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Perinatal and 2-year neurodevelopmental outcome in late preterm fetal compromise: the TRUFFLE 2 randomised trial protocol

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ABSTRACT

Introduction Following the detection of fetal growth restriction, there is no consensus about the criteria that should trigger delivery in the late preterm period. The consequences of inappropriate early or late delivery are potentially important yet practice varies widely around the world, with abnormal findings from fetal heart rate monitoring invariably leading to delivery. Indices derived from fetal cerebral Doppler examination may guide such decisions although there are few studies in this area. We propose a randomised, controlled trial to establish the optimum method of timing delivery between 32 weeks and 36 weeks 6 days of gestation. We hypothesise that delivery on evidence of cerebral blood flow redistribution reduces a composite of perinatal poor outcome, death and short-term hypoxia-related morbidity, with no worsening of neurodevelopmental outcome at 2 years.

Methods and analysis Women with non-anomalous singleton pregnancies 32+0 to 36+6 weeks of gestation in whom the estimated fetal weight or abdominal circumference is <10th percentile or has decreased by 50 percentiles since 18–32 weeks will be included for observational data collection. Participants will be randomised if cerebral blood flow redistribution is identified, based on umbilical to middle cerebral artery pulsatility index ratio values. Computerised cardiotocography (cCTG) must show normal fetal heart rate short term variation (≥4.5 msec) and absence of decelerations at randomisation. Randomisation will be 1:1 to immediate delivery or delayed delivery (based on cCTG abnormalities or other worsening fetal condition). The primary outcome is poor condition at birth and/or fetal or neonatal death and/or major neonatal morbidity, the secondary non-inferiority outcome is 2-year infant general

Strengths and limitations of this study

- Changes in cerebral Doppler measures are considered a strong candidate for triggering delivery following detection of late preterm fetal growth restriction.
- The primary outcome is a composite of perinatal and neonatal outcome, and infants will be followed to determine health and two-neurodevelopment at 2 years to ensure safety and non-inferiority of intervention.
- This appropriately powered UK and European multicentre trial will inform NHS policy and the findings will be generalisable to late preterm fetal growth restriction in other healthcare systems.
- There are limited data available in respect of selecting the threshold of cerebral Doppler change for randomisation.
- Some non-UK centres will not randomise women at the earlier gestation range (32–33+6 weeks) and this could limit the generalisability of the results in this group of women.

health and neurodevelopmental outcome based on the Parent Report of Children's Abilities-Revised questionnaire.

Ethics and dissemination The Study Coordination Centre has obtained approval from London-Riverside Research Ethics Committee (REC) and Health Regulatory Authority (HRA). Publication will be in line with NIHR Open Access policy.

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INTRODUCTION

Third trimester poor fetal growth and compromise are strongly associated with stillbirth, neonatal illness[1] and an increased risk of fetal or neonatal brain injury.[2] The only therapeutic option is delivery of the fetus. This poses a dilemma: delivery too early may incur the complications of prematurity, delivery too late risks further fetal compromise, brain injury and late stillbirth. The problem of when to deliver these babies is twofold: there is no consensus on how to identify fetal compromise and there is no 'ideal' evidence-based monitoring strategy. Current screening strategies include standardised symphysis-fundal height measurement, third trimester ultrasound and umbilical Doppler velocimetry.[3 4] National Institute for Health and Care Excellence (NICE) acknowledges that methods to identify fetal growth restriction (FGR) are 'poorly developed or not tested by rigorous methodology'.

The use of Doppler ultrasound of fetal vessels allows non-invasive assessment of blood flow. Fetal 'cerebral blood flow redistribution', prioritising blood flow toward the brain at the expense of other organs, is a response to an adverse intrauterine environment characterised by hypoxaemia. Ultrasound markers of such fetal compromise include Doppler assessment of blood flow velocity[5–7] and abdominal circumference growth velocity 'drop off' in the third trimester.[8 9] Intervention by delivery of the fetus in response to either evidence of blood flow redistribution or fetal growth slowing has never been tested in a randomised trial. Computerised cardiotocography (cCTG) has been used in several observational studies to determine fetal condition in relation to hypoxaemia and acidosis. The RCOG (Royal College of Obstetricians and Gynaecologists) recommends that research is required to evaluate the effectiveness of third trimester ultrasound assessment, concluding that 'middle cerebral artery (MCA) Doppler may be a more useful test in small for gestational age (SGA) fetuses detected after 32 weeks'[4] but does not define parameters that should trigger delivery. Even with effective screening for FGR, the questions of how to monitor and when to deliver would remain.

A Cochrane review of the management of 'compromised babies' at term showed no difference in perinatal or long-term outcome with a policy of early delivery versus conservative management.[10] Only three trials were included: two included small babies, both part of the DIGITAT (Disproportionate Intrauterine Growth Intervention Trial At Term) study (a small pilot and the main trial),[11] the third included babies with reduced amniotic fluid. There is no Cochrane review on the optimal timing of delivery in late preterm growth restricted babies.

A systematic review included only one trial of timed delivery in late preterm babies. The Growth Restriction Intervention Trial[12] included 547 babies from 24 to 36 weeks of gestation with evidence of preterm growth restriction or compromise, where there was clinical uncertainty whether immediate delivery was indicated. Of these, 210 babies were recruited between 33+0 and 36+6 weeks: 107 women were randomised to early delivery and 103 to delayed delivery. Mortality and a range of neurodevelopmental measures were similar between the groups. These results cannot be used to inform management because of the small number of infants assessed using only umbilical artery Doppler velocimetry, the subjective assessment of the cardiotocograph (ie, not computerised analysis), and the use of clinician's discretion rather than standardised management.

Results from our previous randomised trial of delivery decision-making using Doppler velocimetry and cCTG in pregnancies with FGR at 26–32 weeks of gestation—the TRial of Umbilical Fetal FLow in Europe (TRUFFLE) provided evidence associating monitoring strategies with improved outcomes[13] and guides practice internationally.[14 15] In TRUFFLE (2005–2010) we studied FGR <32 weeks of gestation using cCTG as the standard of care for timing delivery, compared with early or late fetal ductus venosus (DV) Doppler velocimetry changes with a cCTG 'safety net'. Surviving infants whose mothers had been randomised to delivery in late DV changes arm showed better neurodevelopment at 2 years of age.[13]

We then carried out the prospective multicentre observational TRUFFLE 2 Feasibility Study (2017–2018, n=1024). A range of markers of cerebral redistribution were evaluated as potential delivery trigger points in two gestational age bands. These included the MCA Doppler and the umbilical cerebral ratio (UCR); calculated by dividing the Doppler pulsatility index of the umbilical artery by that of the MCA. Participating clinicians suggested greater concern about fetal condition is required to trigger delivery at earlier rather than later gestational ages between 32 and 36 weeks. We, therefore, selected a more abnormal threshold for cerebral redistribution at earlier gestational ages, based on stepped UCR z-score values.[16] Of note was the finding from a prospective study that birth condition, fetal mortality and neonatal morbidity rate were more common among fetuses showing higher UCR z-score, indicating cerebral redistribution, compared with those with a lower UCR z-score (15 vs 9%).[17]

On this basis, we designed this randomised trial of delivery for women identified with late preterm FGR, to test the hypothesis that delivery based on UCR values derived from the feasibility study will safely lead to improved fetal outcomes (TRUFFLE 2).

METHODS AND ANALYSIS

Study design

This is an individual unblinded randomised trial of pregnant women experiencing FGR. Following informed consent, 1560 women will be randomised to either immediate or delayed delivery. Women are being recruited from UK and European centres.

Potential participants are women with singleton non-anomalous pregnancies between 32+0 and 36+6 weeks of gestation in whom a SGA fetus is identified or one whose growth has slowed. This is defined as estimated fetal weight or abdominal circumference <10th percentile and/or having decreased by 50 percentiles since an ultrasound scan at 18–32 weeks. Each centre will use local growth charts. Data is collected on absolute measurements and growth chart-derived percentiles. Once identified as potential participants women receive regular monitoring as per local standard of care for fetal condition, using ultrasound biometry, umbilical and MCA Doppler velocimetry assessments and cCTG (using Dawes-Redman criteria). This is recommended to be repeated every 14 days; these observational data are recorded.

Women become eligible for randomisation when signs of fetal cerebral blood flow redistribution are detected by Doppler, defined below and shown in the study flow chart (online supplemental file 1—flow chart).

Delivery is based on UCR pulsatility index z-scores, of >1.5 (between 32+0 and 33+6 weeks) or >1.0 (34+0 to 36+6 weeks). These correspond to an absolute UCR of ≥1.0 at 32+0 to 33+6 weeks and ≥0.8 at 34+0 to 36+6 weeks. Abnormal UCR measurements must be repeated within 15 minutes–24 hours to confirm these values. This need not be consecutive, so that if the second measurement is normal the patient may still be randomised if a repeat Doppler measurement is abnormal within 72 hours of the first abnormal measurement. Randomisation will occur at the time of the second qualifying UCR measurement and is stratified by centre and gestational age. Randomisation is through the CASTOR website (Amsterdam, NL) into which eligibility, monitoring and outcome data are entered.

Women are consented in a two-stage process. Stage 1 (pre-eligible) consent is not a prerequisite and women may be consented directly for randomisation with stage 2 (eligible for randomisation) consent.

Pre-eligible: consent for observational data collection

Consented for prospective data collection once identified as meeting criteria for SGA or slowed fetal growth (as defined above) but not meeting cerebral Doppler thresholds for randomisation or not willing to be randomised. This will include demographics, medical history, ultrasound findings and outcomes. This consent will include obtaining a personal email address, which is entered into and stored on Castor, and willingness to be contacted in the future for follow-up where women are randomised (online supplemental file 2—consent form for observational data collection).

Box 1 Delivery thresholds based on umbilical artery Doppler for participants in all arms of the study

Umbilical Doppler delivery thresholds.
In all arms absolute indications for delivery include:
- Umbilical artery Doppler with reversed end diastolic flow after entry into the trial, OR
- Umbilical artery Doppler absent end diastolic flow from 34+0 weeks.

Eligible for randomisation: consent for randomisation

Consent for randomisation once cerebral redistribution is identified, with UCR (as defined above) of ≥1.0 at 32+0 to 33+6 weeks and ≥0.8 at 34+0 to 36+6 weeks. This consent will also include contact details and willingness to be contacted in the future for follow-up data collection (online supplemental file 3—consent for randomisation).

Women are randomly allocated to either immediate delivery or delayed delivery as defined below. Randomisation has a 1:1 allocation ratio and stratified based on gestational age (above or below 34 weeks) and centre. Randomisation is conducted on the electronic data capture platform (Castor EDC, Amsterdam, The Netherlands).

Immediate delivery

Participants in the immediate delivery arm will be delivered by Caesarean or induction of labour will be commenced within 48 hours, allowing for administration of corticosteroids and infusion of magnesium sulphate as per local protocol and guidance. Start of induction of labour is defined as administering cervical preparation (cervical balloon, prostaglandins, etc), artificial rupture of membranes or administration of oxytocin.

Delayed delivery

Participants in the delayed delivery arm will be monitored using twice weekly Doppler and cCTG monitoring, or more frequently based on local clinical protocols if required. Umbilical artery Doppler velocities may be measured in this time and delivery may be based on these safety net criteria (see box below). We strongly recommend that MCA measurements are not undertaken during monitoring in the delayed delivery arm. Delivery is indicated when short term variation (STV) is <4.5 ms on cCTG or there are repeated fetal heart rate decelerations. Once participants reach 37+0 weeks of gestation the delivery plan will be based on local protocols.

Study timeline

Study setup: 0–10 months; recruitment/randomisation: 11–36 months. Two years follow-up questionnaires 35–60 months; analyses, writing up, reporting and dissemination: 61–66 months. This equates to 5 and ½ years (66 months).

Study outcome measures

Primary outcome

The primary outcome for the study is a composite of fetal or infant death, composite measure of poor condition at

birth and neonatal morbidity—as defined by presence of any of the following:

1. Poor condition at birth
   - Apgar score at 5 min <7, umbilical artery pH <7.0 or umbilical vein pH <7.1.
   - Need for resuscitation with intubation, chest compressions or medication.
2. Fetal death/ death before neonatal hospital discharge
3. Neonatal brain injury syndromes
   - Infants with a diagnosis consistent with hypoxic ischaemic encephalopathy (HIE): term and near-term infants only.
   - Infants with a diagnosis of intracranial haemorrhage, perinatal stroke, HIE, central nervous system infection, or kernicterus (bilirubin encephalopathy): all infants.
   - Preterm white matter disease (periventricular leukomalacia): preterm infants only.
   - Infants with a recorded seizure confirmed by Electro-encephalogram (EEG).
4. Respiratory support
   - Need for mechanical support of respiration after admission to neonatal unit (NNU), for more than 1 hour; includes need for continuous positive airways pressure (or NIPPV; Noninvasive positive-pressure ventilation) or mechanical ventilation via endotracheal tube but excludes need for supplemental oxygen.
5. Cardiovascular abnormality
   - Hypotensive treatment, patent ductus arteriosus requiring treatment, or disseminated coagulopathy.
6. Sepsis
   - Clinical sepsis with positive blood culture.
   - necrotising enterocolitis requiring surgery.
7. Retinopathy of prematurity requiring treatment (laser or anti Vascular Endothelial Growth Factor (VEGF) injections)

Secondary outcomes

For the baby

Health and developmental outcomes—assessed using Parent Report of Children's Abilities-Revised (PARCA-R) questionnaire at 2 years corrected age and an Infant Health Questionnaire up to 2 years (online supplemental file 4—PARCA-R Questionnaire and online supplemental file 5—Infant Health Questionaire).

The PARCA-R[18] will be completed at 24 months term-equivalent age, this allows derivation of the non-verbal cognitive scale and language development scale. Raw scores from the scales are standardised (by corrected age and gender) to a notional population mean of 100 (SD=15) and the average of these two component scores will be taken as the overall composite score. Corrected age is used for preterm babies (born before 37 weeks) and represents the age of the child from the estimated date of delivery.

The Infant Health Questionnaire[19] will be used to derive the following health outcomes at 6, 12, 18 and 24 months post partum:

- Use of any hospital service (yes/no) and total number of contacts over the 2-year period.
- Admitted to hospital (yes/no) and total number of admissions over the 2-year period.
  - Planned/unplanned admissions to hospital (yes/no) over the 2-year period.
  - Intensive care or not over the 2-year period.
- Attended emergency department (and not subsequently admitted) (yes/no) over the 2-year period.
- Attended Outpatients/clinic (yes/no) over the 2-year period.

For the mother

1. Gestational hypertension developed post study entry
   - As defined by the International Society for Study of Hypertension in pregnancy (ISSHP): hypertension (blood pressure ≥140/90 mm Hg) arising de novo after 20 weeks gestation in the absence of proteinuria.
2. Pre-eclampsia developed post study entry
   - As defined by the ISSHP: blood pressure ≥140/90 mm Hg and significant proteinuria (protein/creatinine ratio of 30 mg/mmol or more).
3. Onset of labour (spontaneous, induction (method), prelabour caesarean section).
4. Mode of delivery (spontaneous vaginal, assisted vaginal, caesarean section).

Doppler quality control

Sonographer standardisation

Each sonographer in each centre taking part in the trial are assessed by the local principal investigator (PI). Each sonographer will submit to the local PI two images: pseudo anonymised ultrasound images for each Doppler parameter (umbilical artery and MCA) each showing a colour Doppler image with the gate placed over the vessel, and the pulsed wave Doppler waveform arising from that image. The local PI will determine whether these images are satisfactory using a predefined quality control scoring system (online supplemental file 6—Doppler image scoring sheet).

Doppler ultrasound criteria

Measurements are obtained in fetuses between 32+0 and 36+6 weeks of gestation. Umbilical artery and MCA pulsatility index images are collected according to specific predefined objective criteria for both the colour Doppler images and pulsed wave Doppler.

Doppler quality control

The local PI will provide details of all sonographers having undergone standardisation in that centre to the Centre for Trials Research (CTR). The CTR will independently request all images submitted to the local PI for the first five patients randomised from each unit, and then for up to 10% of patients thereafter, for

anonymised quality control assessment by the Quality Control Board. All images are collected as pseudo anonymised .jpeg images and saved electronically in a Doppler ultrasound sonographer standardisation file by the PI, with the submitting sonographer identifiable. Images are scored using the predefined scoring criteria. The CTR will manage this process and will provide feedback if necessary, and ensure that members of the TRUFFLE 2 Quality Control Board do not assess images from their own unit.

Participant entry

Preregistration evaluations

- Ultrasound scan of fetal growth between 32+0 and 36+6 weeks of gestation, including measurement of MCA and umbilical artery Doppler velocities.
- cCTG STV analysed using Dawes-Redman criteria.

Inclusion criteria

(All criteria should be fulfilled to be eligible for randomisation)

- Women ≥18 years old.
- Pregnant with singleton non-anomalous fetus.
- Between 32+0 and 36+6 weeks of gestation.
- Estimated fetal weight or abdominal circumference <10 th percentile OR decreased by 50 percentiles since an ultrasound scan at 18+0–32+0 weeks.
- Cerebral redistribution defined as UCR ≥1.0 (between 32+0 and 33+6 weeks) or ≥0.8 (34+0 to 36+6 weeks) repeated within 15 minutes–24 hours.
- Normal STV on cCTG (4.5 msec or above).

Exclusion criteria

- Indication for immediate delivery required within 48 hours.
- Unable to give informed consent.
- Preterm prelabour rupture of the membranes.
- Suspected placental abruption or antepartum haemorrhage.
- Presence of reversed end diastolic flow in the umbilical artery.

Assessment and follow-up

Assessment of the primary outcome is at infant discharge from the NNU and assessment of the key secondary infant outcomes will use the Infant Health Questionnaire and PARCA-R. The Infant Health Questionnaire will be sent out by investigators via Castor at 6, 12, 18 and 24 months post partum. Neurodevelopment is assessed at 2 years age corrected for prematurity using the PARCA-R, also sent via Castor (translated into local language). The window for determining 2-year outcome is from 23.5 to 27.5 months over which range the PARCA-R has been standardised.

Endpoint is 30 months after the estimated date of delivery of the last participant to deliver (24 months follow-up with additional 6 months for data cleaning and additional enquiries).

Statistics and data analysis

Sample size

The trial is powered to detect if immediate delivery following cerebral redistribution is superior to expectant management following cerebral redistribution on this outcome. A difference in the proportion with the primary outcome from 15% in the delayed delivery to 9% in the immediate delivery (from TRUFFLE 2 feasibility study) demonstrates an OR of 0.56. At two-sided 5% significance with 95% power, 780 participants per arm are required, giving 1560 in total. Given the immediacy of this outcome, no loss to follow-up is expected. An important non-inferiority secondary safety outcome is infant neurodevelopment, which is measured by parent completed questionnaire at 2 years using the PARCA-R, as recommended in NICE Guidance,[20] supplemented by infant health information over the intervening 2 years. Assuming a loss to follow-up at 2 years of 20%, 2-year outcomes for approximately 1248 infants are expected (624 per group assuming no difference in the lost to follow-up between the groups). The PARCA-R questionnaire provides a composite score for neurodevelopment with a standardised mean of 100 and SD of 15. With a one-sided significance level of 1%, under a non-inferiority hypothesis, a sample size of 624 in each group achieves a 98% power to detect a non-inferiority margin of difference in the mean PARCA-R score of no less than four points (0.25 of a SD). A margin of no less than three points can be detected with 90% power.

Main analysis

The primary analysis approach for the primary outcome of composite of adverse fetal/neonatal outcomes, maternal secondary outcomes and the Infant Health Questionnaire will be intention to treat with participants analysed in the groups to which they are assigned regardless of deviation from the protocol or intervention received. The PARCA-R will be both an intention to treat and a per protocol analysis, since the hypothesis under examination for these outcomes is a non-inferiority hypothesis. The per-protocol analysis will exclude babies of women who do not receive their intervention as planned. As the trial includes multiple centres (and will involve a reasonable number of participants randomised per centre), the analysis will be based on the individual participant, allowing for clustering between participants within centre using robust SEs. All analyses will additionally adjust for gestational age at inclusion (stratification risk factor used in randomisation) as a fixed factor. For binary outcomes (composite of adverse fetal/neonatal outcomes, gestational hypertension, pre-eclampsia) a logistic regression model will be used to compare this outcome by arm and results presented as ORs and two-sided 95% CI. Continuous outcomes (PARCA-R, Infant Health Questionnaire) will be analysed using linear regression and results presented as adjusted differences in means alongside 95% CIs. The Infant Health Questionnaire will also be examined over time using a repeated measures model, and will include an interaction term for time (6, 12, 18 and 24 months) and

trial arm to investigate any divergent or convergent pattern in Infant Health Questionnaire. The categorical outcomes of mode of delivery and onset of labour will be compared between trial arms by fitting a multilevel ordinal regression model. The neonatal secondary outcome will be examined using the mean PARCA-R score between each trial arm using linear regression, and a one-sided 95% CI constructed to assess non-inferiority. Additional pre-specified sub-group analyses will be carried out to analyse the primary outcome in the whole cohort by those that are <10th percentile (vs ≥10th) and <3rd percentile (vs ≥3rd) based on different growth charts, maternal morbidity (yes/no) and corticosteroid administration (yes/no).[21 22] If numbers are sufficient, we will also describe the intervention effect in the subgroups <3rd percentile versus 4–10th vs >10th percentile but will not statistically tested for intervention effect.

All analyses will be undertaken after database lock following data collection at 2 years. No interim analyses are planned. Missing outcome data but will be accounted for in sensitivity analyses using multiple imputation, where we will assume that outcome data are missing at random given the observed measurements. All planned analyses will be described in detail in a statistical analysis plan, which will be finalised prior to database lock. The reporting of findings will be in accordance with the Consolidated Standards of Reporting Trials guidelines for Randomized Controlled Trials (RCTs). Statistical analysis will be performed in Stata (V.16 or higher).

Data collection

Data collection and randomisation are carried out on a secure cloud-based electronic data capture platform (Castor EDC, Amsterdam, The Netherlands). Participants can only be identified by their recruiting centres using unique trial identifiers. Participant email addresses will be stored for sending follow-up questionnaires within an encrypted section of Castor only their recruiting centre has access to.

Trial monitoring

A Trial Management Group will meet monthly to review study progress and recruitment targets. In addition there will be a Trial Steering Committee and Data Monitoring Committee, with a majority of independent members, to guarantee the safety of study participants.

A clinical trial risk assessment has been developed by CTR at Cardiff University, to determine the intensity and focus of central and on-site monitoring activity in the TRUFFLE 2 trial. Appropriate monitoring levels will be employed and are fully documented in the trial monitoring plan. Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Findings generated from on-site and central monitoring will be shared with the Sponsor, Chief Investigator (CI), PI and local Research & Development (R&D) departments.

Serious adverse events (SAEs) will be reported for randomised participants and their infants. The reporting period is from the point of randomisation until discharge home for the mother and neonate, maternal death is to be reported up to 42 days after delivery. SAEs will be reported on the data capture platform (Castor) in accordance with the UK policy framework for Health and Social care research.

Patient and public involvement

Patient and public involvement (PPI) has been embedded throughout the development of this study.

SANDS, the Stillbirth and Neonatal Death charity in the UK, has been closely involved in the development and design of this study. SANDS is clear that there is an urgent need for better assessment and care of women and their babies in late pregnancy and are fully supportive of the study. They will play an integral role throughout the study and in publicising the study and disseminating results in accessible formats. The research and development lead at SANDS is a member of the Trial Management Group. In their role, they represent members of the public affected by stillbirth and neonatal death.

An FGR PPI panel was convened to discuss TRUFFLE 2 study design. The purpose of the workshop was to ask members of the public for their views on the study, with specific focus on the concept of randomisation, the current situation for the treatment of FGR, and the scope of this study. The FGR panel comprised eight women who had experienced FGR, stillbirth or uncomplicated pregnancies. At the workshop the proposed study design was discussed. Following the workshop, the women were asked to complete an anonymous questionnaire relating to early delivery compared with monitoring the health of the baby in the womb and randomisation. Overall, women were supportive of the study, one stated 'I believe a lot of women will benefit from this study'. Another stated 'The study will have an impact; it will act as a ripple effect on the family and wider public for the better.' Regarding randomisation, most women said that they would be happy to be randomised to either arm while acknowledging that they would need support, one woman stated 'Yes, I would be randomised but would need the right support from the clinical staff. I would need to have 100% trust in my doctors'. Two women from this panel have agreed to be involved in the management of the study as independent members of the Trial Steering Committee. We incorporated the views and feedback of the PPI panel in the drafting of the patient information leaflet and consent forms to ensure clarity and comprehensibility.

Ethics and dissemination

This protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement (see online supplemental file 7—SPIRIT Checklist). The Study Coordination Centre has obtained approval from the London-Riverside Research Ethics Committee (REC) and Health Regulatory Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study has also been submitted to research

ethics committees in all participating countries, and each centre must confirm local ethical and hospital approval before starting recruitment. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Declaration of Helsinki 1964 and later revisions. Publication will be in line with National Institutes of Health Research (NIHR) Open Access policy.

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Contributors BM-F drafted and revised the protocol. BA, ABe, EB, ABh, CB, ACB, JB, PC, EC, IC, AD'A, CE, EF, TF, WG, KH, PK, LK, PL, SL, NM, KMa, GMM, FM, KMy, RN, FP, LR, JR, RKS, TS, JT, HV, GV and LW contributed intellectually to the development of the protocol and revised the draft protocol. EM, JG, CP and JT revised the draft protocol. RC-J wrote the statistical analysis plan. HW designed the data collection database, wrote the statistical analysis plan, contributed intellectually to the development of the protocol and revised the draft protocol. CCL initiated the collaborative project, led the development of the protocol and revised the draft protocol. All authors approved the final version for publication. All members of the TRUFFLE 2 Investigator Group collaborated on the study.

Methodology

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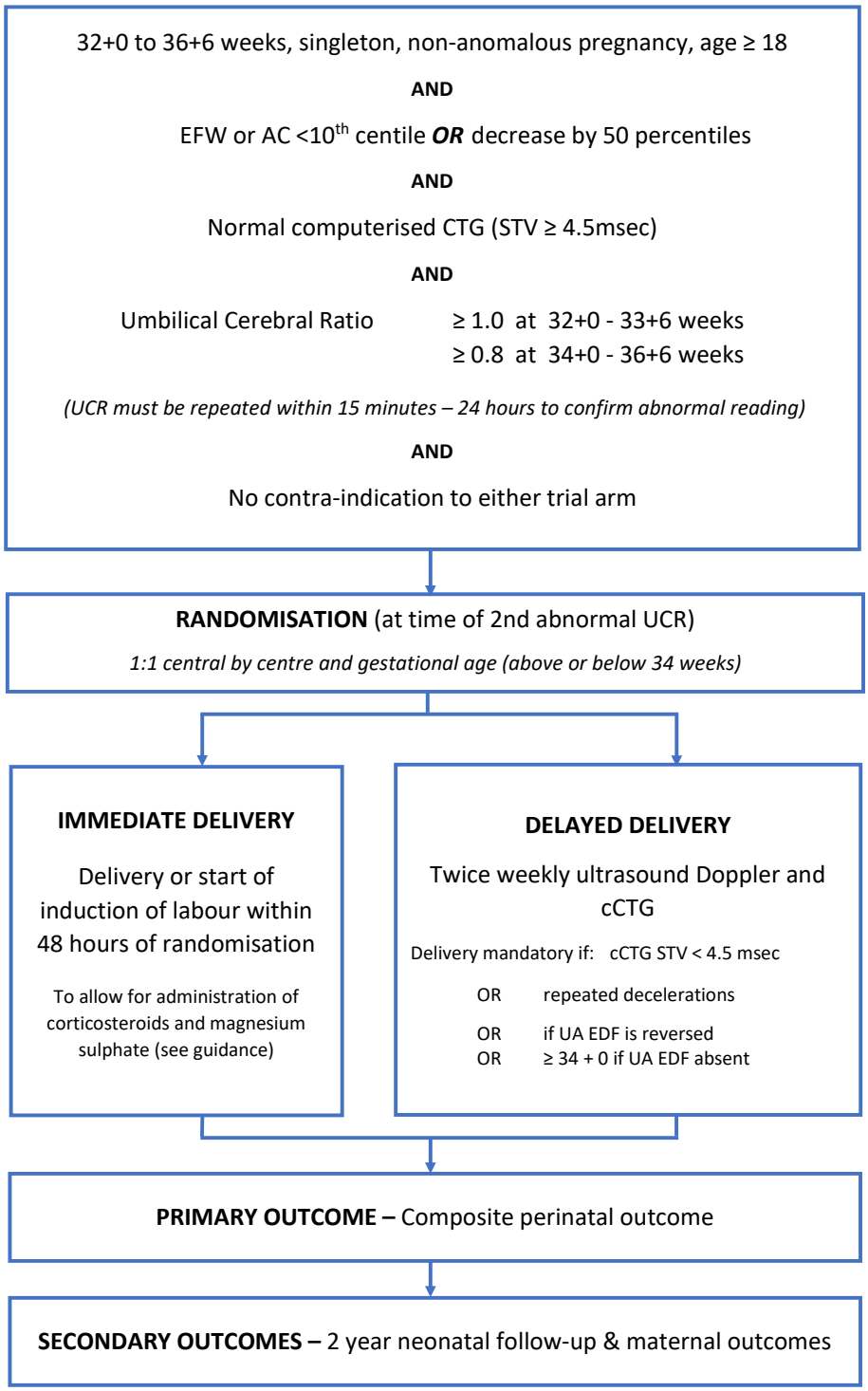
TRUFFLE 2 flowchart



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ADD LOCAL HOSPITAL HEADER

Information Sheet for Research Participants
TRUFFLE 2 study

Study title:

Perinatal and 2 year neurodevelopmental outcome in late preterm fetal compromise: the TRUFFLE 2 Randomised Trial

Chief Investigator:

Professor Christoph Lees, MD FRCOG

Principal Local Investigator:

You are being invited to take part in a research study, called the TRial of Umbilical and Fetal FLow in Europe (TRUFFLE) 2 Study. This leaflet is to help you decide whether to participate. It tells you why this study is being conducted and what taking part will mean for you. Please take time to read it carefully. Please get in touch with the study team if anything is not clear or if you would like more information. Take your time to decide whether or not you wish to be involved.

If you decide not to take part your future care will not be affected. If you do take part but decide later on that you don't want to after all, you can withdraw at any time – you do not have to give a reason and your care will not be affected.

Who is organising the research?

The TRUFFLE 2 study is being carried out in this hospital by …… and their team of doctors and midwives. It is also taking place in centres across the UK and internationally by members of the TRUFFLE research group. This group is made up of researchers and health professionals who specialise in caring for babies and mothers during pregnancy.

This study is sponsored and organised by Imperial College London, with The Centre for Trials Research, Cardiff University managing the trial on a day to day basis. The trial is being funded by the UK National Institute for Health Research (NIHR).

What is the purpose of the study?

Some babies grow more slowly in the womb than expected. This is called 'fetal growth restriction'. The slow growth can be seen on a scan.

Poor growth can be a warning sign about the baby's wellbeing. Doctors have many ways to monitor growth restricted babies, but there is no treatment in the womb; the only treatment is to deliver them. TRUFFLE is investigating the best time for this.

At the end of pregnancy (after 37 weeks) delivery is often recommended as there are fewer risks from birth at that point. Very early in pregnancy (before 32 weeks) doctors usually wait as long as possible, because the risks of premature birth are relatively large.

But when a pregnancy is affected by fetal growth restriction between 32 and 36 weeks of pregnancy, the decision about whether to deliver is more difficult. The possible problems of being delivered early must be balanced against the potential problems for the baby from growing slowly whilst in the womb, including stillbirth.

Currently, doctors don't have good information to help them decide about the best time to deliver a baby between 32 and 36 weeks of pregnancy. At the moment many different approaches are being used. This study aims to find answers about the safest time to deliver the baby.

How will the study work?

Pregnant women whose babies are either smaller or growing more slowly than expected between 32 and 36 weeks of pregnancy will be invited to take part in the screening phase of the study. At this point we will ask your permission to collect information about you and your baby.

Baseline Questionnaire
If you agree to take part in the screening phase of the study, we will ask you for your email address so we can email you a questionnaire to complete. This questionnaire will ask you questions about your ethnicity, job status and drinking and smoking habits.

Apart from this, your care will not change during the screening phase. You will have regular scans and baby heart rate monitoring as normal for small babies. One of the scan tests involves measuring the blood flow through the umbilical cord, and another the blood flow to the baby's brain.

If the blood flow is redirected to the baby's brain, this may be an early warning sign of problems and can be measured by a Doppler ultrasound. The idea is that if the placenta is not working well the baby responds by diverting blood to the most vital organ, the brain. However, many babies have this redistribution pattern remain otherwise perfectly healthy. We can test this by looking at the heart rate pattern. This normally varies moment by moment. You can see this as the line on the monitor being wiggly, rather than flat. The heart rate monitor also calculates a number to measure this pattern objectively. This number is known as short term variation.

If your baby's blood flow is redirected to their brain, but they also have a normal heart rate pattern, some experts would recommend delivery. Others would prefer to wait for the heart rate pattern to change. If you were not taking part in the TRUFFLE 2 trial your treatment would depend on which hospital and/or expert was treating you.

At this point we will invite you to join the main TRUFFLE 2 trial.
If you agree to participate at this stage you will be randomly allocated by a computer to receive one of two methods of treatment.
The two groups are:

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- To begin delivery within two days of the Doppler ultrasound blood flow test showing blood flow being redirected to the baby's brain, but before the heart rate pattern changes.
- To wait to deliver until the baby's heart rate pattern changes. This will typically involve twice weekly appointments for baby heart rate monitoring. Your doctor will recommend the exact frequency of this monitoring.

The way in which you give birth, vaginal or caesarean, will not be altered by participation in the trial. That will be left up to your preference and your doctor's recommendation. Your doctors may advise drugs that would be given routinely to improve baby's health when they are born early. These might include steroid injections for lung development and magnesium sulphate infusion for brain protection. Again, these will not be altered by participation in the trial. Your doctors will tell you what drug regime is normally used in your hospital.

We will assess how your baby is when she or he is first born, and then check their development up to two years of age by emailing you questionnaires to complete.

General Health Questionnaire
A general health questionnaire may be emailed to you 6, 12, 18 and 24 months after your baby is born. This questionnaire will ask you details of any hospital admissions for your baby in the last 6 months.

PARCA-R Questionnaire
The PARCA-R questionnaire may be emailed to you 2 years after your baby is born. This questionnaire is made up of two parts to look at your child's development. The questionnaire will be completed by you and will take 15 minutes.

All these questionnaires will be emailed to the email address you provided to the TRUFFLE 2 trials team. The email will come from no-reply@CastorEDC.com, please make sure you check your inbox around the times described above and let the research midwife know if you change your email address. Once completed the questionnaires will be sent back to the TRUFFLE 2 trials team.

We will also use anonymous information collected in the study to determine if there is a difference in the healthcare costs from the different groups in the TRUFFLE 2 study.

Do I have to take part?

No. It is your choice. If you are willing to be part of the study, you will be asked to complete a consent form. If you prefer not to take part, tell your doctor and we will not ask you again. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive in the future.

What are the possible disadvantages and risks of taking part?

The timing of your baby's birth will be based on which treatment group you are allocated to. The risks of being born too early are mainly of breathing problems for the baby and a very small risk of bleeding in the brain related to prematurity. The risks of waiting are that the baby's condition may deteriorate rapidly such that he or she gets seriously short of oxygen. All of these risks are very small. Neither ultrasound nor baby heart rate monitoring will cause harm to your baby directly.

What are the possible benefits of taking part?

There are no direct benefits to you from taking part in this study. There is some evidence that people who participate in medical research studies have generally better outcomes than those who don't. We hope that many women and their children in the future will benefit from your participation and the information we gain from this study.

What if a problem is detected?

If any unexpected problems are detected over the course of the study, your doctor will treat you as they think best, whatever trial group you are in. If, for example, you were allocated to the "wait for fetal heart rate changes before birth" group and a new problem, such as bleeding behind the placenta, developed such that delivery became the safest option, your doctor would deliver you. In such a scenario we would still wish to follow up you and your baby.

What happens if I withdraw?

If you decide to withdraw from the study, there are two options.

The first option is it withdraw consent to follow the treatment you were randomised to. This request will be respected and you can still give permission to be followed up by the study team and your data still analysed. You can decide to withdraw from the timing of delivery part of the study at any time without explanation. If you do so, your future care will not be affected by your decision.

The second option is to withdraw from the randomised treatment but also from any follow up data being collected as well. You are free to withdraw from follow up, however if many participants withdraw from follow up it could impact our results, we would therefore strongly prefer that you do not do this. If follow up becomes difficult, please discuss this with the study doctors or midwives. We will usually be able to reduce the burden, perhaps by limiting our contact to your GP rather than contacting you directly. Data that has been collected with your permission before you withdraw from follow up will be included in the study analysis.

Will my taking part in this study be kept confidential?

Imperial College London is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Imperial College London will keep identifiable information about you for 10 years.

Further information on Imperial College London's retention periods may be found at https://www.imperial.ac.uk/media/imperial-college/administration-and-support-services/records-and-archives/public/RetentionSchedule.pdf.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information [Dr Christoph Lees Email contact: c.lees@imperial.ac.uk].

LEGAL BASIS

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As a university we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

INTERNATIONAL TRANSFERS

There may be a requirement to transfer information to countries outside the European Economic Area (for example, to a research partner). Where this information contains your personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a European Commission (EC) adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient organisation that incorporates EC approved standard contractual clauses that safeguard how your personal data is processed.

CONTACT US

If you wish to raise a complaint on how we have handled your personal data or if you want to find out more about how we use your information, please contact Imperial College London's Data Protection Officer via email at dpo@imperial.ac.uk, via telephone on 020 7594 3502 and via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ.

If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO). The ICO does recommend that you seek to resolve matters with the data controller (us) first before involving the regulator.

Imperial College London will collect information about you for this research study from Imperial College Healthcare Trust. This information will include your hospital number, contact details and health information, which is regarded as a special category of information. We will use this information to conduct this study and contact you with questionnaires.

How we will use and store your information

The TRUFFLE-2 researchers will use and store information about you and your baby for the purpose of the research. This will include contacting you, your hospital doctors and your family doctor to follow you both up. They will keep your information secure and confidential in accord with European data protection rules. Certain authorised individuals may also look at your medical and research records to check the accuracy of the research study.

Potential use of study data for future research

When you agree to take part anonymous information about your health and care may be provided to other authorised researchers. This use of your information without your explicit permission is strictly regulated and will not identify you.

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We will also ask your permission to contact you in future to participate in future research studies where your identifiable information would be used. Your participation in such research will only be with your consent.

Who has reviewed the study?

This study was given a favourable ethical opinion for conduct in the NHS by the **London- Riverside** Regional Ethics Committee NHS Health Research Authority.

The IRAS reference number is 266400.

What if something goes wrong?

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation. If you are harmed due to someone's negligence, then you may have grounds for a legal action.

Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Dr Christoph Lees Email contact: c.lees@imperial.ac.uk).

The normal National Health Service complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Compliance Office.

Contact for further information:

For more information you can phone:

Research Fellow and Midwife on 02033137316, or Professor Christoph Lees on 02075942104

Or write to either:

TRUFFLE 2 Investigators, Centre for Fetal Care, Queen Charlotte's & Chelsea Hospital, Du Cane Road, W12 0HS, London
Email: Imperial.TRUFFLEstudy@nhs.net

PALS:

If you have any concerns or wish to complain the details of your local Patient Advice and Liaison Service (PALS) are available on your local hospital's website or on www.nhs.uk.

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ADD LOCAL HOSPITAL HEADER

INFORMED CONSENT FORM for DATA COLLECTION

Full Title of Project: **Perinatal and 2 year neurodevelopmental outcome in late preterm fetal compromise: the TRUFFLE 2 Randomised Trial**

Chief Investigator: **Professor Christoph Lees**

Participant number: ☐☐ __ ☐☐☐ __ ☐☐☐

This consent form is for patients who are PRE-ELIGIBLE, who have a small baby with a NORMAL cerebral Doppler.

	Please initial box
1. I confirm that I have read and understand the patient information sheet dated ……/……../……., version ……. for the above trial. I have had the opportunity to ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.	☐
3. I understand that sections of my and my baby's medical notes may be looked at by responsible individuals from Imperial College London, from the NHS Trust or from regulatory authorities where it is relevant to my taking part in this research.	☐
4. I give permission for these individuals to access my and my baby's records that are relevant to this research.	☐
5. **Optional:** I give consent for information collected about me and my baby to be used to support other ethically approved research in the future, including those outside of the EEA.	☐
6. **Optional:** I consent to being contacted to potentially taking part in other research studies.	☐
7. I consent for information from my records to be used as part of the TRUFFLE 2 trial.	☐
8. I understand that this form is NOT consent for randomisation.	☐

_____	_____	_____
Name of Subject	Signature	Date
_____	_____	_____
Name of Person taking consent	Signature	Date
_____	_____	_____
Principal Investigator	Signature	Date

1 copy for subject; 1 copy for Principal Investigator; 1copy to be kept with hospital notes

ADD LOCAL HOSPITAL HEADER

INFORMED CONSENT FORM for RANDOMISATION

Full Title of Project: **Perinatal and 2 year neurodevelopmental outcome in late preterm fetal compromise: the TRUFFLE 2 Randomised Trial**

Chief Investigator: **Professor Christoph Lees**

Participant number: ☐☐ ___ ☐☐☐ ___ ☐☐☐

This consent form is for patients who are ELIGIBLE FOR RANDOMISATION. This means they have a small baby (EFW or AC <10th or fallen 50 centiles) AND an abnormal UCR (repeated to confirm abnormality within 2-24 hours).

Please initial box

Part A

1. I confirm that I have read and understand the patient information sheet dated .../.../... *Version ….* for the above trial. I have had the opportunity to ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my and my baby's medical notes may be looked at by responsible individuals from Imperial College London, from the NHS Trust or from regulatory authorities where it is relevant to my taking part in this research. ☐

4. I give permission for these individuals to access my and my baby's records that are relevant to this research. ☐

5. I understand that my family doctor will be informed of my participation in the trial. ☐

6. **Optional:** I give consent for information collected about me and my baby to be used to support other ethically approved research in the future, including those outside of the EEA. ☐

7. **Optional:** I consent to being contacted to potentially taking part in other research studies. ☐

Part B

8. I consent to be randomised to either immediate or delayed delivery for this trial. ☐

_____	_____	_____
Name of Subject	Signature	Date
_____	_____	_____
Name of Person taking consent	Signature	Date
_____	_____	_____
Principal Investigator	Signature	Date

1 copy for subject; 1 copy for Principal Investigator; 1copy to be kept with hospital notes

Parent Report of Children's Abilities – Revised (PARCA-R Questionnaire)

Your child's health and development at 2 years

In this form we ask you to answer some questions about your child and your family. This information is used to work out how your child is developing now that she/he is just over two years old. **Please complete all the questions as accurately as possible.**

If you need any help completing the questionnaire, or have any queries about the questions, please do not hesitate to ask the doctor about these at your appointment.

For further information about the English version of the PARCA-R questionnaire, please **email**:
parca-r@leicester.ac.uk

Your child's play

As a parent, you will have a good idea of what your child can and can't do. Listed below are a number of activities. Please indicate whether or not your child can do the activity. That is, if you have seen your child do the activity (or something similar) then tick the box under "YES". If you know that your child would not be able to do it, then tick the box under "NO". If you are not sure whether or not your child can do it, then tick the box under "DON'T KNOW". Please answer every question.

Please keep in mind that these questions are for children ranging from 18 months to 4 years. Some activities may be easy for your child, others may be difficult. Most children of your child's age will not be able to do some of the activities.

		YES	NO	DON'T KNOW
1	**Does your child copy things you do such as cuddling a teddy?** (Try it out if not sure by cuddling a teddy and then giving it to your child. Say: Now you cuddle teddy)	☐	☐	☐
2	**When you hide a toy in full view of your child, will s/he look for it and find it?** (Try this out by covering a small toy with a cloth or a cup and seeing if s/he uncovers the toy)	☐	☐	☐
3	**Can your child put a simple piece, such as a square or an animal, into the correct place in a puzzle board?**	☐	☐	☐
4	**Some toys have several holes or openings with different shapes, such as a circle, triangle, and star. Could your child put the shapes into the right openings?**	☐	☐	☐
5	**Can your child stack two small blocks or toys on top of each other?**	☐	☐	☐
6	**Can your child put together, by him/herself, a puzzle or something similar where the pieces fit together?**	☐	☐	☐
7	**If so, can s/he do this for a puzzle with ten or more pieces?**	☐	☐	☐
8	**Can your child mark on a piece of paper using the tip of a crayon, pencil, or chalk?**	☐	☐	☐
9	**Can your child draw a more or less straight line on paper?**	☐	☐	☐
10	**Does your child turn, or try to turn, pages of a book one at a time?**	☐	☐	☐
11	**Does your child ever pretend that one object, such as a block, is another object, such as a car or a telephone?**	☐	☐	☐

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parca-r@leicester.ac.uk

		YES	NO	DON'T KNOW
12	**Can your child stack three small blocks or toys on top of each other by him/herself?**	☐	☐	☐
13	**Does your child ever pretend to do things? For example, riding a horse or making a cup of tea?**	☐	☐	☐
14	**Can your child push a car along the floor with the wheels on the floor?**	☐	☐	☐
15	**Does your child look with interest at pictures in a book?**	☐	☐	☐
16	**Does your child point to pictures in a book?**	☐	☐	☐
17	**Does your child try to copy things you do, such as stirring with a spoon in a cup?**	☐	☐	☐
18	**Can your child stack seven small blocks or toys on top of each other by him/herself?**	☐	☐	☐
19	**Does your child point or show where people or objects are when you ask: "Where is the light?" "Where is Daddy?" or "Where is Teddy?"**	☐	☐	☐
20	**Does your child ever pretend that two dolls are playing together, or are talking to each other, or one is feeding the other?**	☐	☐	☐
21	**Does your child ever play pretend games with another child, pretending to be someone else, such as a mummy, daddy, policeman, or nurse?**	☐	☐	☐
22	**Does your child ever play any game with another child that involves taking turns?**	☐	☐	☐
23	**Does your child ever copy some action shortly (within a few minutes) after s/he has seen it?**	☐	☐	☐
24	**Can your child fetch something, such as a toy, from another room by him/herself when you ask?**	☐	☐	☐
25	**Does your child know where some things belong, such as, that his/her toys belong in a box?**	☐	☐	☐
26	**Does your child ever save or put to one side a biscuit (or snack) for later, on his/her own?**	☐	☐	☐
27	**Have you ever seen your child get together three or more toys before beginning to play with them?**	☐	☐	☐
28	**Have you ever seen your child sort things (blocks, other toys) into groups or piles that go together on his/her own?**	☐	☐	☐

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		YES	NO	DON'T KNOW
29	**If your child wants something out of reach, does s/he go and find a chair or box to stand on?**	☐	☐	☐
30	**When your child uses or plays with a telephone, does s/he speak into the mouthpiece not the earpiece?**	☐	☐	☐
31	**When your child drinks from a cup, is s/he careful about putting it down, trying not to spill it?**	☐	☐	☐
32	**Does your child try to turn doorknobs, twist tops, or screw lids on or off jars?**	☐	☐	☐
33	**Does your child recognise him/her self when looking in the mirror?**	☐	☐	☐
34	**Does your child ever use his/her index (first) finger to point to show an interest in something?**	☐	☐	☐

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parca-r@leicester.ac.uk

What your child can say

1. Children understand many more words than they can say. Here, we are only interested in the words your child SAYS. Please tick all the words you have heard your child say. If your child uses a different pronunciation of a word – e.g., "tend" for pretend, or "duce" for juice – tick it anyway. Please keep in mind that this is only a sample of words; your child may know many other words not on this list.

☐ Baa baa	☐ Cream cracker	☐ Bed	☐ Carry	☐ Last
☐ Meow	☐ Juice	☐ Bedroom	☐ Chase	☐ Tiny
☐ Ouch/ow	☐ Meat	☐ Settee/sofa	☐ Pour	☐ Wet
☐ Uh-oh/oh dear	☐ Milk	☐ Oven/cooker	☐ Finish	☐ After
☐ Woof woof	☐ Peas	☐ Stairs	☐ Fit	☐ Day
☐ Bear	☐ Hat	☐ Flag	☐ Hug/cuddle	☐ Tonight
☐ Bird	☐ Necklace	☐ Rain	☐ Listen	☐ Our
☐ Cat	☐ Shoe	☐ Star	☐ Like	☐ Them
☐ Dog	☐ Sock	☐ Swing	☐ Pretend	☐ This
☐ Duck	☐ Chin	☐ School	☐ Rip/tear	☐ Us
☐ Horse	☐ Ear	☐ Sky	☐ Shake	☐ Where
☐ Aeroplane	☐ Hand	☐ Zoo	☐ Taste	☐ Beside
☐ Boat	☐ Leg	☐ Friend	☐ Gentle	☐ Down
☐ Car	☐ Pillow	☐ Mummy/mum	☐ Think	☐ Under
☐ Ball	☐ Comb	☐ Person	☐ Wish	☐ All
☐ Book	☐ Lamp/torch	☐ Bye/byebye	☐ All gone	☐ Much
☐ Game	☐ Plate	☐ Hi/hello	☐ Cold	☐ Could
☐ Sandwich	☐ Rubbish	☐ No	☐ Fast	☐ Need to
☐ Fish	☐ Tray	☐ Shopping	☐ Happy	☐ Would
☐ Sauce	☐ Towel	☐ Thank you	☐ Hot	☐ If

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How your child uses words

2. We would like to know how your child uses the words s/he can say. Please tick one box for each question below to tell us whether your child uses words like this often, sometimes, or not yet.

Please keep in mind that these questions are for children up to 4 years of age. Many children of your child's age will not be able say some of the words or sentences below.

		OFTEN	SOMETIMES	NOT YET
A1	Does your child ever talk about past events or people who are not present? For example, a child who saw a carnival last week might later say 'carnival', 'clown', or 'band'.	☐	☐	☐
A2	Does your child ever talk about something that is going to happen in the future? E.g. saying 'choo-choo' or 'bus' before you leave the house on a trip, or saying 'swing' when you are going to the park?	☐	☐	☐
A3	Does your child ever talk about objects that are not present? For example, asking about a missing toy not in the room, or asking about someone not present?	☐	☐	☐
A4	Does your child understand if you ask for something that is not in the room? For example, would s/he go to the bedroom to get a teddy bear when you say 'Where's the bear?'	☐	☐	☐
A5	Does your child know who things belong to? For example, a child might point to mummy's shoe and say 'Mummy'.	☐	☐	☐
A6	Has your child started to put together words yet, such as 'Daddy gone' or 'Doggie bite'?	☐	☐	☐

If you answered "Sometimes" or "Often" to question A6, please answer all the questions on the next page.

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3. For EACH PAIR of sentences below – A and B – please tick the one that sounds MOST like the way your child talks at the moment, even if s/he would not say that EXACT sentence. If your child is saying sentences even more complicated than the two examples provided, tick B.

	Talking about something happening right now		Talking about something that already happened		
A7			**A8**		
A	☐	I make tower	☐	Daddy pick me up	
B	☐	I making tower	☐	Daddy picked me up	
A9					
A	☐	That my truck			
B	☐	That's my truck			
A10			**A11**		
A	☐	Baby crying	☐	There a doggie	
B	☐	Baby is crying	☐	There's a doggie	
A12					
A	☐	Coffee hot			
B	☐	That coffee hot			
A13			**A14**		
A	☐	I no do it	☐	I like read stories	
B	☐	I can't do it	☐	I like to read stories	
A15					
A	☐	Biscuit mummy			
B	☐	Biscuit for mummy			
A16			**A17**		
A	☐	Don't read book	☐	Baby want eat	
B	☐	Don't want you read that book	☐	Baby want to eat	
A18					
A	☐	Look at me			
B	☐	Look at me dancing			

Thank you very much for your time

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Survey 'GB_InfantHealthSurvey'

GB_InfantHealthSurvey - InfantGrowth

Number	Question	Answers
	Could you enter below the last weight and height of your child and the date when it was measured. Please use the measurements from your last visit to a child health clinic, or take the measurements yourself.	
1.1	Date of measurement	*(dd-mm-yyyy)*
1.2	Height (cm)	cm
1.3	Weight (Kg)	kg

GB_InfantHealthSurvey - InfantInpatientCare

Number	Question	Answers
	The following questions ask about your child's use of hospital services for the LAST SIX MONTHS only. Please answer all questions as accurately as possible.	
2.1	Has your child been admitted to hospital in the last six months?	○ Yes ◉ No
2.1.1	***If 'Has your child been admitted to hospital in the last six months?' is equal to 'Yes' answer this question:*** In which month was your child admitted in hospital?	○ January ○ February ○ March ○ April ○ May ○ June ○ July ○ August ○ September ○ October ○ November ○ December

2.1.2	***If 'Has your child been admitted to hospital in the last six months?' is equal to 'Yes' answer this question:*** In which year was your child admitted in hospital?	○ 2020 ○ 2021 ○ 2022 ○ 2023 ○ 2024 ○ 2025 ○ 2026
2.1.3	***If 'Has your child been admitted to hospital in the last six months?' is equal to 'Yes' answer this question:*** Was the admission planned or an emergency	○ Planned ○ Emergency
2.1.4	***If 'Has your child been admitted to hospital in the last six months?' is equal to 'Yes' answer this question:*** What was the reason for the admission?	
2.1.5	***If 'Has your child been admitted to hospital in the last six months?' is equal to 'Yes' answer this question:*** Did your child stay overnight in the hospital?	○ Yes ○ No
2.1.5.1	***If 'Did your child stay overnight in the hospital?' is equal to 'Yes' answer this question:*** For how many nights did your child stay in hospital?	
2.1.6	***If 'Has your child been admitted to hospital in the last six months?' is equal to 'Yes' answer this question:*** Did your child receive intensive care?	○ Yes ○ No
2.1.6.1	***If 'Did your child receive intensive care?' is equal to 'Yes' answer this question:*** For how many nights did your child stay in the intensive care?	
2.2	Check Admission	
2.2.1	***If 'Check Admission' is equal to '1' answer this question:*** Has your child been admitted to hospital for a second time in the last six months?	○ Yes ○ No
	----------_SECOND ADMISSION_----------	

GB_InfantHealthSurvey - InfantOutpatientCare

Number	Question	Answers
	The following questions ask if your child attended a hospital outpatient department/clinic for the LAST SIX MONTHS only. Please answer all questions as accurately as possible.	
3.1	Has your child attended a hospital outpatient department/clinic in the last six months	○ Yes ◉ No
3.1.1	***If 'Has your child attended a hospital outpatient department/clinic in the last six months' is equal to 'Yes' answer this question:*** Which type of clinic did your child visit during the last six months?	○ Accident or Emergency ○ Paediatric / Neonatal Follow-up ○ Orthopaedic ○ Audiology / Hearing ○ Eye / Vision ○ General Medicine ○ Dermatology ○ Other
3.1.1.1	***If 'Which type of clinic did your child visit during the last six months?' is equal to 'Other' answer this question:*** Which specialty of outpatient department / clinic did your child visit during the last six months?	
3.1.2	***If 'Has your child attended a hospital outpatient department/clinic in the last six months' is equal to 'Yes' answer this question:*** What was the reason for this visit?	
3.1.3	***If 'Has your child attended a hospital outpatient department/clinic in the last six months' is equal to 'Yes' answer this question:*** How many times did your child visit this clinic during the past half year?	
3.2	CheckOPD	
3.2.1	***If 'CheckOPD' is equal to '1' answer this question:*** Has your child attended a second hospital outpatient department/clinic in the last six months	○ Yes ○ No
	----------_SECOND VISIT_----------	

TRUFFLE 2

Imperial College London

Doppler Image Scoring

For Umbilical Artery:

PULSEWAVE IMAGE (/6)	1 point	0 point
Magnification	Doppler display occupies 50% or more of the image	Doppler display occupies <50% of the image
Angle of insonation	<30 degrees	30 degrees or more
Sweep speed	Doppler spectrum has 4-10 waveforms	Doppler spectrum has < 4 (3 or less) or > 10 waveforms (11 or more)
Sample gate	Large enough to include 3/4th of the vessel diameter	Smaller than 3/4th of the vessel diameter
Appropriate PRF	The waveform fits at least 75% of the pulse wave Doppler scale or PRF (pulse repetition frequency)	The waveform fits < 75% of the pulse wave Doppler scale or PRF
Image quality	Uniform arterial waveforms, no aliasing or background artefacts or fetal breathing movements	Variable arterial waveforms/ aliasing/background artefacts/fetal breathing movements

For Middle Cerebral Arterial: (as above)

PULSEWAVE IMAGE (/6)	1 point	0 point
Magnification	Doppler display occupies 50% or more of the image	Doppler display occupies <50% of the image
Angle of insonation	<30 degrees	30 degrees or more
Sweep speed	Doppler spectrum has 4-10 waveforms	Doppler spectrum has < 4 (3 or less) or > 10 waveforms (11 or more)
Sample gate	Large enough to include 3/4th of the vessel diameter	Smaller than 3/4th of the vessel diameter
Appropriate PRF	The waveform fits at least 75% of the pulse wave Doppler scale or PRF	The waveform fits < 75% the pulse wave Doppler scale or PRF
Image quality	Uniform arterial waveforms, no aliasing or background artefacts or fetal breathing movements	Variable arterial waveforms/ aliasing/background artefacts/fetal breathing movements

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	*see note
Funding	4	Sources and types of financial, material, and other support	4, 14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3, 14
	5b	Name and contact information for the trial sponsor	4
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8, 11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8, 11, Supp File 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11-12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8, Supp Files 2+3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	*see note
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	*see note
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	*see note
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13-14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supp Files 2+3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*Live study documents (such as protocol, consent forms, etc) are continuously reviewed and updated as the trial is ongoing, these all contain version numbers and dates, and each site must demonstrate that they are using the up to date and current version. Contracts between Imperial and each participating site contain information regarding confidentiality, publication, data protection, indemnity, etc.