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Whole body hypothermia for the treatment of perinatal asphyxial encephalopathy

Submission date	Recruitment status	[X] Prospectively registered
21/09/2000	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
21/09/2000	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
21/03/2016	Pregnancy and Childbirth	

Plain English summary of protocol
Not provided at time of registration

Study website
http://www.npeu.ox.ac.uk/TOBY/

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT00147030, NCT01092637

Secondary identifying numbers
MRC ref: G0100126; G0801320

Study information

Scientific Title
Whole body hypothermia for the treatment of perinatal asphyxial encephalopathy: a randomised controlled trial

Acronym
TOBY (TOtal Body hYpothermia)

Study objectives
1. To determine whether whole body cooling for 72 hours in term infants with perinatal asphyxial encephalopathy improves survival without neurological or neurodevelopmental disability at 18 months
2. To confirm the safety of prolonged whole body cooling in full term infants with perinatal asphyxial encephalopathy

The TOBY Children Study: School age outcomes following a newborn cooling trial (TCS) hypothesis:
The aim of this cross-sectional cohort study is to determine the effect of therapeutic hypothermia following perinatal asphyxia on neurological and neuropsychological outcomes and also to assess academic attainment and any additional health, societal or educational costs associated with changes in outcome as a result of the intervention.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. London Multi-centre Research Ethics Committee (MREC), 08/01/2002, ref: MREC 00/02/73
2. TCS study: Charing Cross Hospital Research Ethics Committee, 10/02/2010, ref: 10/H0711/13

Study design
Randomised controlled trial; subsequent cohort study at school age follow up

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Patient information can be found at: http://www.npeu.ox.ac.uk/TOBY/toby_downloads /toby_pil1.pdf

Health condition(s) or problem(s) studied
Perinatal asphyxial encephalopathy, child development, cerebral palsy

Interventions
Full term infants will be randomised within six hours of birth to either a control group with the rectal temperature kept at 37 +/- 0.2 degrees celsius or to whole body cooling with the rectal temperature kept at 33.5 +/- 0.5 degrees celsius for 72 hours followed by slow rewarming. Relevant physiological parameters will be monitored and outcome assessed at 18 months of age by survival and neurological and neurodevelopmental testing.

TCS study:
No intervention, comparison of outcomes at school age in the treatment and control groups.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
The primary outcome for this trial is a combined endpoint: death in the first 18 months of life OR Severe neurodevelopmental disability.

TCS study:
Frequency of survival with an IQ greater than 84; timepoint: 6 years to 7 years and 4 months.

Secondary outcome measures
Secondary outcome measures added as of 16/10/2007:
Short term (before discharge from hospital):
1. Intracranial haemorrhage
2. Persistent hypotension
3. Pulmonary haemorrhage
4. Pulmonary hypertension
5. Prolonged blood coagulation time
6. Culture proven sepsis
7. Necrotising enterocolitis
8. Cardiac arrhythmia
9. Thrombocytopenia
10. Major venous thrombosis
11. Renal failure treated with dialysis
12. Pneumonia
13. Pulmonary airleak
14. Duration of hospitalisation

Long term (at 18 months):
1. Mortality
2. Severe neurodevelopmental disability
3. Multiple handicap, defined as the presence of any two of the following in an infant:

3.1. Neuromotor disability (Level 3-5 on General Motor Function (GMF) Assessment Scale classification), mental delay (the Bayley Scales of Infant Development - Mental Development Indices (MDI) score less than 70), epilepsy, cortical visual impairment, sensorineural hearing loss
4. The Bayley Scales of Infant Development - Psychomotor Development Indices (PDI) score
5. Sensorineural hearing loss: greater than or equal to 40 dB
6. Epilepsy (defined as recurrent seizures beyond the neonatal period, requiring anticonvulsant therapy at the time of assessment)
7. Microcephaly (head circumference more than 2 standard deviations below the mean)

TCS study:
1. Overall IQ from Wechsler Preschool and Primary Scale of Intelligence tests (WPPSI III)
2. Overall Working Memory Test Battery for Children (WMTB-C) Scale
3. Overall Strengths and Difficulties Quotient score (SDQ) for behavioural problems
4. Overall ADHD Score (Du Paul RS IV)
5. Prevalence of Cerebral Palsy
6. Gross Motor Function Classification System level GMFCS)
7. Unimpaired outcome and overall grade of disability
8. Teachers academic achievement score
9. Health Utility Index (HUI-III)
10. Overall number of deaths in each group to age 7 years and 4 months

Overall study start date
01/09/2002

Completion date
01/09/2008

Eligibility

Key inclusion criteria
Infants will be assessed sequentially by criteria 1, 2 and 3 listed below:

1. Infants greater than or equal to 36 weeks gestation admitted to the Neonatal Intensive Care Unit (NICU) with ONE of the following:
1.1. Apgar score of less than five at ten minutes after birth
1.2. Continued need for resuscitation, including endotracheal or mask ventilation, at ten minutes after birth
1.3. Acidosis defined as either umbilical cord pH or any arterial pH within 60 minutes of birth less than pH 7.00
1.4. Base deficit greater than or equal to 16 mmol/l in umbilical cord blood sample or any blood sample within 60 minutes of birth (arterial or venous blood)

If the infant meets criteria 1 then assess for neurological abnormality (by trained study personnel):

2. Moderate to severe encephalopathy consisting of altered state of consciousness (lethargy, stupor or coma) and at least one or more of hypotonia, abnormal reflexes including oculomotor or pupillary abnormalities, an absent or weak suck or clinical seizures, as recorded by study personnel.

If the infant meets criteria 1 & 2 then assess by amplitude-integrated electroencephalography (aEEG) (read by trained study personnel):

3. At least 30 minutes duration of amplitude integrated EEG recording that shows abnormal background aEEG activity or seizures. There must be one of the following:
3.1. Normal background with some seizure activity
3.2. Moderately abnormal activity
3.3. Suppressed activity
3.4. Continuous seizure activity

TCS study:
1. Previously specified that they do not want to be contacted again
2. Previously recruited in the TOBY study within 6 hours of birth
3. Confirmed moderate or severe neonatal encephalopathy

Participant type(s)
Patient

Age group
Neonate

Sex
Both

Target number of participants
325

Key exclusion criteria
1. Infants expected to be greater than 5.5 hours of age at the time of randomization
2. Major congenital abnormalities, such as diaphragmatic hernia requiring ventilation, or congenital abnormalities suggestive of chromosomal anomaly or other syndromes that include brain dysgenesis

TCS study:
Non-participation will only occur if consent is not obtained or contact with the family cannot be achieved. Children who did not take part in the TOBY study are not eligible.

Date of first enrolment
01/09/2002

Date of final enrolment
30/11/2006

Locations

Countries of recruitment
England

Finland

Hungary

Ireland

Israel

Sweden

United Kingdom

Study participating centre
ICSTM at Hammersmith
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Sponsor information

Organisation
Imperial College London (UK)

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Sponsor type
University/education

Website
http://www.imperial.ac.uk/

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council (MRC) (UK) (ref: G0100126)

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
The TCS study has also been funded by the Medical Research Council (MRC) (UK) (ref: G0801320)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results				No	No
Results article	results	01/10/2009		Yes	No
Results article	results of nested trial	01/01/2010		Yes	No
Results article	results	10/07/2014		Yes	No