Trial Protocol

Induction of labour for predicted macrosomia 'The Big Baby Trial'	
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DoH Disclaimer - The views expressed are those of the author and not necessarily those of the NIHR or the Department of Health and Social Care.

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ABBREVIATIONS / GLOSSARY

Abbreviation	Description
AE	Adverse Event
AES	Advanced Encryption Standard
BMI	Body Mass Index
BBT-RS	Big Baby Trial Research System
CASE	Complier Average Causal Effect
CI	Confidence Interval
CONSORT	Consolidated Standards Of Reporting Trials
CSRL	Clinical Sciences Research Laboratories
CRF	Case Report Form
DM(E)C	Data Monitoring And Ethics Committee
EFW	Estimated Fetal Weight
EQ-5D-5L	European Quality of Life Five Dimension Five Level Scale
GAP	Growth Assessment Protocol
GCP	Good Clinical Practice
GP	General Practitioner
GROW	Gestation Related Optimal Weight
HTA	Health Technology Assessment
LTFU	Lost To Follow Up
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
LGA	Large for Gestational Age
MSLC	Maternity Service Liaison Committee
NHS	National Health Service
NICE	The National Institute for Health Care Excellence
NICHD	National Institutes of Child Health and Human Development
NICU	Neonatal Intensive Care Unit
PEN	Potential Eligibility Number
PGP	Pretty Good Privacy Encryption
PNI	Perinatal Institute
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
R&D	Research and Development

RCM	The Royal College of Midwives
RCOG	The Royal College of Obstetricians and Gynaecologists
RCPCH	The Royal College of Paediatrics and Child Health
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SD	Shoulder Dystocia
SGA	Small for Gestational Age
SOP	Standard Operating Procedure
SSQ	Six Simple Questions
TMG	Trial Management Group
TSC	Trial Steering Committee
VPN	Virtual Private Network
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

1.1 Epidemiology and burden of the condition

Shoulder dystocia (SD) is defined as a vaginal cephalic delivery that requires additional obstetric manoeuvres to deliver the fetus after the head has delivered and gentle traction has failed.[1 2] Potential complications for impacted shoulder for the mother include haemorrhage and third and fourth-degree laceration, and for the neonate include fracture of the clavicle or humerus, temporary or permanent brachial plexus injury, hypoxic ischaemic encephalopathy, and neonatal death.[2] Shoulder dystocia causes physical and psychological trauma to both mother and her baby, as it is an obstetric emergency which requires rapid response and intervention, often with limited time to inform and/or explain to the woman and her birth companion what is happening.

Apart from adverse maternal and perinatal effects, shoulder dystocia is also one of the most common reasons for litigation, with settlement of 250 cases from 2000 to 2010 having cost over £100 Million, or approx. £400,000 per case.[3]

Most but not all cases of SD occur in pregnancies where babies are macrosomic, variously defined as above 4kg, 4.5kg, or >90th customised weight for gestational age centile.

Appropriate management of the condition includes clinical awareness, trained staff and appropriate management protocols and emergency drills. Preventive measures start with antenatal awareness of risk factors, including maternal obesity and diabetes and fetal growth and size.

1.2 Definitions for macrosomia

The Royal College of Obstetricians and Gynaecologists (RCOG) Guidelines 1 identified macrosomia >4.5kg as the weight related pre-labour risk factor for shoulder dystocia and this cut-off limit has been confirmed to have the strongest association in a large study since, using an outcome based approach.[4]

1.3 Measuring macrosomia

A weight-for-gestational age limit (large for gestational age, LGA) is required for antenatal prediction, where the critical weight limit is not yet reached but the fetus is growing in a steep trajectory towards it. To consider a fetal/neonatal weight in relation to maternal size, a customised standard is needed and the customised GROW 90th customised centile has now been found in several studies to identify a significant number of additional pregnancies as being at risk which were not recognised by conventional standards for macrosomia, including absolute weight limits (4 or 4.5kg) and population based weight-for-gestational age centiles.[5-8] Typically, babies that were large according to GROW centiles only, tended to weigh less but were still large in relation to the size of the mother. Importantly, GROW accounts for maternal height, widely thought to be a factor in shoulder dystocia.[9] Furthermore GROW was found to be a better predictor for shoulder dystocia than the UK-WHO birthweight standard.[10] An analysis of data from the international SCOPE study cohort found that adverse birth outcomes were not increased in babies that were appropriately grown by customised standards, even if they appeared to have a birthweight which was high according to conventional weight limits or population based centiles.[7] In our NHS database, 84% of babies with birthweight over

4.5kg, are also identified as LGA by customised GROW centiles; in contrast, using 4.5kg as the cut off will miss another 78% of babies that are LGA using GROW centiles.

Earlier delivery should reduce the baby's weight at birth and hence mitigate the main risk factor. For there to be a meaningful difference in the incidence of shoulder dystocia, and to ensure that any possible benefit is not overlooked, we are aiming for an average birthweight difference of 300g or more. This is consistent with the largest preceding RCT[11] where the early delivery protocol resulted in a reduction of birthweight by 287g (CI:336-238g), however the gestational age difference was not stated.

Looking at the West Midlands database (N=161,936) we ascertained that the weekly increment of weight in LGA pregnancies is approximately 200g. We are aiming for a mean difference in gestational age at delivery of 1.5 weeks to reflect a birthweight difference of 300g. This would be made possible by induction from $38+^{0}$ to $38+^{4}$ weeks gestation, or as soon as possible thereafter, before the expected onset of labour in the control group which, from the West Midlands Database is on average $39+^{4}$ weeks gestation. Induction before $38+^{0}$ would further reduce the risk of shoulder dystocia, but would increase risks of prematurity for the baby.[12-15]

However it is uncertain whether this strategy would actually work, whether shoulder dystocia and its associated complications for mother and baby would actually be reduced, and whether there would be an increase in important side effects such as caesarean sections and associated maternal morbidity. Induction of labour can also be traumatic as it can be associated with prolonged painful labour, and may lead to unplanned operative delivery.

1.4 Summary of the existing evidence

Research into early delivery is timely, in light of conflicting messages from RCOG Guideline[1] on one hand, which found little evidence in favour of early delivery of the LGA fetus, and a recent Cochrane review[16] as well as a systematic review and meta-analysis[17] which found in favour of such intervention. Both of these reviews were largely based on the result of the recent French RCT[11] which contributed most cases in the analysis.

Additional urgency to address this issue exists because of a steep increase in maternal obesity over recent years,[18] and evidence that maternal obesity is associated with a slowing of progress of labour.[19] Although routine data on the prevalence of maternal obesity are not collected in the UK, around half of all women of reproductive age (aged 16-44) are overweight or obese.[20] Women who commence pregnancy overweight or obese, or gain excessive gestational weight in pregnancy, have greater risk of fetal macrosomia.

Given the current lack of evidence of benefit of interventions to manage maternal weight in pregnancy[21] and trials ongoing which are assessing postnatal interventions, evidence is urgently needed on whether induction of labour could reduce maternal and fetal complications and minimise or prevent birth trauma when fetal macrosomia is detected.

1.5 Research question

Does induction of labour at $38+^{0}$ to $38+^{4}$ weeks gestation, in pregnancies with a large for gestational age fetuses, reduce the incidence of shoulder dystocia?

1.6 Need for a trial

An investigation into the value of a preventative intervention in the NHS is urgently required before practice based on limited evidence is adopted in the UK. An intervention which could increase vaginal births may result in better longer-term outcomes for women and their infants, with reduced risk of maternal and fetal birth injuries[11] and potential reduction in subsequent NHS costs, although evidence of this is also needed. Although previous trials have considered management in terms of clinical outcomes, studies have failed to address important outcomes for women.

We are not aware of any evidence of women's experiences of being informed that their pregnancy is large for dates, if and how options for management were discussed with them, the impacts on their perceived physical and psychological health, their infant's health, decisions about infant feeding or their satisfaction with birth. Furthermore, women's experiences and perspectives, of how labour and birth were discussed with them have not previously been considered, nor evidence of benefits and potential harms in the short and long term. This is particularly relevant as short-term follow-up could 'miss' important morbidity outcomes, particularly psychological consequences. It is also unknown how many women would accept such a protocol of earlier delivery, or indeed how many would be content to proceed with vaginal delivery rather that requesting caesarean section, once informed about the increased risk of a large for gestational age baby and associated risk.

It is important that a randomised control trial is performed to generate the data needed for women with large babies to make informed choices about their labour onset, likely mode of birth and potential shorter and longer-term impacts which may be associated with the option selected. This will support the need to explain all potential risks and benefits of management, highlighted by the recent Montgomery judgement,[9] and current maternity policy, which emphasises the importance of involving women in all decisions about their care, to ensure that real 'choice' is truly offered (National Maternity Review England 2016).

1.7 Ethical considerations

In any trial involving pregnant women, consideration is needed on the ethical dimensions of the study. Most importantly, women joining the study need to be informed about the potential risk and benefits of joining the study, and the possible risks and benefits of the alternative approaches to delivery (Table 5-7).

We are mindful, that the nub of the Montgomery Case[9] was that Mrs Montgomery had not been adequately appraised of the risks to the fetus, of a vaginal delivery, for a short stature woman, with a large for gestational age fetus. It is important that all women who may be eligible are offered the opportunity to participate in the study, therefore we will ensure the participant information sheet presents the potential risks and benefits clearly accessible format. Our PPI co-applicants are leading on the development of all participant facing materials, together with, a medical ethicist and obstetricians to ensure women are informed. In addition, our participant information sheet, participant information leaflet, consent form and letter to bereaved women have been reviewed and revised by editors from the Plain English Campaign and they have all received a Crystal Mark.[22] Translations will be available for women not fluent in English/Welsh. We will also develop a web based resource for women who would like more detailed information.

Table 5 Risks of Vaginal Delivery with a Big Baby

Risks to Baby	Risks to Woman
We do not know for certain how many big babies will experience shoulder dystocia. We estimate that up to one in 25 big babies will experience shoulder dystocia and will need extra help to deliver their shoulders. Most babies who experience shoulder dystocia will have no long-term effects.	Sometimes the labour can be longer for bigger babies. In the UK 15 in 100 women who are planning to have a vaginal birth will need to have an emergency Caesarean section (please see table 7 below). Some women may need to have a forceps or ventouse (suction) delivery.
One in 10 babies who experience shoulder dystocia will have stretching of the nerves in the neck. This is called brachial plexus injury and can causes loss of movement in the baby's arm. The most common type of brachial plexus injury is Erb's palsy. For one in 10 babies with a brachial plexus injury, the loss of movement will be permanent.	Three in 100 women will have a tear to their vagina that extends into the back passage. This could affect their bowel control if the tear is not identified and repaired.
In babies who experience shoulder dystocia, one in 10 may have a fracture to their collarbone. Four in 100 babies who experience shoulder dystocia may have a fracture to their arm. These heal well.	Sometimes women with a big baby may experience heavier bleeding after the baby is born. In rare cases, some women may need a blood transfusion.
Very rarely, a baby may suffer brain damage if they did not get enough oxygen during the birth because of shoulder dystocia.	

Table 6 Risks of Induction of Labour with a Big Baby

Risks to Baby	Risks to Woman
Inducing labour at 38 weeks is safe for the baby. There is some evidence that inducing labour earlier can lead to jaundice in the baby. This usually has no long-term effects.	Often women who have labour induced will find their labour is longer and more painful than for women who go into labour naturally.
This trial aims to find out if inducing labour early, at 38 weeks, reduces the chance of shoulder dystocia. If the baby experiences shoulder dystocia, the possible complications are shown in table 1.	If the woman has a vaginal birth the risks are shown in table 1. Having labour induced can increase the risk of a tear to the vagina that extends into the back passage.
Babies who are born one or two weeks early are slightly more likely to need extra help at school, for example help with reading. This would affect less than one baby in every hundred born at 38 weeks compared to 40 weeks.	Sometimes if the women is induced she may need an emergency Caesarean section, and the risks of this are shown in table 7.

Table7 Risks of Caesarean Section

Risks to Baby	Risks to Women
One in 10 babies may experience breathing difficulties. Some of these babies will need to have treatment for this in the neonatal unit.	Nine in 100 women report persistent pain at the wound site and in their abdomen for a few months following a Caesarean section.
One to two babies in 100 will have a cut to their skin.	Five in 100 women will need to be readmitted to hospital following a Caesarean section. This might be because their wound isn't healing or because they have an infection.
Some women report that it takes longer to bond with their baby after a Caesarean section.	Six in 100 women will have an infection after a Caesarean section. The infection may involve the scar, their bladder or kidneys, or the lining of their womb.
	One in 1000 women may have an injury to their bladder or bowel during a Caesarean section. This will need repairing.
	Five in 1000 women bleed heavily (haemorrhage) during a Caesarean section. Some of these women will need to have a blood transfusion. In some cases, a woman may need to have a hysterectomy (where the womb is removed) to control the bleeding.
	Five in 1000 women may need to have further surgery after their Caesarean section.
	Six in 10,000 women will have a blood clot in their leg or lung following a Caesarean section.
	One in four women who have a Caesarean section will need another Caesarean section if they attempt a vaginal birth in their next pregnancy. If they have a Caesarean section and decide to try a vaginal birth in their next pregnancy, they would need extra monitoring in labour as there is a risk (one in 200 women) that the scar in the uterus can open during labour.
	If the woman has a Caesarean section in this pregnancy, in their next pregnancy

	there is increased chance of a stillbirth. This is uncommon.
	If the woman has a Caesarean section in this pregnancy and the placenta is low in their next pregnancy, there is an increased chance that the placenta will not come away easily after the baby has been born. This can cause serious bleeding and may mean they need to have a hysterectomy. This is uncommon, but the chance increases with each Caesarean section.

Women and their partners will be given as much time as they need to consider participating in the trial and have the opportunity to discuss participation and ask questions with specially trained clinicians including obstetricians, research midwifes and unit midwifes.

We will ensure that all identifiable data is anonymised and treated as confidential. All data will be stored securely and held in accordance with all applicable UK legislation and WCTU Standard Operating Procedures (SOPs).

2. TRIAL DESIGN

2.1 Trial summary and flow diagram

- This is a multicentre prospective, individually randomised controlled trial with an integrated qualitative process evaluation and economic evaluation. Women ≥18 years with a fetus above 90th customised centile on ultrasound scan at 35+^{0} to 38+^{0} weeks gestation, with a cephalic presentation will be eligible. Women with multiple pregnancy, breech, or transverse lie presentation, induction of labour contra-indicated, fetus with known serious abnormality, home birth or elective caesarean section already planned, caesarean section or induction indicated due to health conditions such as cardiac disease or hypertensive disorders, women taking medications and/or insulin therapy for diabetes or gestational diabetes (women with these conditions who are not taking medication are eligible), women with a current diagnosis of a major psychiatric disorder requiring antipsychotic medications, or women unable to give informed consent e.g. learning or communication difficulties that prevent understanding of the information provided will be excluded. We will also exclude prisoners, Women with a previous stillbirth, previous neonatal death ≤28 days or current intrauterine fetal death. Women will be randomised to either the booking of induction of labour at 38+^{0} – 38+^{4} (intervention) standard care (control). Outcomes are the incidence of shoulder dystocia (primary outcome) and birth trauma, fractures, haemorrhage, caesarean section rate, neonatal asphyxia and length of stay, maternal and paternal experience survey and a health economic analysis (secondary outcomes). Composite outcomes for 1] intra-partum birth injury, 2] prematurity associated problems and 3] maternal intra-partum complications will be reported (secondary outcomes). The flow diagram is presented in figure 1.

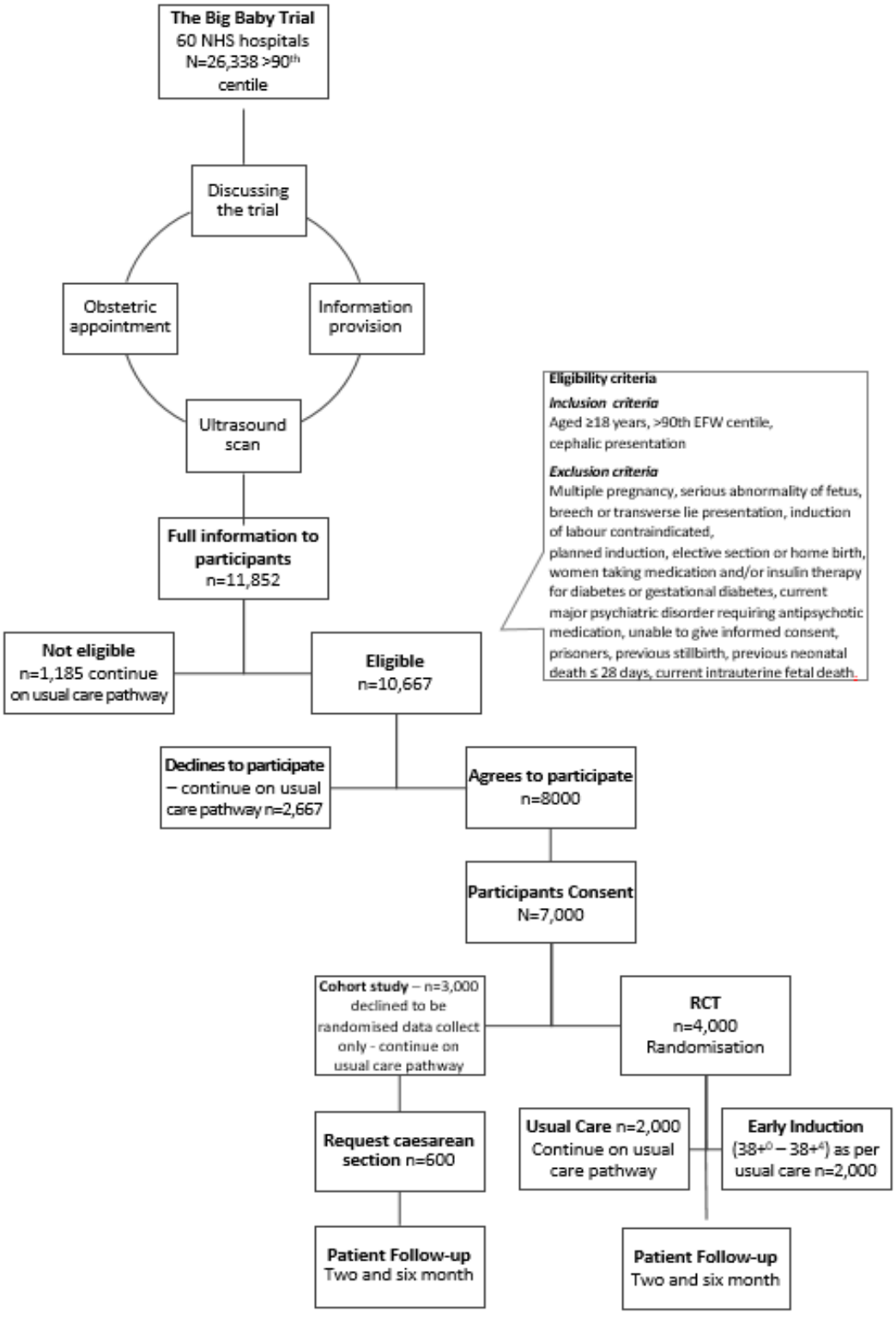

Figure 1 – Flowchart for the Big Baby Trial

2.2 Aims and Objectives

2.2.1 Aim

To investigate the potential benefits and harms of induction of labour in large for gestational age fetuses at $38+^0$ to $38+^4$ weeks gestation.

2.2.2 Primary objective

To determine the effectiveness of induction at $38+^0$ to $38+^4$ weeks gestation in reducing the incidence of shoulder dystocia.

2.2.3 Secondary objective

To evaluate whether: standard care increases the risk of neonatal birth injury, induction increases the risk of infant complications related to prematurity and induction increases the risk of birth injury to the mother.

2.3 Design

A prospective, multi-centre randomised controlled trial of induction of labour at $38+^0$ to $38+^4$ weeks gestation versus standard care, of fetuses that are large for gestational age (>90^{th} customised centile estimated fetal weight (EFW) according to ultrasound at $35+^0$ to $38+^0$ weeks).

A parallel cohort study of women who decline to be randomised. The objective of this cohort group is to confirm generalisability of both the baseline data and the primary outcome data and will comprise of two sub-groups. One sub-group will be for women requesting a planned caesarean section, and one sub-group is for women not planning a caesarean section.

A process evaluation to identify any barriers to efficient recruitment of sites, recruitment and follow-up of participants and fidelity to study protocol will be undertaken in the pilot phase with women and clinicians participating in the study.

Qualitative interviews with women and their partners and/or birth partners.

A parallel heath economic evaluation will assess the cost-effectiveness of the intervention.

2.4 Intervention

The booking of induction of labour at $38+^0$ to $38+^4$ weeks gestational age (266-270 days); method of induction to follow standard practice at participating obstetric unit.

2.5 Control

Standard care.

2.6 Target population

Women with a fetus with an estimated fetal weight >90^{th} customised centile at $35+^0$ to $38+^0$ weeks gestation.

2.7 Setting
60 NHS obstetric units in the UK.

2.8 Eligibility criteria
Potential participants are women with LGA fetuses at $38+^0$ to $38+^4$ weeks gestation, who meet the following eligibility criteria:
2.8.1 Inclusion criteria
- women aged 18 years or over
- women with a fetus above 90^{th} customised estimated fetal weight centile on ultrasound scan at $35+^0$ to $38+^0$ weeks gestation
- women with a cephalic presentation.

2.8.2 Exclusion criteria
- multiple pregnancy
- pregnancy that is breech or transverse lie presentation
- induction of labour contra-indicated
- fetus with known serious abnormality
- home birth or elective caesarean section already planned*
- caesarean section or induction indicated due to health conditions such as cardiac disease or hypertensive disorders*
- women taking medications and/or insulin therapy for diabetes or gestational diabetes; women with these conditions who are not taking medication are eligible
- current diagnosis of major psychiatric disorder requiring antipsychotic medication.
- women unable to give informed consent e.g. learning or communication difficulties that prevent understanding of the information provided
- prisoners
- Previous stillbirth
- Previous neonatal death ≤28 days
- Current intrauterine fetal death.

** If the woman is otherwise eligible for the trial, and was given the Participant Information Sheet prior to booking a planned caesarean section or induction (for suspected LGA baby), she is eligible to be in the cohort group.*

2.9 Outcome measures
All of the within hospital outcomes will be obtained from routinely collected data in each unit. In the event of an unplanned home birth, or birth at another unit, we will collect data from the Ambulance Trust, General Practitioner, or Hospital Trust as appropriate.

At baseline, prior to randomisation we will collect routine demographic data; age, ethnicity, parity, height and smoking status

For women in the parallel cohort study who are planning to deliver by caesarean section the same data (neonatal, infant, and maternal outcomes including the two and six month follow-up questionnaires) will be collected as those who agreed to be randomised. For women in the cohort group not planning a caesarean section a reduced dataset will be collected, see section 2.9.2.5. In addition, for both cohort groups, we will ask for the reasons for declining study participation.

2.9.1 Primary outcome measure

Incidence of shoulder dystocia, definition by (RCOG) as, '*a vaginal cephalic delivery that requires additional obstetric manoeuvres to deliver the fetus after the head has delivered and gentle traction has failed*'. Shoulder dystocia will be confirmed by a notes review, undertaken by an independent expert panel; data on management of shoulder dystocia and its potential complications are an important performance metric for maternity units and will be recorded reliably in the notes.

2.9.2 Secondary outcome measures

2.9.2.1 Fetal outcomes

Intrapartum:

- time recorded between delivery of the head and delivery of the body
- time in labour ward
- time from commencement of active second stage of labour until fetal expulsion
- stillbirths.

Neonatal:

- neonatal death
- birth weight
- gestation at birth
- Apgar score at five minutes
- fractures
- brachial plexus injuries
- admission to the neonatal unit / duration of stay
- hypoxic-ischaemic encephalopathy
- use of phototherapy
- respiratory morbidity
- hypoglycaemia.

Infants:

- proportion under specialist medical care at two months for a problem related to intra-partum experience
- maternal report of infant health concerns at six months
- in hospital health care costs
- hospital readmission within 30 days of postnatal inpatient discharge.

2.9.2.2 Maternal outcomes:

Intrapartum:

- duration of hospital stay prior to delivery
- mode of delivery
- perineal tear (episiotomy or spontaneous 1st to 4th degree perineal tear)
- vaginal/cervical laceration or tear
- primary postpartum haemorrhage (≥500ml)
- retained placenta
- death.

Post-partum:
- sepsis
- fever (>38.0°c)
- duration of hospital stay after delivery
- uptake of breastfeeding
- hospital readmission within 30 days of postnatal inpatient discharge.

2.9.2.3 Longer term outcomes:
Women's physical and psychological health and satisfaction with delivery:
- Experience; six simple questions (SSQ) at two months[23]
- Duration of exclusive breast feeding at two and six months
- Health-related quality of life (EQ-5D-5L) at baseline*, two and six months[24] (appropriate licences to allow reproduction of these questionnaires will be obtained)
- Edinburgh post-natal depression scale at baseline*, two and six months[25]
- Impact of Events Scale two months[26]
- Post-partum bonding questionnaire at two months[27]
- Maternal report of infant health at two and six months
- Urinary incontinence ICIQ-UI short form assessed at baseline*, two and six months[28]
- Faecal incontinence assessed at baseline*, two and six months
- Sexual function at baseline and six months
- Maternal and infant death at six months from HES-ONS linked mortality data. Obtain if the six month follow-up is not completed.
- Participant health resource used for economic analysis for mother and baby at two and six months

All participants will be asked to complete questionnaires, at two and six months post delivery, if they have not previously withdrawn. Participants will receive reminders to complete the questionnaires, either by text or email. If participants have not responded to the questionnaires within 6 weeks of the first questionnaire being sent to the participant, efforts will be made to collect a core set of data by telephone. These core data will include:
- Breastfeeding status at two and six months
- Health-related quality of life (EQ-5D-5L) at two and six months[24]
- Maternal report of infant health at two and six months
- Maternal report of her own health at two and six months

* Within the cohort, only women who deliver by planned caesarean section are required to complete baseline patient reported outcome measure questionnaires

Responses from the Two Month Questionnaire will be reviewed to identify babies who have potentially sustained harm relating to a birth injury. We will request relevant data from site for those babies identified and, blind to treatment allocation, an adjudication committee will classify these as delivery related/not delivery related and for those that are delivery related those likely to have a substantial long term impact and those that are minor or likely to be short lived.

In the event of the death of a baby, no questionnaires will be sent to the bereaved family.

2.9.2.4 Composite outcomes

- **Intra-partum birth injury:** one or both of fractures or brachial plexus injury.
- **Prematurity associated problems:** one or both of use of phototherapy or respiratory support.
- **Maternal intra-partum complications**: one or more of 3rd or 4th degree perineal tear, vaginal / cervical laceration or tear, or primary postpartum haemorrhage.

2.9.2.5 Cohort Data

For participants not requesting a planned caesarean section, the same baseline data as the randomisation group will be collected to include

- Demographics (maternal age, parity, height, weight, ethnic origin)

Minimal outcome data will be collected to include:

- Onset of labour type
- Final mode of delivery
- Shoulder dystocia
- Baby outcome (stillbirth, sex, weight, gestation at birth, customised centile at birth)

2.10 Sample size

2.10.1 Incidence of the primary outcome

The true incidence of shoulder dystocia in our population of interest is uncertain. The data is not included as part of NHS digital's summary of national maternity statistics.

2.10.2 Sample size - randomised controlled trial

The target sample size is 4,000, based on the incidence of "serious shoulder dystocia" in the control arm of the most recent and largest previous trial 16/411 (3.9%). This was defined as: 'difficulty with delivery of the shoulders not resolved by McRobert's manoeuvre,' which is close to our definition of shoulder dystocia: 'a vaginal cephalic delivery that requires additional obstetric manoeuvres to deliver the fetus after the head has delivered and gentle traction has failed.' The average gestation at randomisation in the Boulvain trial[11] was <38 weeks; we might, therefore expect a slightly higher incidence of shoulder dystocia in our population, where we expect delivery to be at a later gestational age and hence babies will be larger, so we have rounded this to 4%.

To show a 50% reduction to 2%, at a 5% significance level with 90% power, requires data on 1,626 women in each arm; 3252 in total. In the Boulvain study,[11] relative risk for "significant shoulder dystocia" was 0.32 (95% CI 0.12 to 0.85). Thus, a 50% reduction is a plausible target that would be considered clinically worthwhile. In the Boulvain study[11] 7.6% (31/408) of those in the intervention arm went into spontaneous labour prior to induction. This is commensurate with our prediction that 7% of our participants will go into spontaneous labour prior to induction, giving further reassurance that we are seeking a plausible effect size.

We are using a more stringent definition of shoulder dystocia than the composite primary outcome used by Boulvain et al., in their primary analysis and the relevant Cochrane review that reported the incidence of shoulder dystocia to be 6.8% in the control group.

There is considerable uncertainly around our sample size estimate. An allowance is needed for loss to for the primary outcome; this should be very small. There may be effects from clustering by site that need to be accounted for; although our analysis of data from the Perinatal Institute indicates that the intra-cluster correlation coefficient for being large for gestational age is <0.00055 suggesting that any effect will be negligible. Most importantly, however, the sample size calculation is very dependent on the baseline rate of shoulder dystocia in our population of interest. For uncommon events such as shoulder dystocia even quite small differences in incidence can have substantial impact on size. For all of these reasons, we have inflated our initial sample estimate of 3252 by 23% to 4,000.

Given the uncertainties around this estimate we will perform a key event analysis, once we have primary outcome data on 1,000 deliveries. We will also ask the DM(E)C to advise on whether any sample adjustment is needed, based on the incidence of shoulder dystocia in the control arm.

2.10.3 Sample size – cohort study

We estimate that 50% of potentially eligible women will decline to participate in the trial. We will seek written consent to collect data on these women and estimate 3,000 will agree, including the estimated 20% who will opt for elective caesarean section.

2.11 Internal pilot

We will assess recruitment when ten sites have been recruiting into the RCT for three months to review the current recruitment rate in those sites. Further sites will continue to open to recruitment during this time. This will provide key data on recruitment rates and inform the decision to progress to the main study. The crucial progression criterion will be a projected recruitment rate of 60 participants per week once all sites are recruiting. We will achieve this either by demonstrating a rate of ≥1 per week from each of our pilot sites, or if there is a shortfall in weekly recruitment by demonstrating a compensatory increase in sites willing to join the study. In the event that the number of women invited to join the study who choose to opt for an elective caesarean section prevent adequate recruitment, or another unsurmountable barrier is identified from the formative process evaluation, we will not proceed to the main study.

2.12 Process evaluation

Within the internal pilot we will undertake an independent formative process evaluation to identify any barriers to efficient recruitment of sites, recruitment and follow-up of participants and fidelity to study protocol. Given the complexity of issues women may need to consider prior to deciding to participate, the views of their partner/nominated birth supporter, and views of clinicians expected to implement the trial protocol, the process evaluation will reflect MRC guidance for complex interventions and need to consider practical effectiveness and key uncertainties[29]. Barriers to recruitment and implementation of the trial protocol will be identified and addressed prior to the main trial.

Interviews with up to 10 clinicians (2-3 from the same three pilot study sites (for example, midwifery labour ward co-ordinators, matrons, leads for antenatal care, Specialty Registrars and consultant obstetricians) will explore barriers to clinician adherence to the study protocol, including arranging and timing of induction, impacts on workload, implications of women's decision making re labour and birth on being advised of a large for dates baby, implications for postnatal care and transfer home. Interviews will take place at the study site, in an office or other quiet room to protect confidentiality.

2.13 Qualitative interviews

We will undertake telephone or face-to-face interviews up to 10-15 women across both groups at three pilot sites (up to 10 women from each group (control, intervention and cohort) at two months postpartum, purposively selected to reflect age, parity and ethnicity) to explore their experiences of participating, including their reasons for taking part (and factors that facilitated/hindered this), experiences of recruitment and randomisation; expectations/understanding of the study and its aims, views of how information on delivery options were presented; if the risks of having a large for gestational age baby were explained and the extent to which women felt informed about their choices (given the recent Montgomery ruling)[9], and reflections on their birth and postnatal recovery experiences. We will ask women for permission to approach their partner to invite them to be interviewed to explore their experiences of supporting the woman in her decision making and views of options for managing birth, aiming to interview 6-9 partners.

All interviews will be audio recorded with participant's permission. We will also interview up to 25-30 women, purposively selected from 4-5 study sites, who have completed study follow up, to explore their experiences of participating in the study, including reasons for taking part (and factors that facilitated/hindered taking part), experiences of recruitment and randomisation (expectations/understanding of the study and its aims, views of how information on birth options, risks of having a large for dates baby for maternal and infant health were explained), views on outcomes of interest, and views of potential decision making for a future pregnancy.

2.14 Informed consent

Women joining the study will be informed about the potential risk and benefits of participating, and the possible risks and benefits of the alternative approaches to delivery. Information about the study, the participant information sheet and participant consent form will be assessed for clarity by the Plain English Campaign and a Crystal Mark will be obtained.

It is very important for this study that we include women who are not fluent in written and/or spoken English. We will work with our participating units to identify the minority languages in which they already provide printed material and arrange for study recruitment and consent materials translated into these languages. Translators will be required during recruitment to allow those who are not sufficiently fluent in spoken English to be adequately informed about the trial. For those women who are fluent in spoken English and unable to self-complete baseline questionnaires, the research midwife will help them to complete these.

All women will have as much time as they need to consider participating in the trial, have the opportunity to discuss participation, ask questions and consult with health care professionals, family and friends.

A web based resource will also be available containing all participant facing materials, an information sheet about the data we are collecting and why we are collecting it, further information about shoulder dystocia, study publications and links to key organisations are available from the project website at: https://www2.warwick.ac.uk/fac/med/research/ctu/trials/bigbaby.

Written informed consent must be sought by a medically qualified doctor or midwife who is delegated to do so before the woman can be recruited into the trial.

2.15 Randomisation

Randomisation will be provided by WCTU using an on-line web application accessible to all recruiting sites. If for any reason the on-line service is not available, a backup telephone service will operate week days between 9:00 and 17:00. Women will be randomised using minimisation, balancing site, fetal weight centile (≤95th EFW centile, >95th EFW centile) and maternal age (≤35 years of age, >35 years of age).

WCTU randomisation service (Mon-Fri 09:00hrs - 17:00hrs)
Telephone [024 7615 0402] Fax [024 7615 1586]

To ensure allocation concealment, randomisation will only take place once all baseline data have been collected. Women will be randomised to either the booking of induction ($38+^{0}$ - $38+^{4}$) or 'standard care' and will be informed immediately of the randomisation outcome.

Details of the women's participation in the trial will be sent to her General Practitioner together with a copy of the participant information sheet. Details will also be recorded in the participant's hospital notes.

2.16 Post randomisation withdrawals and exclusions

In accordance with the Declaration of Helsinki, each participant is free to withdraw from the research study at any time (including follow-up) without providing a reason and without prejudice, if they so wish. Women are informed of their rights in the participant information sheet. Unless a women explicitly withdraws their consent, they and their infant will be followed-up wherever possible and data collected as per the protocol until the end of the trial. Should a women decide to withdraw after randomisation, after the intervention or should the investigator(s) decide to withdraw the participant, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. The reason for withdrawal will be recorded in the Case Report Form (CRF). If the reason for withdrawal is an Adverse Event (AE), monitoring of the participant and infant will continue until the outcome is evident. The specific event will be recorded in CRF.

2.17 End of trial

The trial will end when the database is locked following data entry from the last follow-up. The trial will be stopped prematurely if:

1. Mandated by the Ethics Committee.
2. The TSC, based on the recommendations from the DM(E)C, decide the trial should end.
3. HTA funding ceases.

The HRA Research Ethics Committee will be notified in writing within 15 days if the trial has been concluded or terminated early.

3. METHODS AND ASSESSMENTS

3.1 Participant recruitment

The configuration and organisation of obstetric services in the NHS varies locally and regionally. With input from expert clinicians and midwives on the TMG and in consultation with our pilot obstetric units, we have found differences in service provision and obstetric care pathways. For example, some women have an ultrasound scan and appointment with the care team on the same day, whilst in other units these occur separately. In some units the ultrasonography will be performed by midwives and in other units by radiographers. Also, women with LGA babies present in different ways.

Some women will be identified from serial fundal height measurements or have serial ultrasound scans and understand early on, through discussions with their care team, that there is a possibility of having a LGA baby. Others will present unexpectedly, following an ultrasound scan for another reason, such as, a raised BMI, a medical condition, reduced fetal movements, low lying placenta or polyhydramnios etc.

The Growth Assessment Protocol (GAP) programme surveillance system, which is implemented in 84% of all NHS Trusts and Health Boards in the UK will be used to plot the women's fundal height measurements on a Gestation Related Optimal Weight (GROW) Chart. A fetus above the 90th customised centile indicates referral for a confirmatory ultrasound scan. Some women will be identified from serial fundal height measurements or have serial ultrasound scans and understand early on, through discussions with their care team, that there is a possibility of having a LGA baby. Others will present unexpectedly, following an ultrasound scan for another reason, such as, a raised BMI, a medical condition, reduced fetal movements, low lying placenta or polyhydramnios etc. Therefore, in order to minimise disruption to women's standard care pathway and the usual running of obstetric services and optimise recruitment to the trial, potentially eligible women will be identified via a number of different routes. Women can be identified by clinicians including midwives, obstetricians or radiographers, and in ante-natal clinics, at their ultrasound scan, in labour ward triage or fetal well-being day assessment units.

The trial can be discussed and information provided to potentially eligible women who are identified as having an LGA fetus >90th centile any time between 28+^{0} and 38+^{0} weeks gestation. This will help provide as much time as possible to consider participating in the trial, have the opportunity to discuss participation, ask questions and consult with health care professionals, family and friends. Trial posters and information leaflets will be available to introduce women to the trial at the earliest opportunity. Full trial information provision via a participant information sheet and trial discussion will be undertaken by a medically qualified doctor or midwife who has been delegated to do so.

Additionally, the consultant/consultant midwife*, or doctor acting on behalf of the consultant, who is in charge of the women's care will be required to provide 'obstetric confirmation' in order to confirm that the woman is medically suitable to be entered into the trial and receive either a booking for induction of labour or standard care. This could be completed anytime from 28+^{0} weeks gestation, but must be completed prior to randomisation between 35+^{0} and no later than 38+^{0} weeks gestation. If the consultant, or

doctor acting on behalf of the consultant is not available to sign the recruitment checklist themselves prior to randomisation (e.g. located at a different site), the doctor confirming eligibility can gain verbal obstetric confirmation of medical suitability and can sign and date the recruitment checklist in anticipation of written obstetric confirmation. The discussion with the obstetrician/doctor responsible for the women's care must be contemporaneously documented in the patients' medical records and the recruitment checklist signed and dated by the doctor confirming eligibility on their behalf. The obstetrician/doctor providing obstetric confirmation must then sign the recruitment checklist at a later date, which may be post randomisation. Written confirmation should be sought as soon a practically possible.

A confirmatory ultrasound scan will be performed between $35+^{0}$ to $38+^{0}$ weeks gestation to confirm the fetus is >90^{th} centile after which confirmation that the women meets all of the eligibility criteria will be confirmed by a doctor named on the delegation log by completing the eligibility form. At this point consent can be sought by a medically qualified doctor or midwife delegated to so, and if obtained, the baseline data collected and randomisation performed.

*Consultant midwife for the purposes of this trial is defined as - a senior clinical midwife, who is practice based and provides expert specialist care in a defined area of midwifery/maternity care and who has the job title 'Consultant Midwife'. Consultant midwives are responsible for leading research and evaluation, education and training within their area of expertise, as well as demonstrating professional leadership and consultancy.

Table 8 – Research Schedule

Key elements	Gestational age (weeks / days)																		Postnatal follow-up (months)					
	28	29	30	31	32	33	34	35	36	37	38+0	38+1	38+2	38+3	38+4	38+5	38+6	39	40+	1	2	3	4	5	6
Discussing the trial and information provision[1]	●	●	●	●	●	●	●	●	●	●	●														
Obstetrician appointment	●	●	●	●	●	●	●	●	●	●	●														
Research midwife appointment	●	●	●	●	●	●	●	●	●	●	●														
Ultrasound scan								●	●	●	●														
Confirm eligibility[2]								●	●	●	●														
Obtain consent[3]								●	●	●	●														
Baseline data collection/Randomisation								●	●	●	●														
Intervention – an appointment for induction											●	●	●	●	●										
Control – standard care								●	●	●	●	●	●	●	●	●	●	●	●						
Cohort study								●	●	●	●	●	●	●	●	●	●	●	●						
Follow-up[4]																				●	●			●	●

● Indicates the time-frame to undertake a key element

Indicates the earliest a key element can start

[1] **Discussing the trial and information provision:** Women may be introduced to the study via trial posters and information leaflets. Full trial information provision via a participant information sheet and trial discussion will be undertaken by a medically qualified doctor or midwife delegated to do so.

[2] **Eligibility** must be confirmed by a medically qualified doctor delegated to do so

[3] **Obtain consent** to participate in the trial will be undertaken by either a medically qualified doctor or midwife delegated to do so

[4] **Two and Six Month Follow-up** not needed for cohort participants not planning a caesarean section.

4. ADVERSE EVENT MANAGEMENT

We will follow WCTU's SOP 17 part 2 on 'Safety' for all Adverse and Serious Adverse Events. Serious Adverse Events will be collected from the time of randomisation until 30 days after initial discharge following delivery. No Serious Adverse Events will be collected after 30 days following initial discharge from hospital following delivery.

Women will be asked about any Adverse or Serious Adverse Events on the two month follow-up questionnaires. If potential Serious Adverse Events are identified on the two month questionnaire as occurring within the 30 day post discharge timeline, these will be reported on the Serious Adverse Event Form; details of any other Adverse Events or Serious Adverse Events will be recorded as outcomes in the questionnaires and not reported.

Serious Adverse Events will not be collected for any of the cohort participants.

4.1 Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with this treatment/intervention. For this trial, only AEs (unintended sign, symptom, or disease) affecting the woman or her baby which may potentially be related to the pregnancy, delivery or care of the neonate will be collected.

Adverse Events will be collected for participants in the Randomised Controlled Trial group, and cohort participants who are electing to have a planned Caesarean section. The Adverse Events will be collected from recruitment up until the initial discharge from hospital following delivery. AEs that occur in either the woman or infant should be recorded as part of the routine data collection on the Case Report Form (CRF). If there are in-patient or out-patient hospital visits in the 30 days after initial discharge following delivery, these will be collected at the 30 day unscheduled readmission form in the Case Report Form.

Table 9 contains some common AEs in this population where data are collected as outcomes and these data do not need to be duplicated in the AE log.

Table 9 – Example Adverse Events already collected as outcomes via the CRF

Woman
Increased duration head to body delivery interval
Increased duration of first stage of labour
Increased duration of second stage of labour
Operative delivery, forceps, ventouse, caesarean section
Shoulder dystocia
Episiotomy
First or second degree tear
Post-partum haemorrhage at delivery <1000ml
Blood transfusion due to delivery
Fever >38.0°C in labour or within 24 hours post-partum

Retained placenta, manual removal
Baby
Low APGAR score (1 or 5 minutes)
Hypoglycaemia prior to discharge following birth
Neonatal jaundice prior to discharge following birth
Hypoxic-ischaemic encephalopathy prior to discharge following birth
Seizures in the first 24 hours after birth

4.2 Serious Adverse Events

A Serious Adverse Event (SAE) is an AE that fulfils one or more of the following criteria:

1. results in death
2. is immediately life-threatening
3. requires hospitalisation or prolongation of existing hospitalisation
4. results in persistent or significant disability or incapacity
5. congenital abnormality or birth defect (these will not be reported as an SAE for this trial as it is extremely unlikely that the intervention would affect congenital abnormalities/birth defects; these will be collected as a study outcome)
6. requires medical intervention to prevent one of the above, or is otherwise considered medically significant by the investigator

SAEs that occur in the woman or infant detected by site staff need to be reported to WCTU within 24 hours of site staff becoming aware of the SAE. WCTU can be informed by a telephone call or email to the Trial Management Team (contact details in Table1). There is no requirement for the initial report to be fully completed, additional data can be forwarded to the Trial Management Team as it becomes available. If SAEs are identified by the Trial Management Team, for example as a result of responses to Questionnaires, the relevant site staff will be informed, and requested to provide additional data as appropriate.

There are a number of events that would meet a definition of SAE that are relatively common in pregnancy and therefore for the purposes of this trial these events **will not be** reported as SAEs. Details of SAEs exempt from reporting are listed in Table 10, but these must however be collected in the relevant sections of the CRF as they are study outcomes and comparative rates will be monitored by the DM(E)C.

Table 10 – SAE reporting requirements

	Expected SAEs that **do not** require reporting (recorded in the CRF)
Woman	Antenatal hospital admission related to pregnancy or admission to hospital for delivery
	Third degree tear
	Fourth degree tear
	Cervical laceration
	Sepsis in labour (and prophylactic antibiotics for the infant post-delivery)
	Post-partum haemorrhage at delivery ≥1000ml
	High EPDS, a score of 13 or over
Infant	Clavicle fracture
	Humeral fracture
	Brachial plexus injury
	Congenital abnormalities or birth defects
	Hospitalisation/prolongation of hospitalisation for respiratory tract infections
	Hospitalisation/prolongation of hospitalisation for jaundice
	Hospitalisation/prolongation of hospitalisation for urinary tract infections
	Hospitalisation/prolongation of hospitalisation for weight loss lasting less than 5 days
	Hospitalisation/prolongation of hospitalisation for reflux
	Hospitalisation/prolongation of hospitalisation for constipation
	Hospitalisation/prolongation of hospitalisation for feeding support

Some examples of SAEs that **do** require immediate reporting are described in **Table 11.**

Table 11 – SAE reporting requirements

	SAEs that **do** require immediate reporting to WCTU
Woman	Maternal death
	In-patient admission and/or readmission* to intensive care or high dependency unit at any time during pregnancy/postnatal period
	Re- admission to hospital within 30 days of initial post-natal discharge unless listed in Table 10
	Antenatal in-patient admission **not** related to pregnancy
	Transfer out of the maternity unit for further inpatient care
	In-patient admission to a mental health unit
	Symphysiotomy
	Any other event that meets the definition of an SAE and isn't listed in Table 10
Infant	Still birth
	Infant death
	In-patient admission to neonatal unit
	In-patient re- admission to hospital within 30 days of initial postnatal discharge, except for conditions noted in Table 10.
	Any other event that meets the definition of an SAE and isn't listed in Table 10

* A hospital admission is defined here as an overnight stay in the hospital.

4.3 Assessing Serious Adverse Events for causality and expectedness

For any adverse events that fulfil the criteria for 'serious' and require immediate reporting (as per Table 11), a clinical assessment of causality should be made as to whether the event is related to the booking of or induction of labour (see Table 11). Causality must be assessed by a clinical doctor who has been delegated this responsibility on the study delegation log. Professors Quenby or Bick will review the event and assess causality on behalf of the sponsor, in addition to the clinical assessment made at site.

If either the site or the sponsor determine that there is a possible, probable or definite relationship to the intervention, then an assessment of expectedness must also be completed. This is the responsibility of the trial management team with medical assistance if required. Expectedness assessment will consider whether the event has been previously documented in the specificity and severity reported.

Unexpected is defined as - the type of event that is not listed in the protocol as an expected occurrence or is not previously documented in the protocol or other trial related literature.

Related and unexpected SAEs will be expedited to the HRA Research Ethics Committee, the Sponsor and the Chairs of the TSC and DM(E)C within the required timelines. In the event that Professors Quenby and Bick are not available we will seek advice from the on-call consultant obstetrician at UHCW. Professors Quenby or Bick will have the discretion to upgrade any events they feel require escalation but will not be able to downgrade any clinical opinion made at site.

Table 12 - Serious Adverse Event Taxonomy

Relationship to trial intervention*	**Description**
Unrelated	There is no evidence of any causal relationship.
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after the trial intervention). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

* This will always be **unrelated** if the woman went into spontaneous labour, was in the standard care group or had an elective C-Section prior to onset of labour

Table 13 - Expected Serious Adverse Events (events that have been previously documented to have occurred in women who have a medical induction of labour)

Woman
In-patient admission* for postnatal wound infection
In-patient admission for postnatal sepsis/possible sepsis
In-patient admission for postnatal urinary tract infection
In-patient readmission for secondary PPH/retained products of conception
In-patient readmission for vulval haemorrhage
In-patient readmission for genital tract infection
In-patient (re)admission for pre-eclampsia
In-patient readmission for thrombosis
In-patient readmission for epilepsy
In-patient admission for reduced fetal movements
Baby
Cyanosis
Poor SATs
Grunting
Respiratory morbidity
Prolonged hospitalisation/in-patient readmissions for respiratory support

* A hospital admission is defined here as an overnight stay in the hospital.

5. DATA MANAGEMENT

5.1 Data Collection and Management

All data will be stored securely and held in accordance with the relevant UK data protection legislation. The case report forms will be designed by the Chief Investigators, Medical Statistician, Programmers, Senior Research Fellow and representatives from obstetric units. Anonymised data will be entered onto the secure password protected trial data base, either at WCTU, or at the hospital site and accessible only by authorised members of the team. Participants will be identified by a unique trial identification number which will be recorded on all CRFs. Participant contact details required for shoulder dystocia confirmation, sending reminders, two and six month follow-up, clarifications, invitation to participate in interviews, contacting the participant or their child in the future, will be held separately within the main database. How participant information is managed by the research team will be clearly detailed in the participant information sheet and consent obtained.

5.2 Collecting Follow-up Data

In the UK 8.54 women per 100,000 will die during pregnancy, delivery, or in the six weeks after giving birth; of these 5.08/100,000 are indirectly related to the pregnancy. These women typically have known health problems (the commonest being heart disease) which means that they are unlikely to be considered suitable for an expectant approach to delivery. It is therefore the remaining 3.46/100,000 of maternal deaths where cause of death is directly related to pregnancy that are of concern for this study. This figure includes early pregnancy deaths, pre-eclampsia, and suicides all of which are unlikely in our population of interest meaning that actual risk of maternal death for women in our study is likely to be around 1.8/100,000. Nearly all of these will occur prior to discharge. It is only thrombo-embolism and early post-partum suicide that might occur after discharge; i.e. <1.45/100,000. We need to add to this the risk of a co-incidental death in the post-partum period. Overall co-incidental death rate is 1.75/100,000 of which no more than 20% is likely to be post-partum. This means that the post-discharge maternal mortality before the two months follow up date is unlikely to be >2/100,000; or around a one in seven chance of a single such death across the whole study prior to the two month follow up. The late death rate (between six weeks and 52 weeks) is 13.79/100,000. Assuming this rate is stable over time and that there are 17 weeks between two month and six month follow-up then we might expect no more than around 5/100,000 deaths. Assuming, that half of these are going to be in women with known health problems who would not have been included in the study then rate would be 2.5/100,000 – or no more than around a one in six chance that this occurs across the whole study between the two follow-up points.[30]

Given the low probability of there being any post-discharge maternal deaths, we have decided not to screen for maternal deaths following discharge, but instead focus our efforts on identifying perinatal deaths. In the event that we become aware of any maternal deaths we will exclude the child from follow-up to avoid any unnecessary distress to the surviving family.

Overall there are 5.61 perinatal deaths per 1,000 total births up to 28 days post-delivery, comprising 3.87 stillbirths and 1.74 neonatal deaths;[30] in our study this equates to 22.44 infants in the randomised study (N=4,000) and 3.41 infants in the cohort study for women having an elective section. These figures are an overestimate of the likely number of perinatal

deaths during this trial, because these figures include infants from 24+0 weeks and in this study the earliest a women can enter the trial process is 28^{+0} weeks. Whilst these are rare occurrences, they are extremely distressing, and can have long term psychological consequences for the mother such as anxiety and depression.[31]

It is important that in the conduct of this trial, we act to minimise distress for participants and their families; to achieve this we will do the following

- Check the hospital electronic record system for notification of neonatal death in all infants participating in the study who were discharged home, prior to prompting or contacting women about completing two and six month follow-up.
- Where a neonatal death is recorded, we will liaise with hospital bereavement service to determine if the woman is known to them, if she is, the first contact will come from a member of the hospital bereavement service; if not, the first contact will come from the research midwife or an experienced member of the research team. In all cases the first contact will be personal, by telephone;
- We will develop 'outcome specific questionnaires' so women will only receive questionnaires specific to their circumstances (table 12) i.e. women whose infant has died will not receive prompts or follow-up infant questionnaires;
- We will develop outcome specific guidance to support the trial team in collecting follow-up data; we have red-flagged outcomes that are particularly sensitive or distressing.

There are routine NHS data that will provide information on deaths. However, the time taken in accessing these data is disproportionate when compared to the follow-up time intervals of interest for this study.

Very occasionally, information contained in a participant's response to a form may indicate an issue which may jeopardise the safety of the participant or her child. If there is any indication in a participant's response of a serious problem, or any issue in relation to their personal safety, or that of their child, the person checking the data will report this immediately to the CI or a specified senior clinical member of the research team who will decide on whether further action is required. If further action is required the CI (or designated clinician member of the team) will contact the participant to seek more information and establish the level of concern and whether the participant is currently receiving support from her GP or consultant. Following this discussion the CI (or designated clinical team member) will decide if information should be disclosed to the participant's GP or consultant. If disclosure is thought to be required the participant should be informed and ideally agree to the disclosure.

In rare instances disclosure to the GP or consultant without informing the participant might be considered necessary if the CI (or designated clinical team member) thought it unsafe to inform the participant.

If a response to the Edinburgh post-natal depression scale identifies that a participant has an overall score of 13 or above or if question 10 'The thought of harming myself has occurred to me' is ticked as any option other than 'never', the WCTU coordinating centre will inform the local research team in writing. The local research team will be asked to follow their local hospital policy and contact the women if necessary. The local research team will also be required to document in writing to the WCTU coordinating centre that they have been informed by WCTU coordinating centre of the score and are handling the case as per their local hospital policy.

The CI (or designated clinical team member) will record the incident, steps taken, and outcome.

Table 14 – guidance for collecting follow-up data

Outcome	Process
Outcome one: Woman and Infant are discharged home with no significant health concerns.	**1.** At six weeks screen the hospital electronic records for notification of an infant death. **a. No notification of infant death** - invite or prompt woman to complete the two-month follow-up for herself and her infant. **b. Notification of infant death** – Do not make further contact with the family. **2.** If no notification of infant death at six weeks check the hospital records at 22 weeks for subsequent notification of infant death. **a. No notification of infant death** - invite or prompt woman to complete the six-month follow-up for herself and her infant. **b. Notification of infant death** – Do not make further contact with the family.
Outcome two: Woman discharged home and her infant is stillborn or died in hospital.	**1.** Do not make further contact with the family.
Outcome three: Woman discharged home but her infant has serious health concerns or is receiving palliative care.	**1.** At six and 22 weeks using hospital number check electronic participant records for notification of an infant death - undertake a detailed review of the hospital case notes, follow-up any transfers to other hospitals / hospice or contact the infant's neonatologist prior to prompting or sending two and six months questionnaires. a. **No notification of infant death** - invite or prompt woman to complete the two-month follow-up for herself and her infant. **Notification of infant death** – Do not make further contact with the family. b. **No notification of infant death** - invite or prompt woman to complete the six-month follow-up for herself and her infant.

	Notification of infant death - Do not make further contact with the family.
Outcome four: Woman discharged home but her infant has significant health concerns for which they are receiving treatment.	**1.** At six and 22 weeks using hospital number check electronic participant records for notification of an infant death - undertake a detailed review of the hospital case notes, follow-up any transfers to other hospitals / hospice or contact the infant's neonatologist prior to prompting or sending two and six months questionnaires. **a.** No notification of infant death - invite or prompt women to complete the two-month follow-up for herself and her infant. **b.** Notification of infant death – Do not make further contact with the family.
Outcome five: Women discharged home but her infant has significant health concerns and remains in hospital at two and / or six months.	**For the woman** **1.** At six weeks telephone contact first, to discuss completing the two-month follow-up for herself. Ask permission to make contact again for the six month follow-up – record decision. **2.** At 22 weeks telephone contact first, to discuss completing the two-month follow-up for herself. **For the infant** **1.** The research midwife will collect the data.
Outcome six: Infant discharged home no significant health concerns. Residence different from mother.	**1.** At six weeks check the hospital records for notification of an infant death. a. **No notification of infant death** - invite or prompt guardian / adoptive parent to complete the two-month follow-up for the infant. b. **Notification of infant death** - Do not make further contact with the guardian or adoptive family. **2.** If no notification of infant death at six weeks check the hospital records at 22 weeks for subsequent notification of infant death. a. **No notification** of infant death - invite or prompt guardian / adoptive parent to complete the two-month follow-up for the infant. b. **Notification** of infant death - Do not make further contact with the guardian or adoptive family.
Outcome seven: Women discharged home to residence different from infant.	**3.** At six weeks telephone contact first, to discuss completing the two-month follow-up for herself. Ask permission to make contact again for the six month follow-up – record decision. **4.** At 22 weeks telephone contact first, to discuss completing the two-month follow-up for herself.
Outcome eight:	**1.** Do not make further contact with the family.

In-hospital maternal death and infant discharged home with / without significant health concerns.	

Indicates particularly sensitive or distressing outcome which requires specialist contact

If any core data items are missing from a participants follow up questionnaire, attempts will be made to contact the participant to collect these in accordance with the procedure stated in the data management plan.

5.3 Database

The database will be developed by the Programming Team at WCTU. All specifications (i.e. database variables, validation checks, screens) will be agreed between the programmers and appropriate trial staff.

5.4 Data storage

All study related documentation and data will be stored in accordance with all applicable regulatory requirements and access restricted to authorised personnel. Data will be stored on the University of Warwick secure servers hosted in an on-premises data centre. Sharing of electronic data between the University of Warwick and PNI will be in accordance with WCTU SOP 15 part 3 'Data Transfer' and require data sharing agreements to be in place. Participants will provide consent to their data being shared with PNI as detailed in the consent form.

5.5 Data archiving

The trial records and associated documentation of the 4,000 randomised participants (women and infants) will be archived for 25 years; the trial records and associated documentation of the anticipated 3000 participants in the cohort study will be archived for 10 years (WCTU SOP 23 'Data Archiving'). Data collected within the Big Baby Study may be important resource for future research. For example, exploring the long-term effects for children with brachial plexus injury, as there is anecdotal evidence of an association between brachial plexus injury and epilepsy. To allow for such future research we will:

1. Contact the children of mothers enrolled in the randomised trial when they are aged 16-18 to ask for permission to keep their data and contact details for future research; if at that time no further research is planned we will not approach for consent to use data for future research. We will only approach those for whom we have obtained consent for further research. All data for which we do not have consent to keep will be destroyed after 25 years. We are here drawing a distinction between the archived data relating to the completed trial and the permission to the active use of data we hold for the purposes of future research.
2. For the children of mothers enrolled in the cohort study we will first make a decision after ten years as to whether there are important future research questions that can be addressed by approaching this group again. If no further work is anticipated we will destroy the data. If future work is planned then we will keep the data until children are aged 16-18 and approached them at this time to keep their data for future research. If we do not have consent to keep the data it will be destroyed at this time.

In order to be able to contact children born within the study in the future we will use data held by NHS digital (or any successor organisation) to obtain their contact details.

6. DATA ANALYSIS

6.1 Statistical analysis

All analyses will be by intention to treat at the time of randomisation. Not all women will have a vaginal delivery as planned. We will therefore collect numbers having a caesarean section broken down by type/indication as defined using the Robson score. A detailed statistical analysis plan will be developed by the trial statisticians and approved by the TSC and DM(E)C.

Our primary analysis will be based on the assessment of the incidence of shoulder dystocia between intervention and control. Comparison between the intervention groups will be made using logistic regression models both adjusted and unadjusted using appropriate covariates. Other secondary binary outcomes will be analysed in a similar way. Continuous outcomes will be analysed using linear regression models; again both adjusted and unadjusted analyses will be computed. Non-compliance will be taken into account using a CACE (Complier Average Causal Effect) analysis and if required, sensitivity analyses will be computed (for example, assessment of missing data using multiple imputation).

6.2 Interim analysis

We will conduct key event analysis after data are available on 1,000 participants. This will allow the DM(E)C to make recommendations about adjustment to the target sample size in the light of data on recruitment and outcome incidence, and to consider continuation of recruitment, taking into account early data on the observed differences between the groups and safety information.

While we have designated a 'primary' outcome, understanding the effect of induction for macrosomia is far more nuanced than simply whether it affects the process measure of shoulder dystocia. It is important to determine whether it has any impact on the primary target of the intervention, but effects on other outcomes will affect interpretation of the findings; for example, if we find a reduction in the incidence of shoulder dystocia, but no differences in fetal wellbeing outcomes and harm on one or more maternal outcome(s). Women and clinicians might here conclude that induction should not be recommended in spite of a positive effect on the primary outcome. We will work with our PPI group during the lifetime of the study to develop a better understanding of how we should interpret the findings and on the interpretation once the main analyses are available.

6.3 Subgroup analyses

We will conduct a pre-planned conventional subgroup analyses using an interaction term for two key variables; maternal body mass index and fetal weight centile. Additionally we will apply data mining techniques we have developed to describe sub-groups using multiple parameters in a previous IPD meta-analysis.[32] These include recursive partitioning, adaptive peeling and a Bayesian approach. This will allow us to identify any combinations of baseline characteristics that might predict better or worse responses to induction. We will apply all

three methods to a random sample of half of the data and then validate any promising clinical predication rules identified in the second half of the sample.

6.4 Sensitivity analyses

Although the RCOG recommended customised GROW charts are currently in use in 76% of Trusts and Health Boards in the UK, and are expected to be used in 85% by the time this trial is set to start, other competing methods to assess EFW exist including the traditional Hadlock 10 fetal weight curve, as well as fetal weight curves by Intergrowth (currently used in Oxford)[33] and WHO[34] (due to be published in early 2017). As explained in the background, we have substantial concerns about this approach as it fails to adequately account for variations in maternal physiology and stature, and there is mounting, independent evidence which we have referenced, to suggest that customised GROW curves define LGA which is more strongly associated with adverse outcome. Nevertheless, we will undertake sensitivity analyses to assess how women who were included in our study would also have been identified as being large for gestational age by these other standards.

6.5 Cohort study

We will also compare the parallel cohort and the trial participants, comparing outcomes among women who request an elective caesarean section and those who receive induction or standard care in this trial. This is a non-randomised comparison, and we will therefore seek to control bias as far as possible by adjustment for baseline covariates.

6.6 Analysis of qualitative data

In the pilot study, analysis will commence as soon as all interviews are completed to maximise the learning from the pilot phase and inform progression to the main study. For the second qualitative study, we will ensure women's views are available to inform the main trial report and papers. Qualitative interview data will be analysed prior to knowing the results from the quantitative "outcomes" analysis to avoid bias in interpretation of findings. Interviews will be transcribed and analysed using the Framework method for thematic analysis. The key topics and issues emerging from interviews will be identified through familiarisation with the interview transcripts by two researchers (JF, DB) who will initially work independently and then come together to discuss and agree the final coding framework. A series of thematic charts will be developed according to the coding framework, and data from each transcript summarised under each theme, enabling examination of similarities and differences of views within and between transcripts, and use of a constant comparative approach. Quantitative and qualitative data on acceptability of the trial and other aspects of feasibility from the women's, their partners and clinician' perspectives will be integrated using mixed methods matrices.

6.7 Economic analysis

Data will be collected on the health service resources used in the treatment of each woman and infant during the period between randomisation and hospital discharge. The trial data collection instruments and data extracted from routine health systems will record the duration and intensity of intrapartum, postnatal and neonatal care, based on standard criteria for level of care, as well as maternal and neonatal complications. Details of the resources associated with induction of labour and normal or alternative modes of delivery, as well as staff time, tests, procedures, drugs and equipment will be recorded. Current UK unit costs will

be applied to each resource item to value total resource use in each arm of the trial. A per diem cost for each level of intrapartum, postnatal and neonatal care will be calculated by the health economics researcher from detailed questionnaires completed by NHS finance departments, giving cost data and apportioning these to different categories of patient using a 'top-down' methodology. Trial participating centres will be visited to ensure consistency in cost apportionments. The unit costs of clinical events that are unique to this trial will be derived from the hospital accounts of the trial participating centres, although primary research that uses established accounting methods may also be required.

An incremental cost-effectiveness analysis will be performed. In the baseline analysis, the economic evaluation will be expressed as the incremental cost per case of shoulder dystocia prevented. A long-term economic evaluation will also project the lifetime clinical and economic consequences of induction of labour at $38+^{0}$-$38+^{4}$ weeks' gestation of fetuses that are large for gestational age, and will be expressed as the incremental cost per quality-adjusted life year (QALY) gained. The long-term economic evaluation will require the application of decision-analytic methods and estimation of subsequent health status and health care costs over the lifetime of an adversely affected compared to a healthy mother and infant.[35]

The decision-analytic model will be framed by the potential sequelae of induction of labour in this clinical context, the appropriate model type (e.g. Markov model, discrete-event simulation) and the appropriate analytical framework (e.g. cohort analysis, individual-level simulation). The decision-analytic model will be populated, in part, using data collated by economic questionnaires completed by the trial participants at two months and six months postpartum, and supplemented where necessary using the best available information from the literature together with stakeholder consultations. The postnatal economic questionnaires will detail the use of hospital and community health services by each woman and infant following the initial hospital discharge. The decision-analytic model will also consider the economic consequences of potential medico-legal claims that result from adverse events during the intrapartum and neonatal periods. The economic questionnaires completed by the trial participants at two months and six months postpartum will provide EuroQol EQ-5D-5L data for the women at each time point. Responses to the EQ-5D-5L will be converted into health utilities using established utility algorithms for the purposes of QALY estimation.[36] Given the methodological limitations surrounding preference-based outcomes measurement in young children, it will be necessary to model the relationship between developmental outcomes in the children and multi-attribute utility measures. This will draw upon longitudinal datasets containing economic measures that are held by the co-applicant team.

Long term costs and health consequences will be discounted to present values using discount rates recommended for health technology appraisal in the United Kingdom.[37] We will use non-parametric bootstrap estimation to derive 95% confidence intervals for mean cost differences between the trial groups and to calculate 95% confidence intervals for incremental cost effectiveness ratios. A series of probabilistic sensitivity analyses will be undertaken to explore the implications of uncertainty on the incremental cost-effectiveness ratios and to consider the broader issue of the generalisability of the study results. In addition, cost-effectiveness acceptability curves will be constructed using the net benefits approach.

In a separate economic analysis that will be based on individual-level observations of costs and outcomes collected within the context of the RCT and the parallel cohort study, we will also aim to compare the cost-effectiveness of the trial interventions with a policy of elective caesarean section in women that meet the trial inclusion criteria. This separate analysis will take the form of an observational study based economic evaluation that will use propensity score matching and doubly robust methods to account for confounders.

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Ethical conduct of the trial

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation and WCTU Standard Operating Procedures (SOPs).

7.2 Sponsor

The University Hospitals Coventry and Warwickshire NHS Trust will act as sponsor for the trial.

7.3 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. Negligent harm cover will be provided by standard NHS arrangements. NHS Indemnity does not give indemnity for compensation in the event of non−negligent harm, so no specific arrangements exist for non−negligent harm for this trial.

7.4 Regulatory / ethical approvals

Health Research Authority approval and approval from each relevant NHS Trust Research & Development (R&D) departments will be obtained before participants are enrolled in the trial.

7.5 Trial registration

The trial's International Standard Randomised Controlled Trial Number is 18229892

7.6 Trial timetable and milestones

Table 15 - Tasks and Milestones

Tasks	Time period (months)
Trial preparation: approvals (ethics, R&D), research governance (oversight committees (TMG, TSC and DM(E)C), staff training), develop project management plan, registration, contracting, new appointments, send capacity and capability questionnaires to trial sites, trial administration processes (participant files, master file), trial branding, and social media.	-3 - -1 (pre-start)
Trial set-up: liaise with trial pilot sites, track R&D, develop randomisation service, develop data collection process, prepare training manual, print recruitment information (introduction letter, participant information sheet, participant information leaflet, posters) and prepare site-initiation materials.	1 - 3
Site set-up: Initially 60 sites; four per month (not including the first and last months, August and December).	4 - 22
Participant recruitment: n=4,000 randomised.	5 -30
Feasibility: process analysis when ten site have recruited for three months approx. n=159; adjustments as required.	Around 10
Follow-up: two and six months.	7 - 38
Interim analysis: when data on primary outcome on n=1,000 women is available; adjustments / approvals as required.	Around 17
Data analysis	36 - 40
Dissemination: final report, publications, press release, social media, newsletter and a dissemination event.	38 - 42

7.7 Administration

Trial coordination will be based within Warwick Clinical Trials Unit, The University of Warwick, Gibbet Hill Campus, Coventry, CV4 7AL

7.8 Trial Management Group

The Trial Management Group (TMG) comprises co-investigators, allied experts and project management staff and is responsible for the day-to-day running of the project (table 1). Significant issues that may arise will be reported by the Chair to the Trial Steering Committee and / or Data Monitoring Committee (DM(E)C). The TMG will meet monthly throughout the project and will invite key staff from collaborating and external organisations and investigators from participating sites as required.

7.9 Trial Steering Committee

The Trial Steering Committee (TSC) comprises independent lay members, experts in obstetrics, neonatal and maternal medicine, statistics and health economics (table 2). The TSC will approve the final trial protocol, advise on all aspects of the trial conduct, monitor trial progress, review relevant information from other sources, consider recommendations from the DM(E)C and advise on protocol amendments. They will assess recruitment in the pilot stage, and will consider modification or termination of the trial (in consultation with the

DM(E)C) in the event of poor recruitment. They will meet regularly throughout the project and not less than once a year.

7.10 Data Monitoring Committee

The Data Monitoring Committee (DM(E)C) comprises independent experts in statistics, obstetrics and gynaecology, urogynaecology and paediatrics (table 3). They will ensure close monitoring of outcomes during the trial. Analyses of the accumulating data will be presented to the committee who will advise of any excess of adverse events, including shoulder dystocia, which in either group would justify early closure of the study. Frequency of reporting will be at the discretion of the (DM(E)C). The trial statistician will attend all DM(E)C) meetings and the Co-Chief Investigators and Trial Co-ordinator will attend the open part of the meeting.

7.11 Investigator meetings

Investigator meetings will be held during recruitment and key staff from participating sites will be invited. The meetings will review trial progress, recruitment and discuss any emerging issues.

7.12 Essential documentation

A Trial Master File will be set up in accordance to WCTU SOP 11 - 'Essential Documentation' and held securely at Warwick Clinical Trials Unit, The University of Warwick, Gibbet Hill Campus, Coventry, CV4 7AL. Investigator Site Files will be prepared and distributed to participating obstetric units involved in the trial.

8. MONITORING AND QUALITY ASSURANCE

8.1 Training

SQ has undertaken the Chief Investigator training and all clinicians involved in obtaining consent will be required to complete a Good Clinical Practice course. A programme of training will be provided to all clinicians and allied staff participating in the trial and will include: the principles of good clinical practice, the importance of the trial, background, the trial protocol, process mapping for trial entry, inclusion and exclusion criteria, ethical issues and consent, randomisation procedures, data collection and documentation, using the Big Baby Trial Research system (BBT-RS) and completing and maintaining training logs. All training information and materials will be available via the trial website (https://www2.warwick.ac.uk/fac/med/research/ctu/trials/bigbaby). Training will also be given to members of the research team to ensure that telephone calls or emails from participants, relatives or legal representatives are answered sensitively and appropriately. All new staff will complete a trial induction and training programme.

8.2 Data quality

Data entered into the trial database, either from hard copies of CRFs or on-line, will be checked for accuracy and completeness by WCTU in accordance with the trial data management plan.

8.3 Quality assurance

A risk assessment will be undertaken and will form the basis of the trial monitoring plan. Sites will be visited during the recruitment period to audit the quality of the trial process and documentation. Additional site visits may be required, if triggered by issues raised in the monitoring plan.

8.4 Visits to sites

Following site initiation, the research team will be in regular contact with units by email, telephone and face-to-face, to support with the day-to-day management of the trial, and identify and discuss any problems with compliance to the protocol, recruitment pathway, barriers to recruitment, 'Site Master File' completeness.

9. PATIENT AND PUBLIC INVOLVEMENT

9.1 The Erb's Palsy Group

During the planning and development of this trial we have worked collaboratively with Karen Hillyer (Chair) and Jackie Dewdney (Board Member) of The Erb's Palsy Group (www.erbspalsygroup.co.uk). This is the leading charity in the UK, and it offers advice, information and support to children and families affected by Erb's Palsy.

Karen and Jackie are leading on the development of all participant facing materials, including an introduction letter, participant information sheet, participant information leaflet, posters. In addition to their personal experience, they have extensive knowledge of participants' experience of shoulder dystocia and its associated complications, and are therefore well placed to ensure the materials provide full information about participation in the trial, in a clear and accessible format.

As co-applicants Karen Hillyer and Jackie Dewdney are involved in all aspects of trial management and attend monthly TMG meetings. Their input will help inform the interpretation of the final results and dissemination of the findings.

10. DISSEMINATION AND PUBLICATION

To raise midwifes' awareness about the trial we will publish an article in the British Journal of Midwifery. We will publish the protocol and the final trial results in fully open access high impact peer reviewed journals. We will submit abstracts to major national and international conferences, including RCM, RCPCH annual conferences, RCOG World Congress, and British Maternal and Fetal Medicine conference, for dissemination to service users, researchers, public health and NHS sectors. We will issue a press release through the Warwick Press Office.

We will hold three dissemination events in three locations, Manchester, Coventry and London and invite key stakeholders at the end of the study, including participants, representatives from PPI organisations, clinicians (midwives and doctors) involved in the care of pregnant women, research midwives who worked on the study, managers, policy makers and experts in the field. The first event will be held at Warwick University; there will be a live interactive webcast of the meeting and the event will be filmed and uploaded as a Podcast on the project website. If our findings suggest that a change in current practice is needed we will approach NICE and RCOG to request they consider an update to their guidelines in the light of new evidence.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org). Authorship of all trial publications will be agreed in accordance with the WCTU SOP 22 'Publication and Dissemination'.

All publications will be submitted to the NIHR-HTA Programme for approval prior to submission for publication.

Links to all findings, reports, publications and events will be available via the project website (https://www2.warwick.ac.uk/fac/med/research/hscience/ctu/trials/bigbaby).

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