND randomised trial; premature birth AND labor, obstetric AND randomised trial from January 2011. Again, we found no new randomised trials to address the question of the best mode of delivery for women in preterm labour or undergoing planned preterm birth.

Information from observational studies adds to, rather than resolves the controversy. Importantly, observational studies evaluate actual birthing method, and not planned birthing method. (Since women and their caregivers can only plan a birthing method, evidence on actual birthing method not entirely helpful.) Notwithstanding, observational data shows with evidence of worse outcomes[5, 6] better outcomes[7, 8] and no difference[9] for babies delivered by caesarean section, compared with vaginal births. It is plausible that planned delivery by caesarean section could reduce either death or disability in preterm babies compared with the control standard of care of vaginal delivery. Indeed, a 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[8]. Another study has shown that neonatal mortality is lower babies born by caesarean section[10]. Conversely, caesarean section is associated with higher NHS costs and greater complications for the mother[11] and there is conflicting evidence of benefit for preterm babies[3, 5, 6].

It is possible that the optimal mode of preterm birth will differ by subgroups of women and babies. Subgroups that have been mentioned in the preparation of this protocol (by either

our trial team, lay and professional survey respondents, or Delphi participants) include twin compared with singleton pregnancies; different gestational ages; different presentations of the baby (cephalic or breech); babies with signs of intrauterine growth restriction; and babies where the woman is already in preterm labour compared with those in whom labour has not started. Importantly, the consensus at the Delphi was that all these subgroups are important, that any trial should be comprehensive and include any women and baby having a preterm birth.

Although NICE endorses caesarean section for those birthing preterm with breech presentation (extrapolating from randomised trials of term babies, where there are some advantages to delivery by caesarean section[13]), the consensus of the Delphi survey was that the group of babies with breech presentation should also be included.

RATIONALE FOR STUDY

Given the above clinical uncertainties, this protocol describes a trial to answer the question: "Which is the best planned mode of birth, for women birthing preterm". We aim to answer which is best for each of mother and baby, acknowledging that what is best for mother might not be best for baby, and vice versa.

As described above, our interventions are "planned mode of birth" not actual mode of birth. Some women planning a caesarean section will have a vaginal birth before a caesarean section can take place. And we anticipate that in the scenario described in this protocol, that women and caregivers planning a vaginal birth, will opt for a caesarean section if there are clear clinical indications in labour, such as severe and acute fetal distress.

Our outcomes are health outcomes, because we believe that information on these outcomes is crucial for women and caregivers to make informed decisions about optimal mode of delivery. We acknowledge that women's experiences are important, and we anticipate that any clinical trial on the best planned mode of birth would include a qualitative approach to evaluate experiences. In planning the sample size for this trial we have assumed that an absolute difference in health outcomes of 5% for each of the primary maternal and baby outcomes would be sufficient to influence decision making, and that, conversely, an absolute difference of less than 5% in rates of the primary maternal or baby outcome would not be of material significance.

STUDY OBJECTIVES

OBJECTIVES

Primary Objective

The primary objective of this study is to determine in women birthing preterm whether there is 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.

Secondary Objectives

The secondary objectives of this study is to determine, in women birthing preterm, whether there are any differences in any of the secondary clinical outcomes (neonatal and maternal morbidities) or in maternal satisfaction or in healthcare costs those planning a vaginal birth compared with those planning birth by caesarean section.

ENDPOINTS

Primary Endpoint

- Neonatal composite of alive at 6 months after birth or to home discharge (whichever is sooner) without significant intraventricular haemorrhage (IVH) (defined as grade 3 or 4 IVH) or cystic periventricular leukomalacia[1].

Secondary Endpoints

- Maternal – major maternal morbidity (as a composite and individual components:
- postpartum haemorrhage >= 1 litre,
- admission to the main intensive care unit for more than 24 hours
- bowel injury requiring repair
- bladder injury requiring catheterisation for more than 48 hours
- other organ damage
- postnatal anaemia Less than 70g/dl (or requiring a transfusion)
- postnatal infection (sepsis) requiring intravenous antibiotics for more than 48 hours
- anal sphincter injury
- postnatal depression requiring in patient admission
- hysterectomy
- return to theatre for any other reason
- confirmed thromboembolic disease
- posttraumatic stress disorder
- hospital stay > = 7 days

Neonatal outcomes:

- incidence of Apgar scores less than 7 at 1 and 5 minutes
- early (less than 72 hours of life) mortality
- mortality before 6 months of age/discharge home alive
- significant intraventricular haemorrhage (IVH) (defined as grade 3 or 4 IVH)
- cystic periventricular leukomalacia

Costs
costs of major maternal morbidities from recruitment to 6 months postnatally
costs of major neonatal morbidities from recruitment to 6 months postnatally

STUDY DESIGN
CASSAVAplus is an open label adaptive individual patient randomised trial. It is anticipated that it will take 3 months to set the study up, 36 months for recruitment, another 12 months for the outcome data to mature (last patient last visit) and 3 months for final data analysis: four and half years in total.

Individual participants (pregnant women) will be involved from early in their pregnancy (when we will tell them about the study in principle), through the second and third trimester when it becomes apparent that they are at higher risk of preterm birth (when they will be recruited), through the birthing process (where agreement to participation will be reconfirmed) and until six months postnatal (when any final outcome data will be gathered).

CASSAVAplus will take place in NHS obstetric units in the UK and (if there is interest) Ireland.

STUDY POPULATION
NUMBER OF PARTICIPANTS
The planned screening of size is 10,000 women in order to obtain the sample size of 2400 women, recruited in 65 UK NHS obstetric units over a three year period, with up to 12 months of follow up after recruitment (6 months post birth). In total, the study will last 4.5 years.

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)

PARTICIPANT SELECTION AND ENROLMENT

IDENTIFYING PARTICIPANTS

Participants who are at high risk of preterm birth (either group A or group B in 4.1.2) will be identified by their clinical caregiver. The caregiver will give verbal information about the study, and invite the potential participant to get more information, either from a member of the study team, or from written information, or information in some other media.

Additionally, women who may not previously have been identified at high risk, but who present in preterm labour (4.1.4) will also be approached to determine whether they wish to participate.

CONSENTING PARTICIPANTS

Women who fulfil the criteria in 4.1.2 will be recruited into the study. They will be asked whether they wish to complete a consent form at this stage, or whether they prefer to wait until preterm birth is considered likely to occur within the next 72 hours. Women fulfilling the criteria in 4.1.4 will be asked to complete a consent form.

The consent process will be undertaken by clinicians who have had some study specific training. We are cognisant of the challenges of consent in the acute situation, and will use strategies developed by others in these settings, including video information (as in the ASSIST study) and those employed in the GOT-iT study.

Participants will be permitted to consider the information for as long as they wish. For those fulfilling the criteria in 4.1.4, birth may be imminent: if they are unable to make a decision about participation as labour advances they will become ineligible for participation.

INTERVENTION

Planned caesarean section

COMPARATOR

Planned vaginal birth

(Note, if a specific indication for caesarean section develops or is identified in labour, then a caesarean section should be performed. This will not be a protocol violation. If the attending obstetrician would NOT have performed a caesarean section in the same scenario with a term baby, this will be a protocol violation)

SAMPLE SIZE CALCULATION

This sample size has been determined using the entire population cohort. In practice, we will perform subgroup analysis (see below). The point estimate is likely to differ between subgroups, hence subgroup analysis is likely to minimise variability and improve study power.

The incidence of the primary outcome was 29% in the vaginal delivery group and 17% in the caesarean section group in an observational study of babies between 23-31 weeks gestation[8]. Importantly, this comparison was performed by actual (not planned) method of delivery and involved babies at a lower mean gestational age than planned in CASSAVAplus. We have assumed for the purpose of CASSAVA plus that the incidence of the primary outcome will be 20% in the vaginal delivery group and 15% in the caesarean section group. A sample size of 2200 (1100 in each group) will give the study 85% power to identify this absolute difference of 5% in the primary outcome rates in the two groups, if such a difference exists. In practice, will recruit 2400, to allow for modest losses to follow up and dropout rates.

In an average sized delivery unit, where 5000 babies are born each year, 8% will be born before 37 weeks gestation. If one quarter of these are eligible for the study, this means 100 women will be eligible for recruitment in each centre each year. Assuming a participation rate of 25% (to allow for women who do not wish to participate, and scenarios where no personnel trained in study procedures are available, this means that 25 women can be recruited each year from each site. Over a three year recruitment period, with 50 sites (there were 65 in OPPTIMUM), this would result in recruitment of 3550 participants. Hence we are confident that our recruitment target is achievable.

PROPOSED ANALYSES

A full statistical analysis plan will be written before any data are unblinded. Briefly, study data will be analysed on an intention to treat basis. Those who are “not compliant” with the study intervention and those who withdraw will be included in this intention to treat analysis, unless they specifically withdraw consent for their data to be used. We will record the proportion of women who birth by a method other than the one they are randomised to, and the reasons for this – (eg maternal choice, clinical indications etc). Clinically indicated “crossovers” between groups will not be considered as lack of compliance [eg women who are randomised to planned vaginal birth, but in whom a clinical indication for caesarean section arises].

Primary and secondary outcomes will be compared in the two groups. We anticipate that the rate of the neonatal outcome (in both groups) will be strongly influenced by gestation of delivery. For this reason, the primary analysis will be in the subgroups of $\leq$ 28 weeks gestation, 28-32 weeks gestation, and 32 - 36^{+6} weeks gestation. Proportions in each group will be compared using chi squared tests and presented as odds ratios (95% confidence intervals). Continuous data will be compared using t tests or Mann whitney u as appropriate,

and weighted mean difference (95% CI) calculated. Data checking will be used to minimise the amount of spurious or incorrect data; there will be no imputation for missing data.

This will be an adaptive study, to most rapidly determine which treatment allocation is “best”, whilst minimising the number of women recruited into the “worst” treatment group. Initially we will allocate women to each group in a 1:1 ratio. Once the trial starts, interim analyses of the primary outcome will be performed on a regular basis and will be used to determine the ratio of women allocated to each treatment group. As data accumulates, we aim to allocate a greater proportion to the treatment group with the lowest incidence of the primary outcome. Initially we will use the entire cohort for this: as data accumulate, we will differentially modulate recruitment between subgroups. Once there are sufficient data to show an absolute difference in neonatal outcome of 5% or more in any gestational age subgroup at the 99% confidence level (eg $p < 0.01$), recruitment to that subgroup will be halted. Recruitment to the other subgroups will continue. A detailed protocol with rules for stopping and ratio of allocation to treatment groups will be written prior to initiating the study.