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When to deliver small babies between 32 and 37 weeks - TRUFFLE 2

Submission date 05/09/2019	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 20/04/2020	**Overall study status** Ongoing	
Last Edited 28/04/2025	**Condition category** Pregnancy and Childbirth	

Plain English summary of protocol

Background and study aims
In the last months of pregnancy, babies who are smaller or who grow more slowly than expected are at higher risk of dying in the mother's womb. Some of these smaller babies who survive may have developmental problems later in infancy. Doctors have many ways to monitor such babies in the womb but until the baby is born, the only treatment available is to deliver the baby.
If the pregnancy has reached its full term, induction of labour is the usual option. If the baby is preterm (before 37 weeks of pregnancy), the right course of action is less clear. Delivering the baby early, as soon as there are signs of problems, will minimise any damage due to lack of oxygen in the womb, but the baby may suffer harm as a result of being born prematurely. This study is looking at the balance of risks linked with continuing the pregnancy a little longer or delivering the baby early.

Who can participate?
Pregnant women whose babies are either smaller or growing more slowly than expected between 32 and 36 weeks of pregnancy will be invited to participate in the study.

What does the study involve?
Babies will be closely monitored with ultrasound scans, Doppler tests for blood flow and computerised heart rate tests. All these tests are regularly used in normal maternity care and are safe. If the Doppler test shows changes in the blood flow to the baby’s brain, mothers will be randomly assigned to one of two groups: in one group the babies will be delivered immediately. In the other group the babies will continue to be monitored closely. Babies in the second group will be delivered if computerised analysis of the baby’s heart rate shows signs of deteriorating health. The health of all the babies will be recorded at birth, and their development checked at two years of age.

What are the possible benefits and risks of participating?
The timing of the baby’s birth will be chosen at random. The risks of being born too early are mainly 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 the baby directly.

Patient and Public Involvement (PPI)
Sands, the stillbirth and neonatal death charity, is the main stillbirth support charity in the UK and has been closely involved in the development and design of TRUFFLE 2 RCT. Senior SANDS Research Members (Charlotte Bevan and Laura Price) took part in TRUFFLE meetings in Naples 2016 and Berlin 2017. Sands is clear that there is an urgent need for better assessment and care of women and their babies in late pregnancy and supports the study.
The topic of this trial has also been prioritised by the Royal College of Obstetrics and Gynaecology's (RCOG) Stillbirth Clinical Studies Group, and addresses three of the James Lind Alliance (JLA) Stillbirth Priority Setting Partnership's priorities. The study is closely aligned with the NHS 'Saving Babies' Lives Care Bundle', one of whose four key components is the detection of fetal growth restriction. The study also has support from patient groups aligned with the European TRUFFLE centres. As part of the Feasibility Study (www.truffle-study.org), 14 women commented on the objectives of the trial as a pilot in one centre. All supported the objectives and 12/14 would consider participation.

Where is the study run from?
Imperial College NHS Trust (UK)

When is the study starting and how long is it expected to run for?
June 2020 to April 2027

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Prof. Christoph Lees, christoph.lees@nhs.net

Study website
http://www.truffle-study.org/

Contact information

Type(s)
Scientific

Contact name
Prof Christoph Lees

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
266400

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
19QC5491, CPMS 45166, NIHR127976, IRAS 266400

Study information

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

Acronym
TRUFFLE 2

Study objectives
Current study hypothesis as of 27/07/2020:
Delivery on the basis of cerebral blood flow redistribution reduces a composite of perinatal poor outcome, death and short-term hypoxia-related morbidity without a worsening of neurodevelopmental outcome at 2 years.

Previous study hypothesis:
Delivery on the basis of cerebral blood flow redistribution reduces a composite of perinatal poor outcome, death and short-term hypoxia-related morbidity (efficacy outcome)

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 04/02/2020, Ethics Board: London Riverside Research Ethics Committee (Chelsea & Westminster Hospital, 369 Fulham Road, London, SW10 9NH, UK; +44 (0)207 104 8340, 0207 104 8199; riverside.rec@hra.nhs.uk), REC ref: 20/LO/0031

Study design
Multicentre individually randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Fetal growth restriction

Interventions
Current interventions as of 27/07/2020:
Women will be randomised to delivery or conservative management (cCTG monitoring and traditional ultrasound). The randomisation process will be completed through the CASTOR website.

Participants in the immediate delivery (intervention) arm will be delivered (or induction of labour started) within 48 hours, allowing for administration of corticosteroids and infusion of magnesium sulphate as per local protocol/guidance.

Participants in the delayed delivery (control) arm will be closely monitored using twice-weekly Doppler and cCTG monitoring. Delivery is indicated when STV < 4.5msec on cCTG or there are repeated decelerations.

Assessment of the primary outcome will be at infant discharge from the NNU and assessment of the key secondary infant outcomes using the general health questionnaire and PARCA-R. The general health questionnaire will be sent out by the Castor website at 6, 12, 18 and 24 months postpartum. Neurodevelopment will be assessed at 2 years age corrected for prematurity using parent-report: PARCA-R. The window for determining 2-year outcome will be from 22-28 months over which range the PARCA-R has been standardised.

Previous interventions:
Women will be randomised to delivery or conservative management (cCTG monitoring and traditional ultrasound). The randomisation process will be completed through the CASTOR website.

Participants in the delivery arm will be delivered within 48 hours, allowing for administration of corticosteroids and infusion of magnesium sulphate as per local protocol/guidance.

Participants in the conservative arm will be closely monitored using twice-weekly Doppler and cCTG monitoring. UCR may be measured in this time but women may not be delivered based on this. Delivery is indicated when STV < 4.5msec on cCTG or there are repeated decelerations.

Two-year developmental outcomes - research administrators will contact the women at 20 - 22 months corrected age in order to establish baby’s whereabouts and discuss the PARCA-R test which must be performed at 24 months and establish in which language this should be tested.

After the PARCA-R is undertaken by the parents, the questionnaire is sent back to the central two year follow up assessment office of University College London (or, if this is not possible a jpeg or pdf may be emailed) for scoring and data entry to the CASTOR website.

Intervention Type
Other

Primary outcome measure
Current primary outcome measure as of 27/07/2020:
Composite poor condition at birth and neonatal adverse outcome. Any of the following:
1. Poor condition at birth
1.1. Apgar score at 5 minutes <7, arterial pH of <7.0 or venous pH of <7.1
1.2. Resuscitation with intubation, chest compressions or medication
2. Fetal death/death before neonatal hospital discharge
3. Neonatal brain injury syndromes
3.1. Infants with a diagnosis consistent with hypoxic ischaemic encephalopathy: term and near-term infants only
3.2. Infants with a diagnosis of intracranial haemorrhage, perinatal stroke, hypoxic ischaemic encephalopathy (HIE), central nervous system infection, and kernicterus (bilirubin encephalopathy): all infants
3.3.Preterm white matter disease (periventricular leukomalacia): preterm infants only
3.4. Infants with a recorded seizure confirmed by EEG
4. Respiratory support
4.1. Need for mechanical support of respiration after admission to NNU, for more than 1 hour – includes need for continuous positive airways pressure (CPAP or NIPPV) or mechanical ventilation via and endotracheal tube – but excludes need for supplemental oxygen
5. Cardiovascular abnormality
5.1. Hypotensive treatment, ductus arteriosus treatment, or disseminated coagulopathy
6. Sepsis (clinical sepsis with positive blood culture, or necrotising enterocolitis requiring surgery)
7. Retinopathy of prematurity requiring treatment (laser or anti-VEGF injections)

Previous primary outcome measure:
Success of delivery measured using:
1. Intrauterine fetal death or neonatal death before hospital discharge
2. Gestational age at delivery
3. Birthweight
4. Birth condition (Apgar score, cord pH)
5. Admission to neonatal unit
6. Neonatal brain injury syndromes
7. Respiratory support
8. Number of neonatal unit admission days
9. Level of neonatal care
10. Morbidity including duration of respiratory support, chronic lung disease, severe intraventricular haemorrhage grade III/IV, necrotising enterocolitis requiring surgery, retinopathy of prematurity requiring treatment.

Secondary outcome measures
Current secondary outcome measures as of 27/07/2020:
For the baby:
1. Health and developmental outcomes assessed using PARCA-R questionnaire at 2 years and the general health questionnaire up to 2 years corrected age. The PARCA-R will be completed at

24 months from correct age. It allows the following scales to be derived: 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 where preterm babies (born before 37 weeks) use estimate date of delivery as opposed of date of birth.
2. The general health questionnaire (REF) will be used to derive the following health outcomes at 6, 12, 18 and 24 months postpartum:
2.1. Use of ANY hospital service (yes/no) and total number of contacts over the 2 year period
2.2. Admitted to hospital (yes/no) and total number of admissions over the 2 year period
2.3. Planned/unplanned admissions to hospital (yes/no) over the 2 year period
2.4. Intensive care or not over the 2 year period
2.5. Attended A&E (and not subsequently admitted) (yes/no) over the 2 year period
2.6. Attended Outpatients/clinic (yes/no) over the 2 year period

For the mother:
1. Gestational hypertension as defined by the International Society for Trial of Hypertension in pregnancy (ISSHP): hypertension (blood pressure ≥140/90mmHg) arising de novo after 20 weeks gestation in the absence of proteinuria
2. Pre-eclampsia as defined by the ISSHP: (blood pressure ≥140/90mmHg AND significant proteinuria (protein/creatinine ratio of 30 mg/mmol)
3. Onset of labour (spontaneous, induction (method), prelabour cesarean)
4. Mode of delivery (spontaneous vaginal, assisted vaginal, caesarean)

Previous secondary outcome measures:
1. For the baby:
Two-year developmental outcomes assessed by the PARCA-R performed at 24 months
2. For the mother:
2.1 Pre-eclampsia, as defined by the International Society for Study of Hypertension in pregnancy (ISSHP): (blood pressure ≥140/90mmHg AND significant proteinuria (protein /creatinine ratio of 30 mg/mmol)
2.2 Induction of labour (method)
2.3 Mode of delivery (spontaneous vaginal, assisted vaginal, caesarean)

Overall study start date
01/12/2019

Completion date
30/04/2027

Eligibility

Key inclusion criteria
Current inclusion criteria as of 27/07/2020:
All criteria should be fulfilled to be eligible for randomisation:
1. Women ≥ 18 years old
2. Pregnant with singleton non-anomalous fetuses
3. Between 32+0 and 36+6 weeks of gestation
4. Estimated fetal weight or abdominal circumference <10th percentile OR decreased by 50 percentiles since an ultrasound scan at 18+0-32+0 weeks

5. Cerebral redistribution defined as UCR >1.0 (32+0-33+6 weeks) or >0.8 (34+0-36+6 weeks) measured at least twice in any 24 hours period
6. Normal STV on cCTG (4.5 msec or above)

Previous inclusion criteria:
For screening:
1. Women ≥ 18 years old
2. Pregnant with singleton fetuses at risk of compromise:
2.1 Between 32+0 and 36+6 weeks of gestation and
2.2 Estimated fetal weight or abdominal circumference <10th percentile OR abdominal circumference decreased by 50 percentiles from 18-22 week scan

For randomisation:
3.1 Cerebral redistribution defined as UCR z-score >1.5 (32-33+6 weeks) / >1.0 (34-36+6 weeks) and:
3.2 Normal STV on cCTG (> 4.5msec) and:
3.3 No contraindications to either trial treatment arm

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
319 participants per arm are required, giving 638 in total

Key exclusion criteria
Current exclusion criteria as of 27/07/2020:
1. Indication for immediate delivery required within 48 hours
2. Unable to give informed consent
3. Preterm prelabour rupture of the membranes (PPROM)
4. Suspected placental abruption or antepartum haemorrhage
5. Presence of reversed end diastolic flow in the Umbilical Artery

Previous exclusion criteria:
1. Indication for immediate delivery within 48 hours
2. Unable to give informed consent
3. Preterm prelabour rupture of the membranes (PPROM)
4. Suspected placental abruption or antepartum haemorrhage

Date of first enrolment
01/10/2020

Date of final enrolment

30/04/2025

Locations

Countries of recruitment
Austria

Belgium

Czech Republic

England

Estonia

Germany

Italy

Norway

Poland

Spain

United Kingdom

Study participating centre
Queen Charlotte's and Chelsea Hospital
Imperial College NHS Trust
DuCane Road
London
United Kingdom
W12 0HS

Study participating centre
Queen Elizabeth Hospital
Edgbaston
Birmingham
United Kingdom
B15 2WB

Study participating centre
Liverpool Women's NHS Foundation Trust
Crown Street

Liverpool
United Kingdom
L8 7SS

Study participating centre
The Princess Alexandra Hospital NHS Trust
Hamstel Road
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United Kingdom
CM20 1QX

Study participating centre
Queens Medical Centre
Nottingham University Hospitals NHS Trust
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
St George's Hospital
St George's University Hospitals NHS Foundation Trust
Blackshaw Road
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London
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SW17 0QT

Study participating centre
St. James's University Hospital
Leeds Teaching Hospitals NHS Trust
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
East Suffolk and North Essex NHS Foundation Trust
Colchester District General
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Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
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NW1 2PG

Study participating centre
Chelsea and Westminster Hospital NHS Foundation Trust
369 Fulham Road
London
United Kingdom
SW10 9NH

Study participating centre
Guy's & St Thomas' NHS Foundation Trust
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SE1 7EH

Sponsor information

Organisation
Imperial College London

Sponsor details
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Sponsor type

University/education

Funder(s)

Funder type
Not defined

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
31/12/2025

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No