Improving early decisions in neonatal encephalopathy by monitoring heartbeat variability (HeartBeat Study)

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Protocol authorised by:
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Date: 20.3.2017
Signature:

This protocol describes the Heartbeat Study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator. This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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Sponsor:
Imperial College London is the sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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STUDY SUMMARY

TITLE
Improving early decisions in neonatal encephalopathy by monitoring heart rate variability (HeartBeat Study)

DESIGN
Prospective observational multicentre cohort study

BACKGROUND
Hypoxic ischaemic encephalopathy (HIE) is the single most common cause of death and lifelong neurodisability in term babies. Although cooling treatment improves outcomes for these babies, early identification (within six hours of birth) of 'at risk infants' remains challenging. Consequently, not all babies who need treatment will receive it and other babies receive treatment unnecessarily. Furthermore, neuroprotection from cooling may be lost if baby remains stressed during treatment, but accurate methods of measuring stress in babies are lacking. This results in suboptimal care of babies with HIE. Real-time stress monitoring would allow intervening towards stress reduction, such as by tailoring neonatal neurodevelopmental care or optimising sedation. This could improve the outcome of babies.

AIMS
Primary aim:
To examine the accuracy of heartbeat variability (HRV), within six hours of birth, to predict adverse neurodevelopmental outcome at 18 to 22 months in encephalopathic babies.

Secondary aims:
- To examine the relation between heartbeat variability and stress in encephalopathic babies.
- To identify clinical interventions associated with reduced heartbeat variability in encephalopathic babies.
- To describe the trajectory of normal heartbeat variability changes in healthy term babies during the first 24 hours after birth.

METHODS
The study is open for all centres participating in the Magnetic Resonance Biomarker Consortium (MRBC). This is a consortium of tertiary neonatal centres in the UK using harmonised cross platform sequences for magnetic resonance imaging and spectroscopy. The current members are Medway Hospital, Norwich Hospital, Coventry University Hospital, Royal Victoria Infirmary, Newcastle upon Tyne and Imperial NHS Trust. We will recruit a total 140 term babies with hypoxic ischaemic encephalopathy. We will collect continuous electrocardiography (ECG) data, hourly Neonatal Pain Agitation and Sedation Scale (NPASS) and 12 hourly salivary cortisol, for the first five days after birth. We will also record various clinical interventions, and noise and light levels that the baby is exposed to, for the first 5 days after birth.

We will analyse the raw ECG using Matlab® with in-house algorithms to quantify specific linear and non-linear measures of HRV. All recruited encephalopathic babies will have brain

magnetic resonance (MR) imaging and spectroscopy using harmonised protocols, within 2 weeks of age and neurodevelopmental assessment (Bayley version III) at 18 to 22 months of age, as a part of clinical care, or as a part of MR biomarker studies in MRBC. This data will be collected and used for the Heartbeat study to examine the association between heart rate variability with brain injury and neurodevelopmental outcome.

In addition, we will collect the ECG data from 100 healthy term babies for the first 24 hours after birth, to describe the trajectory of normal heartbeat variability in healthy term babies.

DATA ANALYSIS AND OUTCOME MEASURES

The prognostic accuracy (sensitivity, specificity, 95% confidence intervals) of early heartbeat variability using optimal cut-off values will be reported for the primary outcome. Logistic regression models adjusted for potential confounders will be used to report secondary outcomes.

POPULATION

Newborn babies with hypoxic ischaemic encephalopathy and healthy term babies.

DURATION

2 year recruitment followed by 18 to 22 months follow-up

POTENTIAL BENEFIT TO PATIENTS AND THE NHS

Once the most accurate HRV indices and thresholds are identified, this data can be readily incorporated into a bed side real-time monitoring device, for wider use in the NHS. This device may have several clinical implications, including (i) improving access to treatment and the number of babies who benefit from being offered cooling; (ii) avoiding cooling therapy to low risk infants with hypoxic ischaemic encephalopathy (iii) maximising the therapeutic effect of cooling by reducing stress; (iv) enabling tailored neonatal nursing care based on real-time monitoring of neonatal stress and thus improving the long-term outcomes of babies with hypoxic ischaemic encephalopathy.

1. INTRODUCTION

1.1 BACKGROUND

Hypoxic ischaemic encephalopathy occurs when a complication during birth causes a lack of oxygen and blood flow to the baby's brain, potentially leading to damage. In high-income countries, it occurs in 1 to 6 per 1000 live births (1). Approximately 1 in 3 babies with moderate or severe hypoxic ischaemic encephalopathy will die soon after birth. Worldwide, approximately 1 million babies die from this condition every year (2). More than half of the survivors develop life-long disability (3,4). This represents a huge health and economic burden for the child and for the society, with estimated life-time costs of £600,000 per infant in the UK (5) in addition to litigation costs of £130 million per annum (6). Unfortunately, hypoxic ischaemic encephalopathy is not completely preventable, and can occur despite optimum antenatal and perinatal management.

Cooling treatment reduces death and improves survival without disability after neonatal encephalopathy and is currently offered as standard care in the neonatal unit, for babies with moderate or severe hypoxic ischaemic encephalopathy (7). This treatment consists of lowering the baby's core temperature to 33.5^{o}C during 72h, using a cooling bed, followed by gradual rewarming. Cooling is cost-effective and offers 20% additional disability-adjusted life years (8). Estimates are that cooling treatment saved over £25 million per year to the NHS (9) since its introduction in 2007, as well as improved the lives of thousands of babies.

Early identification of at risk babies with hypoxic ischaemic encephalopathy

Cooling is effective only if initiated within six hours of birth. As the clinical picture of hypoxic ischaemic encephalopathy evolves over the first days after birth, early detection of moderate or severe encephalopathy remains a challenge. Eighteen per cent of babies in the UK cooling registry had no or mild encephalopathy (9), thus may have been subject to cooling treatment unnecessarily. This not only increased intensive care costs, but exposed babies to the adverse effects of cooling and hospitalisation unnecessarily. Anecdotally, some babies who are initially considered to have no or mild encephalopathy, hence not offered cooling, develop signs of moderate or severe encephalopathy after six hours of age and have adverse long-term outcomes. This frustration is felt by clinical teams struggling to make time-constrained decisions but also by parents who question the benefits their babies could have attained from being offered cooling treatment. Maternal reports in parent forums witness several of these cases.

Apart from clinical examination, the only bedside tool to identify 'at risk' encephalopathic infants is amplitude-integrated electroencephalography (aEEG), which measures electrical activity of the brain, based on 3 needles placed in the baby's scalp. However, the incremental benefit of aEEG over a clinical neurological examination is unclear and is no longer considered an essential criteria for treatment (10). A recent meta-analysis from our group (11) suggests that the accuracy of aEEG within six hours of birth to predict long-term adverse outcome is poor (area under the summary ROC curve: 0.39). Early serum biomarkers present equally poor accuracy, with little clinical utility for treatment decision (12). Although magnetic resonance (MR) can accurately identify 'at risk' infants (13), an MR scan within six hours of birth is impractical outside selected centres like ours; hence MR is of limited value in identifying candidates for cooling and supporting clinical decision.

Stress during cooling therapy

Preclinical data suggests that the neuroprotective effect of cooling may be lost in presence of stress (14,15). Sedation during cooling was addressed differently by the various cooling trials, and the counterproductive effects of stress were acknowledged in most studies (3,16). Equally, current sedation practices vary widely across NHS hospitals, and controversy exists over the safety of neonatal sedation (17). It is also possible that over-sedation may worsen the brain injury during cooling (18).

In the absence of reliable methods for real-time stress monitoring, nurses often rely on shivering and increase in heartbeat to assess stress. Neither of these is accurate, as shivering is uncommon in newborns (due to brown fat metabolism) and cooling reduces heartbeat. There are no validated pain assessment tools for babies undergoing cooling treatment (19). This is because these tools often rely on a combination of behavioural and physiological signs that are unreliable during hypoxic ischaemic encephalopathy. Real-time monitoring of cortisol, the current standard stress marker, is unrealistic due to lab return times.

Which nursing interventions could help reducing neonatal stress in babies with hypoxic ischaemic encephalopathy is unknown. Research on the benefits of developmental care for babies in the neonatal unit refer largely to preterm infants and are not sufficiently powered to make standard recommendations (22). Nonetheless, as *Developmental Care* is rebranded as the new *Neuroprotective Care* (23), its principles apply to term babies, including those with brain damage. These studies highlight the importance of adequately monitoring stress levels so that responsive nursing care can be implemented, individually, towards stress reduction.

1.2 RATIONALE FOR CURRENT STUDY

Heartbeat variability for assisting early clinical decision-making

In healthy states, the heart experiences small complex and irregular accelerations and decelerations. This is called heartbeat variability (HRV). The simplest way to measure heartbeat variability is by quantifying the changes in the interval between successive RR peaks in the baby's electrocardiogram. Heartbeat variability decreases following a variety of illnesses such as traumatic brain injury, asphyxia and sepsis (24–26). The latter has been extensively evaluated and commercially exploited for early detection of sepsis in premature babies, claiming to detect neonatal sepsis 24h before the onset of clinical signs (27), thus reducing mortality from sepsis by 20% (28). Nonetheless, different pathophysiology may affect specific features of heartbeat variability, requiring individualised studies (29).

Disturbance of autonomic system is a hallmark of perinatal hypoxic events (30). Heartbeat variability gives a non-invasive assessment of the autonomic control of heartbeat, via sympathetic and parasympathetic nervous systems (31–33). Changes in heartbeat following hypoxia have been described in animal studies (34–36) and in adults and children following traumatic brain injury (37–42). Reduced heartbeat variability is associated with adverse neurodevelopment outcome in very low birth weight babies after preterm brain injury (43,44) as well as with cerebral palsy at 3 years (45). Evidence also suggests that heartbeat variability changes before and during seizures (46,47), which significantly helps identifying 'at risk' babies. As an added benefit, heartbeat variability could also help monitor progress and assess therapeutic response.

Potential benefit to patients and the NHS:
Once the most accurate HRV indices and thresholds are identified, this data can be readily incorporated into a bed side real-time monitoring device, for wider use in the NHS. This device may have several clinical implications, including (i) improving access to treatment and the number of babies who benefit from being offered cooling; (ii) avoiding cooling therapy to low risk infants with hypoxic ischaemic encephalopathy (iii) maximising the therapeutic effect of cooling by reducing stress; (iv) enabling tailored neonatal nursing care based on real-time monitoring of neonatal stress and thus improving the long-term outcomes of babies with hypoxic ischaemic encephalopathy.

2. STUDY AIMS

Primary:
- To examine the accuracy of heartbeat variability within six hours of birth to predict adverse neurodevelopmental outcome at 18 to 22 months in babies with hypoxic ischaemic encephalopathy

Secondary:
- To examine the relation between heartbeat variability and stress in encephalopathic babies.
- To identify clinical interventions associated with reduced heartbeat variability (increased stress) in encephalopathic babies.
- To describe the trajectory of normal heartbeat variability changes in healthy term babies during the first 24 hours after birth.

3. STUDY DESIGN

The Heartbeat Study is a prospective observational multicentre cohort study. It will be open for all centres participating in the Magnetic Resonance Biomarker Consortium (MRBC). This is a consortium of tertiary neonatal centres in the UK using harmonised cross platform sequences for magnetic resonance imaging and spectroscopy. The current members are Medway Hospital, Norwich Hospital, Coventry University Hospital, Royal Victoria Infirmary, Newcastle upon Tyne and Imperial NHS Trust. We will recruit a total of 140 babies with neonatal encephalopathy over a 2 year period. We will collect continuous electrocardiography (ECG) data, hourly neonatal pain and agitation scores (NPAS) and 12 hourly salivary cortisol, for the first five days. We will analyse the raw ECG using Matlab® with in-house algorithms to quantify specific linear and non-linear measures of HRV. In addition, 100 healthy term babies will be recruited from postnatal wards to examine the trajectory of normal heartbeat variability in healthy term babies.

3.1 IDENTIFICATION OF POTENTIAL PARTICIPANTS AND RECRUITMENT

HIE Cohort
All term babies admitted to the participating neonatal units with hypoxic ischaemic encephalopathy will be screened for eligibility by the clinical team and study procedures will be initiated. Informed consent will be obtained at a later stage by a delegated member of the team (see below).

Healthy cohort
A research nurse will screen all babies in labour ward or postnatal ward to identify potential healthy participants. If eligible, parents will be invited to participate.

3.2 STUDY PROCEDURES AND SCHEDULE OF EVENTS

Hypoxic ischemic encephalopathy cohort

Procedure 1 (ECG data storage): As soon as a baby meeting the inclusion criteria is admitted to the neonatal intensive unit, the clinical team will attach a single channel ECG monitor (Faros180®) to the baby.
This device will continuously store the ECG data for 5 days (figure 1). For out-born infants, the neonatal transport team will start the ECG data collection using Faros180®, so that the data collection begins within six hours after birth.

Figure 1. Faros180® ECG data logger

After five days, the ECG data will be transferred to the central repository at Imperial College London, and stored securely in encrypted drives. Alternatively, iXtrend® software can be used to directly export the monitoring data to a study laptop, in real-time.

Procedure 2 (Cortisol levels): On admission, after starting the ECG data storage, a salivary cortisol sample will be obtained. This will be repeated 12 hourly for 5 days and can be done by parents if they wish. The samples will be stored at -20 C immediately after collection (anonymised using the study number and date/time of collection), and then transported to Imperial College London for analysis in batches. Surplus samples, if any, will be stored for future research.

Procedure 3 (NPASS): Neonatal Pain Agitation and Sedation Scale (NPASS) is a bedside scoring tool to quantify pain and agitation, which has been validated for babies receiving sedation (70) and is commonly used in neonatal units. The NPASS is based on five criteria: crying/irritability, behavioral state, facial expression, extremity tone and vital signs. The neonatal nursing staff will collect hourly NPASS scores from admission to day 5, into a tablet computer or a paper form.

Procedure 4: (Recording interventions and environmental factors): The nursing staff will also record the timing of care events and therapies into a daily events log, into a tablet computer or a paper form. This will include all stressful procedures such as intubation, cannulation, venipuncture, and details of various medications that the baby may be receiving. In addition, bedside light (Lux) and noise levels (decibels) will be continuously recorded for the first 5 days, using dedicated light and sound data loggers.

Other data collection
We 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).

To assess brain injury, MR imaging and spectroscopy will be performed within two weeks of birth, as part of standard clinical care (e.g. all babies receiving cooling therapy) or as part of the MARINAC study, which the parents may have decided to participate. However, if no MR scan is offered as part of the clinical scan and parents do not wish to participate in the MARINAC study, MR data will not be collected.

Neurodevelopmental assessment including Bayley scales of infant development (BSID-III), gross motor function system classification, and hearing and vision assessment will be performed at 18 to 22 months of age as part of standard clinical care. All participating centres in the MARBLE consortium, have dedicated neurodevelopmental paediatrician, who will undertake these assessments. If the baby is followed up in a hospital that is different from the recruiting centre, we will contact local teams to request copies of neurodevelopmental assessments undertaken. We may undertake a further follow-up evaluation of the recruited babies at school age, subject to future funding. This will be explained in the information leaflet.

Parents will be contacted regularly via preferred method of contact. Study newsletters will be sent to parents, unless they opt out.

Healthy term baby cohort
After obtaining informed written consent from parent(s), a research nurse will then attach the Faros180® to the baby. ECG will be collected for a maximum period of 24 hours. Parents will be requested to keep a log of various events happening during this time, including nappy changes, feeding, crying etc. After 24 hours, the research nurse will remove the ECG leads and download the ECG data for further analysis. Study advertisement for healthy volunteer babies will be placed in postnatal wards and other appropriate places in the hospital.

4. PARTICIPANT ENTRY

4.1 Hypoxic ischemic encephalopathy cohort
Inclusion criteria (all four criteria should be met)

- Full term babies (>36 weeks)
- Requiring resuscitation at birth due to perinatal asphyxia and/or 5 minute Apgar score <6.

- Structured clinical neurological examination (modified Sarnat stage) within six hours of age suggestive of encephalopathy (mild, moderate or severe)
- Age less than six hours at the time of admission to the neonatal unit

Please note that blood gases and cerebral function monitoring are not part of the inclusion criteria, and these may be normal or abnormal. Babies may or may not receive therapeutic hypothermia.

Exclusion criteria

- Babies with lethal congenital malformations or cardiac conditions that could affect heartbeat variability
- Participation in any controlled trials of investigational medical products (C-TIMPS)

Withdrawal criteria

Given the observational nature of this study and the lack of risks to the health of the baby, withdrawal should occur only upon parental request.

4.2 Healthy term baby cohort

Inclusion criteria

- Healthy full term babies (>36 weeks) and birth weight between 9th to 91st centile
- Age less than six hours at the time of study enrolment

Exclusion criteria

- Babies requiring any medication or phototherapy
- Perinatal maternal fever

Withdrawal criteria

- Given the observational nature of this study and the lack of risks to the health of the baby, withdrawal should occur only upon parental request.

5. ADVERSE EVENTS

Given the observational design of this study, there are no anticipated risk of adverse events associated with study participation.

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.
Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening– refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations or done by a delegated person according to the study delegation log. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 REPORTING PROCEDURES

All adverse events will be recorded during hospitalisation using the case report form. Babies who suffer hypoxic ischaemic encephalopathy are expected to have higher mortality and morbidity up to 2 years of age.

All serious adverse events that are not expected to occur in babies with hypoxic ischaemic encephalopathy (systemic venous thrombosis, massive intracranial bleeds), should be reported to the Chief Investigator by completing an SAE form and sending it within 24h. Please send any SAE forms to: v.oliveira@imperial.ac.uk, telephone 0044-20-33132473

The Chief Investigator must notify the Sponsor of all unexpected SAEs.
If there was any unexpected SAE which would be considered study related, the Chief Investigator will report to the Ethics Committee, within 15 days of becoming aware of the event, using the SAE form. Local investigators should report any SAEs as required by their Sponsor and/or Research & Development Office.

6. ASSESSMENT AND FOLLOW-UP

The 18 to 22 month follow-up assessment marks the end of the study. Parents will be asked if they would like to find out about the study results and via which method.

7. STATISTICS AND DATA ANALYSIS

7.1 SAMPLE SIZE AND STATISTICAL ANALYSIS PLAN

Primary Aim (n=140)

To establish heartbeat variability as clinical tool for treatment decision, a high sensitivity to identifying adverse long-term neurodevelopmental outcome is required. Neurodevelopmental outcome will be dichotomised [(normal + mild abnormality (favourable) versus moderate or severe abnormality (unfavourable)] (72), based on the results of the neurodevelopment assessment performed at 18-22 months.

The sample size calculation was based on getting a reasonably precise estimate of the sensitivity within 8% of the population value. Assuming a sensitivity of 90%, using 95% confidence level, 54 babies with adverse outcome are required. Approximately 45% of all babies may have an unfavourable outcome, hence a total sample size of 120 is required. Assuming 10% attrition (according to our other studies), therefore we will recruit 133 babies (rounded to 140). If the sensitivity were higher (e.g. 95%), this sample size would give approximately a 6% precision of estimate.

An initial analysis will examine heartbeat variability values in babies with and without an adverse long-term neurodevelopmental outcome, using either the unpaired t-test or Mann-

Whitney test, depending on the distribution. Optimal thresholds for predicting adverse outcome will be estimated using ROC curves, and the prognostic performance (e.g. sensitivity, specificity) will be reported with corresponding confidence intervals. Additionally, the relationship between heartbeat variability and neurodevelopmental outcome in survivors will also be examined using logistic regression models. Adjustments will be made for potential confounders.

Secondary Aims

Hypoxic ischemic encephalopathy cohort

To examine the association between heartbeat variability and cortisol levels and NPASS scores, a sample size of approximately 60 babies, would have an almost 90% power to detect a medium sized correlation of 0.4 between the variables (assuming a 5% significance level).

Correlation will be used to initially examine the association between variables. Subsequently linear regression will be used to re-examine the relationship after adjusting for potentially confounding variables. Finally, the clinical procedures associated with a 25% reduction in heartbeat variability will be described (73).

Healthy term baby cohort

To describe the normal trajectory of HRV in the first 24h of life in healthy term babies, we will record the heartbeat variability in 100 babies during the first 24h of life and use descriptive statistics to define measures of central tendency and dispersion.

8. REGULATORY ISSUES

8.1 REGULATORY & ETHICS APPROVAL

This study has been reviewed and approved by the health Research Authority and the [name of REC] Research Ethics Committee. 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, Helsinki 1964 and later revisions.

8.2 CONSENT

Healthy Cohort

A delegated research nurse will approach the parents of newborn babies within the first hours after birth to explain the study and invite the parents to participate. Parents will be given written information to read before deciding whether they wish to participate.

HIE Cohort

Since the study aims to obtain information that will inform better early treatment decisions, i.e., within 6h of birth, it is essential that the data collection begins as soon as possible after birth, and certainly before 6 hours of age. Hence, the ECG data and salivary cortisol collection may begin before informed parental consent is obtained (deferred consenting).

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). If the parents do not wish to participate in the study, data collection will be interrupted and the ECG data and saliva samples obtained up to that point will be discarded.

Whether or not the parent(s) decide to take part in the study shall not affect the clinical decisions made during the care of the baby, neither the quality of care provided. All participants are free to withdraw from the study at any time without giving reasons and without prejudicing further treatment.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study according to the Data Protection Act, UK. Personal identification data including telephone numbers and all contact details will be stored as (i) as hardcopies in a research folder in locked cupboards in site principal investigators office, and Imperial college London research office (ii) NHS computers at the recruiting sites (only for babies recruited from that site) (iii) Secure and encrypted server at Imperial College London.

All data will be linked anonymized using a study code, at the recruiting site. The Case reports forms will be electronic so that this can be filled in by the recruiting centres directly into the research database (Redcap). No patient identifiable data will be held in the research database, and the cases will be anonymized (linked) as described above. The data base will be hosted in a secure and encrypted Imperial College server or an approved private cloud server. Neonatal nursing staff will record NPASS scores and other hourly monitoring data in HIE babies, and parents record status on the baby in case of healthy babies in post-natal wards. This data will be collected either on a paper form or a dedicated application in a tablet computer using the study number, and no personal data will be collected.

MRI scans and ECG data 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. All research data will be stored at Imperial College London, for a period of 10 years.

Summary of the data storage and flow is given in the table below

Document/Data	Type	Personal identifiers	Storage location	Security
Signed consent forms (hard copy)	Paper copy	Yes	Recruiting site	Locked cupboards in restricted access area.
Signed consent form (scanned electronic copy)	Scanned PDF	Yes	Imperial College London	Secure and encrypted server

Electronic case report form	Redcap database	No	Imperial College London	College or secure external Cloud server
Personal identifiable data (name, address, contact details)	Paper and electronic copy	Yes	Recruiting sites and Imperial College London	Locked cupboards in restricted access area and secure encrypted servers
ECG data	EDF files in FAROS monitor	No	Imperial College London	Restricted access computers
MRI data	Dicom files	No	Imperial College London and local sites	Restricted access computers and PACS at the recruiting sites

8.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

The National Institute of Healthcare Research and Imperial College London funds this study. There are no payments offered to the study participants but travel expenses and loss-of-income expenses may be covered for some parents returning to hospital for follow-up appointment.

8.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition)

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the Centre for Perinatal Neuroscience Imperial College London. For any queries, please email v.oliveira@imperial.ac.uk.

10. PUBLICATION POLICY

Primary study outcomes will be examined only after the end of follow-up period. Secondary study outcomes will be examined after the end of recruitment period (during follow-up time).

Study results will be published in relevant peer-reviewed scientific journals as well as in open-access journals as per college policy.

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Appendix 1

Schedule of events in babies with hypoxic ischaemic encephalopathy

Procedure	Frequency	Day 1		Day 2		Day 3		Day 4		Day 5		1 - 2 weeks	18 - 22 months
ECG	Continuous	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX		
NPASS	1 hourly	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX		
Cortisol	12 hourly	X	X	X	X	X	X	X	X	X	X		
Light/Sound	Continuous	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX		
Events log	As & when	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX		
MRI	Once											X	
BSID 3	Once												X

ECG: Electrocardiogram; NPASS: Neonatal Pain, Agitation and Sedation Scale; BSID 3: Bayley scales of infant development Version 3; MRI: Magnetic resonance imaging.