ISRCTN13423963 https://doi.org/10.1186/ISRCTN13423963

Erythropoietin and darbepoetin treatment to reduce brain injury after birth asphyxia

Submission date	**Recruitment status**	[X] Prospectively registered
09/07/2020	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
20/08/2020	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
21/01/2026	Neonatal Diseases	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Hypoxic Ischemic Encephalopathy (HIE) is also known as birth asphyxia related brain injury and happens when the brain does not receive enough oxygen or blood flow during the time of birth. Birth asphyxia related brain injury is the most common cause of death and neurodisability in term babies.
Previous studies have shown that brain cooling (hypothermic neuroprotection) can reduce brain injury in some of the affected infants. However, despite cooling a proportion of these babies may still have disability, varying from minor to more severe. This injury is often a result of ongoing damage to the brain cells and is more common if there is an associated infection. Cooling therapy has substantially improved the outcomes of babies with HIE in the past decade. However, an unacceptably high rate of adverse outcomes is still seen in cooled babies with moderate or severe HIE, hence better treatments and further optimisation of cooling therapy are required.
Erythropoietin (Epo) and Darbepoetin alfa (Darbe) are FDA-approved drugs for treating anemia, with a proven safety profile in newborn infants and have potential neuroprotective benefits in neonatal encephalopathy. Darbe has similar effects to Epo and requires less frequent administration. Several recent reviews have highlighted Epo as one of the most promising treatments to augment hypothermic neuroprotection. Epo has acute effects and restores brain cells, this is essential for the repair of injury and normal neurodevelopment in animal models. It is possible that these drugs may reduce brain injury further when used alongside cooling therapy in babies with HIE.
The aim of this study is to examine the effects of Epo and Darbe on proton magnetic resonance spectroscopy thalamic N-acetylaspartate (NAA) level in babies with neonatal encephalopathy undergoing cooling therapy.

Who can participate?
Babies born with over 36 weeks gestational age with HIE and undergoing cooling therapy

What does the study involve?
The babies will be randomly allocated to erythropoietin, darbepoetin or usual care within the first 24 hours of life. As part of their routine clinical care, the babies will have an MRI scan between 1 and 2 weeks of age to see if they have any visible brain injury, so that the researchers

can make a prediction of the long-term implications on their health. A blood sample will be collected on admission and when they are around 80 hours old for research purposes. The researchers will examine subtle genetic variations that can influence how babies respond to this type of brain injury. Data from the babies' clinical records will be collected, and the results of other tests they may receive as a part of their routine care. This may include an aEEG/EEG (brain activity recording), a brain ultrasound scan, and blood tests. Babies will also have a detailed neurological assessment at 2 years of age to see how they are developing.

What are the possible benefits and risks of participating?
Epo and Darbe may reduce brain injury in babies with HIE. Also, the study may help to improve the treatment of babies with HIE in the future. There are no reported adverse effects of Epo and Darbe in newborn infants. Occasional side effects like joint pains, clotting problems, headache, hypertension, influenza-like illness and skin reactions are reported with prolonged use over several months in adults. None of these have been reported in newborn infants, although the researchers will closely watch for the haemoglobin levels of the baby during Epo treatment. Cooling is remarkably safe and is used as standard therapy for birth asphyxia-related brain injury. It may lower the platelet (blood clotting) levels in the baby's blood. The researchers will monitor the platelet levels as usual and will administer platelet transfusions if required.

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

When is the study starting and how long is it expected to run for?
August 2019 to September 2026

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

Who is the main contact?
1. Prof. Sudhin Thayyil, s.thayyil@imperial.ac.uk
2. Ms Stuti Pant

Contact information

Type(s)
Scientific

Contact name
Prof Sudhin Thayyil

Contact details
Centre for Perinatal Neuroscience
Department of Paediatrics
Imperial College London and Imperial Neonatal Service
Du Cane Road
London
United Kingdom
W12 0HS
+44 (0)203 313 8515
s.thayyil@imperial.ac.uk

Additional identifiers

ClinicalTrials.gov (NCT)
NCT04432662

Clinical Trials Information System (CTIS)
2020-002831-31

Integrated Research Application System (IRAS)
277361

Central Portfolio Management System (CPMS)
45286

Study information

Scientific Title
Erythropoietin and Darbepoetin in Neonatal Encephalopathy (EDEN) study

Acronym
EDEN

Study objectives
Erythropoietin and darbepoetin therapy will reduce brain injury on magnetic resonance imaging and increase in thalamic NAA at 1 to 2 weeks of age.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 27/05/2020, West of Scotland REC5 (West of Scotland Research Ethics Service, Ward 11, Dykebar Hospital. Grahamston Road, Paisley, PA2 7DE, UK; +44 (0)141 314 0213; WoSREC5@ggc.scot.nhs.uk), REC ref: 20/WS/0057

Primary study design
Interventional

Study design
Randomized; Both; Design type: Treatment, Drug, Imaging, Cohort study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Neonatal encephalopathy

Interventions

The EDEN study is a three-arm open-label pilot randomised controlled trial. This study will be conducted in 15 tertiary neonatal units in the UK; seven with 3 Tesla MR scanners and eight with 1.5 Telsa MR scanner, using the optimised MR spectroscopy sequences.

20 healthy adult volunteers will be recruited at Imperial NHS Trust and Imperial College London over a 2-month period. All volunteers will be scanned at 1.5 Telsa and 3 Tesla MR scanners, and the sequences will be optimised to obtained comparable thalamic NAA levels.

This will allow the researchers to develop comparable 1.5 Tesla and 3 Tesla MR spectroscopy sequences for obtaining similar thalamic N-acetyl aspartate levels.

The researchers will recruit 220 term or near term (>36 weeks) babies with neonatal encephalopathy over a 2-year period. Parents will be informed about the study at the earliest appropriate opportunity (after being explained about their baby's clinical status and when they feel ready) and be given a parent information leaflet (PIL). Parents wishing to participate in the study will be asked to sign an informed consent form, once ready, and be given a copy for their records (with the PIL).

After parental consent, the encephalopathic infants at <24 hours of age undergoing therapeutic hypothermia will be randomised to one of the following groups:
Arm 1: Erythropoietin (1000 U/kg) IV once a day x 5 doses along with cooling therapy
Arm 2: Darbepoetin Alpha (10 mcg/kg) IV single dose given less than 24 hours of age along with cooling therapy
Arm 3: Cooling only (usual care)

Babies recruited from Imperial NHS trust will have a 16-channel video electroencephalography (EEG), and those recruited from other centres will have amplitude-integrated EEG (aEEG) measurements for the first 80 hours. The researchers will collect 0.5 ml of blood at the time of randomisation and again at 80 hours of age from all recruited babies for gene expression studies. The blood (venous or arterial) will be collected in a PAXGENE bottle, at the time of routine clinical sampling, whenever possible.

Details of antenatal and post-natal events, and other routine clinical and imaging data will be collected. The researchers will also obtain relevant clinical data from the participants' medical records or from GP/local hospital if needed (GPs will be informed of study participation unless otherwise requested by parents). They will also collect the MR imaging data that is acquired as a part of routine clinical care. Parents will be contacted regularly via their preferred method of contact. Study newsletters will be sent to parents, unless they opt out.

All babies will have detailed neurodevelopmental evaluation including Bayley scales of infant development (BSID-III or IV if available), gross motor function system classification (GMFCS), and hearing and vision assessment between 18 to 24 months of age, as a part of routine clinical care. Severe disability will be defined as any one of the following: both cognitive and language composite BSID-III scores <70, GMFCS level 3–5, hearing impairment requiring hearing aids or blindness. Moderate disability will be defined as both cognitive and language composite scores BSID-III between 70 and 84 and one or more of the following: GMFCS level 2, hearing impairment with no amplification or a persistent seizure disorder. The outcomes will also be assessed by categorisation of these scores and by including mortality as an outcome. Adverse outcome will be defined as death or, in survivors, moderate or severe disability.

Intervention Type
Mixed

Primary outcome(s)
Mean (SD) of thalamic NAA level in babies treated with Epo and Darbe when compared with untreated infants, measured using magnetic resonance spectroscopy between 1 and 2 weeks after birth

Key secondary outcome(s)
Number of babies in whom thalamic NAA level could be accurately quantified in magnetic resonance spectroscopy in 3 Tesla and 1.5 Tesla MR scanners, measured between 1 and 2 weeks after birth

Completion date
30/09/2026

Eligibility

Key inclusion criteria
Study 1: Healthy adult volunteers

Study 2: Babies (> 36-week gestation and birthweight > 1.8 kg) requiring resuscitation at birth with evidence of acute perinatal asphyxia (metabolic acidosis in cord and/or blood gas (pH< 7.15; BE > -12) within 1h of birth; acute obstetric event) AND the need for continued resuscitation or ventilation at 10 minutes and a 10 min Apgar score < 6 AND evidence of moderate or severe HIE on an NICHD neurological examination performed between 1 and 6h of birth AND cooling was initiated before 6 h of age.

Participant type(s)
Mixed

Healthy volunteers allowed
No

Age group
Mixed

Sex
All

Total final enrolment
0

Key exclusion criteria
Study 1:
1. Adults with disease
2. Adults with metal implant fitted, such as a pacemaker or artificial joint
3. Pregnant adults

Study 2:
1. Babies with lethal congenital malformations
2. Concomitant participation in other research projects
3. Lack of parental consent

Date of first enrolment
01/09/2020

Date of final enrolment
30/09/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
St Mary's Hospital
Imperial College Healthcare NHS Trust
Praed Street
London
England
W2 1NY

Study participating centre
Medway Maritime Hospital
Medway NHS Foundation Trust
Windmill Road
Gillingham
England
ME7 5NY

Study participating centre
Liverpool Women's NHS Foundation Trust
Crown Street
Liverpool
England
L8 7SS

Study participating centre

Homerton University Hospital NHS Foundation Trust
Homerton Row
London
England
E9 6SR

Study participating centre
Freeman Hospital
The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Freeman Road
High Heaton
Newcastle-upon-Tyne
England
NE7 7DN

Study participating centre
Queen Elizabeth Medical Centre
University Hospitals Birmingham NHS Foundation Trust
Trust HQ, PO Box 9551
Edgbaston
Birmingham
England
B15 2TH

Study participating centre
Addenbrookes Hospital
Cambridge University Hospitals NHS Foundation Trust
Hills Road
Cambridge
England
CB2 0QQ

Study participating centre
Bradford Royal Infirmary
Bradford Teaching Hospitals NHS Foundation Trust
Duckworth Lane
Bradford
England
BD9 6RJ

Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care 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

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository. Personal identification data including telephone numbers and all contact details will be stored as:
1. Hardcopies in a research folder in locked cupboards in site principal investigators office, or Imperial College London research office
2. NHS computers at the recruiting sites (only for babies recruited from that site)
3. Secure and encrypted server at Imperial College London for storage of personal data.
All data will be linked anonymized using a study code, which will be stored as
1. hardcopies in a research folder in locked cupboards in site principal investigators office, or Imperial College London research office
2. NHS computers at the recruiting sites (only for babies recruited from that site)
3. Secure and encrypted server at Imperial College London for storage of personal data.
Linked anonymized data will be stored in all other places, as described below.

1. Electronic transfer by magnetic or optical media, email or computer networks
The case reports forms will be electronic so that this can be filled in by the recruiting centres directly into the research database (Redcap). Redcap is a GCP compliant database with audit trails and widely used for CTIMPs by many major research universities in the UK and USA (https://www.project-redcap.org). No patient identifiable data will be held in the research database, and the cases will be anonymized (linked) as described above. The database will be hosted in a secure and encrypted Imperial College or private cloud server. MRI scans will be again anonymized using the study number and encrypted with a password prior to transfer by electronic media. Imperial College file transfer protocol will be used for data transfers. Patient identifiable data need to be transferred only through NHS emails or NHS.net emails which have enhanced facilities for transfer of personal data.
2. Use of personal addresses, postcodes, faxes, emails or telephone numbers
These data are essential for maintaining regular contact with parents of the recruited babies. As the study involves long term follow-up, the researchers have seen that without regular contact from the research team at Imperial, follow-up rates are low. Furthermore, some babies may come to imperial for 24-month assessment or Imperial team may go to the local hospital to undertake this assessment.
These will be stored as:
1. Hardcopies in a research folder in locked cupboards in site principal investigators office, or Imperial College London research office
2. NHS computers at the recruiting sites (only for babies recruited from that site)
3. Secure and encrypted server at Imperial College London for storage of personal data.
Storage of personal data on any of the following:
1. Manual files including consent forms, and personal data – Research folder in locked cupboards in site principal investigators office, or Imperial College London research office
2. NHS computers – Personal data will be stored in a dedicated password-protected folder. All NHS computers have facilities for storage of personal data.
3. University computers – personal data will be stored only in a secure and encrypted server at Imperial College London which has got enhanced features for storage of personal data
4. Laptop computers – NO personal data will be stored on laptop computers. However, linked anonymized and password-protected data will be stored in laptops belonging to Imperial College London, which has enhanced security features.
All personal data will be stored for a period of 10 years and will be destroyed using standard Imperial College London protocols (including removal by specialist software's for electronic data), unless parental consent for further research is obtained at that time.
The researchers are hoping to undertake long-term follow-up of the recruited babies (subject to further funding), hence it is essential to store identifiable data at Imperial College London.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			20/09/2023	No	No
Participant information sheet	version v3	07/05/2020	20/08/2020	No	Yes
Protocol file	version V3	07/05/2020	20/08/2020	No	No