PARENT INFORMATION LEAFLET

Erythropoietin and Darbepoetin in Neonatal Encephalopathy Study

(The EDEN Study)

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Information leaflet for parents

We understand that this may be a difficult time for you. However, we think it is important for you to know about this particular study, taking place in our neonatal unit. This leaflet explains why the research is being done and what it will involve. Please take time to read the information carefully. One of our team members will go through the information sheet with you and answer any questions you have.

What is neonatal encephalopathy?
Neonatal encephalopathy is also known as 'birth asphyxia related brain injury' and happens when the brain does not receive enough oxygen or blood flow around the time of birth. It is not always known what causes this, but we do know that it can lead to brain injury. How well your baby recovers depend on how severe this brain injury is.

Why are we doing this study?
A team of doctors and scientists based at Imperial College London have been investigating Hypoxic Ischemic Encephalopathy (HIE) for the past two decades. Previous studies have shown that brain cooling 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, 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 is 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 Erythropoietin as one of the most promising therapies 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.

Why is my baby suitable for this study?
We are recruiting babies who have neonatal encephalopathy following birth asphyxia. Your baby has suffered from birth asphyxia hence is eligible to take part in the study. We want to examine the neuroprotective benefit of Epo and Darbe in babies with neonatal encephalopathy undergoing cooling therapy.

What does whole body cooling involve?
The normal core body temperature of babies is around 36.5°C. During cooling, each baby's core body temperature is reduced to 33.5°C using a special cooling mattress. After the completion of cooling, babies are slowly re-warmed to their normal body temperature. Cooling therapy is effective only if started within six hours of birth.

Babies also receive some slight sedation during cooling to make sure that they are not stressed. The rest of their clinical care, including feeding, will be exactly the same as for any other baby with neonatal encephalopathy.

What is involved in participating in this study?

Your baby will be assigned by chance within the first 24 hours of life to one of the following groups

- Group 1: Erythropoietin IV once a day x 5 doses along with cooling therapy
- Group 2: Darbepoetin Alpha IV single dose given less than 24 hours of age along with cooling therapy.
- Group 3: Cooling only (usual care)

As part of their routine clinical care, your baby will have an MRI scan between 1 and 2 weeks of age to see if they have any visible brain injury, so that we can make a prediction of the long-term implications on their health. Your baby's doctor will discuss the results of the MRI scan with you, including any incidental findings on the MRI.

The MRI takes approximately one hour, and neonatal nurses and/or doctors will closely monitor your baby during the scan. We often give babies an oral sedative for MRI scanning, which they usually tolerate very well. Most babies will sleep through the scan with this sedation and wake up soon after the scan for a feed. In most babies, the MRI scan is performed before the baby is discharged home. Occasionally, your baby may be discharged prior to the MRI scan, and the scan will be performed as an outpatient appointment. In this case, your baby will continue to be monitored for a few hours after the scan, to make sure that they are fully awake, and have had a good feed before going home.

Your baby will have a number of blood investigations as part of their standard care during his/her admission to the neonatal unit. A small part (~0.5ml) of these samples will be collected on admission and when your baby is around 80 hours old for research purposes. We will examine subtle genetic variations that can influence how your baby responds to this type of brain injury.

We will also collect the data from your baby's clinical records, 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. Your baby may also have a detailed neurological assessment at two years of age as part of their routine clinical care, to see how they are developing. We will collect the data from this assessment for the purpose of this study.

We will also collect information from the mother's medical notes at the time of birth, to find details of any antenatal medical problems and the results of any important tests.

How will you administrate the medication and what is the dosing schedule?
All babies receiving cooling therapy for brain injury will be having a cannula in the vein for receiving fluids and other medicines as a part of their clinical care. We will use the same cannula.
If you are consenting to administration of Epo or Darbe therapy, your baby may receive one of the following dosing schedules.

The first group of babies will receive Erythropoietin 1000units/kg/dose intravenously once a day, we will continue this medicine for 5 days. The second group of babies will receive a single dose of Darbepoetin 10 mcg/kg/dose intravenously within 24 hours of birth. The third group of babies won't receive any of this medication (usual care). We will inform you which dosing regime your baby will receive.

What are the possible risks of taking part?
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 we 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 your baby's blood. We will monitor the platelet levels as usual and will administer platelet transfusions if required.

MRI does not use X-rays or any harmful ionizing radiation and there are no known adverse long-term effects. MR scans are noisy and require babies to be still. Hence, we will use adequate ear protection for the baby and may give light sedation by mouth.

Does my baby have to take part?
Your baby does not have to take part in this study if you do not want him/her to be involved. If you do agree for your baby to take part, you will be given this information sheet to keep and will be asked to sign a consent form. You will be given a copy of the signed consent form for your records.

Whether or not you agree for your baby to take part, this will not affect the standard of care you and your baby receive in any way. Depending on your hospital's policy, your baby may still have the MRI scan and neurological assessment at two years of age.

What happens when the research study ends?
The final assessment for this study is at the time of the MRI scan (before two weeks of age).

What if relevant new information becomes available?
It is possible that new information may become available during the course of the study (2-3 years). It is unlikely that this will affect your baby's involvement with this study. If the study is stopped early because of new information, you will be informed about this.

What will happen if I do not want to carry on with the study?
Your baby's participation in this study is entirely voluntary. You are free to decline for your baby to enter or for your baby to withdraw from the study at any time without having to provide a reason. If you choose to do this, it will in no way affect your baby's future medical care. We may ask you for your consent to use the information already collected so far, or as a part of standard clinical care, for research purposes.

What if there is a problem?
Imperial College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College London 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 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 local Principal Investigator (Name xx, Tel: xxx). The normal National Health Service complaints services are also available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Compliance Office.

Will my taking part in this study be kept confidential?
All information collected about your baby (or other family members) during the course of this research will be kept strictly confidential. We may inform your baby's GP about him or her taking part in this research and will seek your permission to do so. Once your baby reaches two years of age, we may also collect any additional information from your GP or from any other hospital where your baby might have received clinical care. All babies who receive NHS care also have their clinical data stored at the National Neonatal Research Database at Imperial College London. We will seek your permission to access these data for research purposes.

General data protection transparency statement

Imperial College London is the sponsor for this study based in the United Kingdom. We will be using information from you and your baby's 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 after the study has finished.

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. You will also be provided with additional GDPR wording to accompany this patient information leaflet.

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 [Principle Investigator contact details].

LEGAL BASIS

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.

[NHS/other site] will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Imperial College London and regulatory organisations may look at your medical and research records to check the accuracy of the research study. [NHS site] will pass these details to Imperial College London along with the information collected from you and your baby's medical records. The only people in Imperial College London who will have access to information that identifies you will be people who need to contact you to neurodevelopmental follow up of your baby or audit the data collection process. The people who

analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details. [NHS/ other site] will keep identifiable information about you from this study for 10 years after the study has finished.

Imperial College London will also collect information about your baby for research from the national neonatal database, based at Imperial College London. This information will include your baby's name, NHS number, contact details and health information, which is regarded as a special category of information. We will use this information to the purpose of the current research.

The information about your baby could be used for research in any aspect of health or care and could be combined with information about you from other sources held by researchers, the NHS or government, in future. Where this information could identify you or your baby, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance. Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

Who will have access to my case/research records?
All the data and images collected as part of this study will be stored both on a secure computer locally, and centrally at Imperial College London. Only the researchers involved in this study will have access to the data collected during the course of this study. The 2018 Data Protection Act safeguards the use of some types of personal information. This places an obligation on those who record or use personal information, but also gives rights to people about whom information is held. If you have any questions about data protection, please contact a member of the research team or PALS (patient advice and liaison service) or the Data Protection Officer. The results from our project will be published as papers in medical journals. No data will be published that allows for individuals to be identified in any way. If requested, we will be able to send you copies of any papers published when we have completed the study. The study may also form part of a postgraduate research project (MD or PhD).

Who do I speak to if I have further questions or worries or complaints?
In the first instance please contact the Principal Investigator locally. If you wish to speak to someone not directly involved in the study, please contact PALS at the local hospital.

What will happen to the results of the study?
This study will run for three years. The results of the study will be made available to doctors and nurses caring for babies like yours across the world. You and your baby will by no means be identified in any report or publications about the study. We can send you a summary of the final results, if requested.

Who is organising and funding the research?
The study will be run at several national and international sites. It is funded by the National Institute for Health Research. Imperial College London is the main sponsor. Doctors will not be paid for including you in the study, nor do participants receive payment.

Who has reviewed/ approved the study?
All research in the NHS is looked at by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed and approved by West of Scotland Research Ethics Committee.

Please do not hesitate to ask if you have more questions.

Local Principal Investigator
Name and contact details