# ACUMEN Study

## Participant Information Sheet

**We are inviting your baby to take part in a first in human clinical study titled – ACUMEN: Acute High Dose Melatonin for Encephalopathy of the Newborn**

- Please take time to read the following information carefully. Before you decide we would like you to understand why the research is being done and what this involves for you and your baby.
- Discuss it with friends and relatives if you wish.
- If you choose for your baby not to take part, this will not affect the care your baby receives in any way.
- Your baby can stop taking part in the study at any time, without you needing to give a reason.
- Ask us if there is anything that is not clear, or if you would like more information.

### Important things that you need to know

- We are inviting parents/legal guardian(s) of babies born with hypoxic-ischaemic encephalopathy (HIE) receiving cooling to help with this study.
- Preclinical research has shown that melatonin is safe and protects the brain from further injury after HIE.
- Melatonin has been safely given to babies in small studies before, either by mouth or through a vein.
- We have developed a new melatonin preparation to be given directly into the bloodstream through a vein (IV intravenous) for babies with HIE: **Melatonin (50mg/ml) in Ethanol solution for infusion**
- This is the first time this melatonin preparation will be given to babies alongside cooling for HIE.
- This first-in-human (phase 1) study aims to find the safest dose of melatonin for babies with HIE.

If your baby takes part in the study, they will continue to receive the usual care for babies with HIE, which includes intensive care and cooling treatment for 72 hours. Your baby will also be monitored with brain activity tests (aEEG/EEG and NIRS) and a more detailed brain scan (MRI/MRS).

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### How to contact us

If you have any questions about this trial, please talk to your study doctor or nurse:

**SITE DETAILS**
Insert name of PI here
Insert address
Insert email address
Insert phone number

# 1 Why are we doing this study?

## What is Hypoxic-Ischaemic Encephalopathy (HIE)?

**Hypoxic-Ischaemic Encephalopathy (HIE)** is a condition that occurs when a baby suffers from a lack of oxygen (*hypoxia*) or reduced blood flow (*ischaemic*) impacting the brain (*encephalopathy*) around the time of birth.

## Why do we need other treatments?

The only treatment currently available to protect the brain after injury is cooling (also called *therapeutic hypothermia*). Cooling has been shown to reduce brain injury in some babies with HIE. Before cooling became standard care, parents like you took part in clinical trials, which helped make it a common treatment for babies with HIE. While cooling can reduce the damage caused by HIE, some babies still have long-term problems. The long-term effects of brain injury may include delay in reaching developmental milestones, and difficulties with learning, thinking, speaking and moving (sometimes called cerebral palsy).

To improve outcomes for babies with HIE, it is important to explore other treatments that can work alongside cooling. Preclinical research suggests that melatonin is safe and reduces brain damage when the first dose is given within 6 hours after birth.

## What is Melatonin?

Melatonin is a natural hormone our body makes to help regulate sleep. It is safe and is used in children to treat sleep problems when taken by mouth. However, since babies with HIE might not absorb melatonin well if taken by mouth, we need to give melatonin directly into the bloodstream through a vein (intravenous – IV).

Melatonin is a potential new treatment for HIE. Multiple research studies in animals have demonstrated that high doses of melatonin alongside cooling can provide better brain protection compared to cooling alone. Results from these studies show that, for melatonin to work well, high levels of melatonin in the blood (15-30mg/L) are needed within 6-8h of baby being born. These levels are much higher than the natural levels of melatonin the body makes (about 10,000 times higher).

However, its effectiveness in babies is not yet known, and this study aims to find out whether melatonin can be safely given to newborns and whether it reaches the levels in the blood that were found to be beneficial in multiple animal studies.

Preclinical research shows that Melatonin helps protect the brain after HIE in several ways:

1. **Melatonin removes harmful chemicals (free radicals)** that build up after HIE. If left to build up, these chemicals can further injure the brain.
2. Melatonin reduces harmful **inflammation** that could lead to further brain injury.
3. **Melatonin helps the cells' energy factories (mitochondria)** work better, thereby reducing cell damage.
4. Melatonin acts on special **receptors** in the body that help protect the brain.

### What are we trying to find out?

In the ACUMEN study, we want to find the dose of melatonin that is both safe and achieves "helpful" or therapeutic levels to give to babies with HIE who are receiving cooling.

This is the first time we will be using a preparation of melatonin, purposely developed for babies with HIE. This drug is called **Melatonin in Ethanol 50mg/ml solution for infusion.** We want to find the right dose of melatonin we need to give babies to achieve the "helpful" blood melatonin levels we believe protects the brain.

## 2 Why is my baby being asked to take part?

Your baby is invited to take part in the ACUMEN study for these reasons:

- Your baby has HIE, is in a stable condition, receiving cooling treatment and is being closely monitored in the Neonatal Intensive Care Unit (NICU), which makes them suitable for this study.
- Your baby is at risk of on-going brain injury and might benefit from the addition of melatonin to the standard treatment of cooling.

## 3 What do I need to know about the treatments used in this study?

### How is melatonin given?

We have developed a new melatonin medicine for use in babies with HIE. This melatonin is in liquid form and contains a very small amount of ethanol (alcohol) (see below).

All babies in the study will receive a first dose of melatonin within 6 hours of birth, followed by 5 smaller doses every 12 hours starting 24hrs after the first dose. These doses will continue during the cooling period. The melatonin will be given slowly over 2 hours

either through a small line inserted into a vein (called a cannula), a line in the belly button area (UVC – umbilical venous catheter) or a longer line in a large vein (called a long line).

### Is melatonin safe?

In our preclinical studies, high doses of melatonin did not cause any problems with vital signs (such as blood pressure). In another small clinical trial of newborn babies, doses of 5 mg/kg were given through a vein safely using a different melatonin preparation without any side-effects. Higher doses of up to 25 mg/kg have also been given safely to babies via a feeding tube into the stomach.

Melatonin has been used in various doses, routes, and preparations in newborns and other patient groups in previous clinical studies. It has been given both through a vein (intravenously) and by mouth (via a feeding tube), with no major safety concerns reported.

In this study, as we do not know the exact dose needed to achieve the helpful blood levels of melatonin previously established in the laboratory, we will start with the lowest dose (5mg/kg) and gradually increase it in a "dose-escalation" approach. Your baby will be recruited to a dose level and there will be no change in the dose they will receive during the study. All babies will be monitored carefully for side-effects.

### What is the ethanol adjuvant excipient?

As babies with HIE may not absorb melatonin well when given by mouth, melatonin should be given directly into the bloodstream via a vein (IV).

To make melatonin into a liquid form, we needed to add a chemical that helps melatonin dissolve (called an excipient). In this melatonin preparation, a small amount of ethanol (alcohol) is used. This is already found in other common medicines used in newborn care (e.g., furosemide, iron, phenobarbital).

Preclinical research shows that ethanol can also help protect the brain, which is why it is included as an "adjuvant" (helpful) excipient. After each dose of the study drug, your baby's blood alcohol levels will be checked alongside melatonin levels to ensure they stay below a level considered to be safe (below 0.25g/L).

## 4 What will I need to do if I want my baby to take part?

### Can my baby definitely take part?

Not all babies that receive cooling will be able to take part in the study. The study has participation criteria to ensure that we do the safest thing for your baby.

If your baby meets the study requirements, the doctors looking after your baby will already have approached you to request permission for the ACUMEN research team to discuss this study with you. You will be given information on the study and will have the opportunity to ask any questions you may have regarding the study.

## What if my baby meets the study entry requirements?

If your baby meets all the entry requirements for the ACUMEN study, the research nurse/doctor who is part of the neonatal unit team will go through the next key steps with you.

We may ask you to give us your consent verbally in the first instance. The research team will then go through a form with you which you will sign to confirm and provide your written consent for your baby to take part in the study.

## What will happen to my baby during the study?

Your baby will already be receiving cooling treatment as part of their usual care. As part of the study, your baby will also get a dose of the melatonin within the first 6 hours of your baby's birth. After the first dose, your baby will receive five smaller doses every 12 hours. The melatonin will be given through a vein as an infusion over 2 hours.

Please be assured that your baby will still receive the same standard of high-level neonatal care whether you choose or choose not to take part in the study.

**Monitoring**

Your baby will receive standard neonatal intensive care as all babies receiving cooling treatment. This may include breathing support with a ventilator. Your baby will also have lines placed either in their belly button, arms, or legs. These are important for monitoring your baby's vital signs (like blood pressure and heart rate), for giving medicines and to keep your baby hydrated, and for blood tests.

Your baby will also have brain monitoring as part of their care:

- **Video Electroencephalography (aEEG/EEG):** Your baby's brain activity will be continuously monitored during cooling and rewarming using sensors placed on their head. This helps us check for seizures (fits) and track brain activity. As part of this monitoring, a video of your baby will also be recorded to ensure we can accurately match brain activity with your baby's movements and behaviours. The monitoring in the ACUMEN study will be more detailed than regular systems already used in some hospitals, which will help us record brain activity more accurately.
- **Modified Sarnat Neurological Examination:** Your baby's neurological examination will be assessed at multiple time points throughout their participation in the study, including soon after study entry and at regular intervals

during their hospital stay. These assessments will be recorded on video aEEG/EEG to allow for later central review and confirmation of neurological scores.

- **Near-Infrared Spectroscopy (NIRS) Imaging**: This is a safe, non-invasive test that uses light to measure how much oxygen is in your baby's brain. It helps us understand how well the brain is receiving oxygen and will be continuously monitored during cooling and rewarming. This test is also used in some hospitals already and will be part of the ACUMEN study.

**Imaging**

As part of your baby's care, we will take some images of your baby's brain. These will include:

- **Cranial Ultrasound** – a quick and painless scan done at the bedside. It is routinely used for all babies in neonatal units. It helps check the structure of the brain, look for bleeding and detect changes related to HIE. This scan is safe and does not involve any radiation.
- **Magnetic Resonance Imaging (MRI)** – this is a more detailed brain scan which looks at the brain's structure and any changes after HIE and is part of your baby's standard care.
- **Magnetic Resonance Spectroscopy (MRS)** – MRS is an additional scan that is performed during the main MRI scan, which may not yet be used at all hospitals for babies with HIE but will be part of the ACUMEN study. MRS looks at chemical changes in the brain after HIE and may help us learn more about your baby's future developmental milestones. This scan will be done at the same time as the MRI scan. This additional scan lasts less than 10 mins and therefore your baby is unlikely to require any extra sedation than that already given for their standard MRI scan. In total the scans will take about 90 mins.

With your permission we would like to collect and store copies of these scans whilst your baby is taking part in this study.

**Blood Tests:**

As part of your baby's standard care, blood tests will be done to check the cell count, liver and kidney function, and infection markers.

**Additional Assessment:**

As part of this study, we will do some extra tests and procedures to monitor your baby's health and learn more about how they are doing. These are in addition to the care your baby is already receiving.

With your permission, the study team will take a very small amount of blood – less than 1 dessert spoon (8mL) in total over the course of the study. We will obtain these samples using the line already placed as part of your baby's standard care, so we can avoid the

need for extra needle pricks (timepoints listed in the table below). If this is not available, blood tests with a needle may be needed but limited only to the absolute essentials (melatonin and alcohol blood levels).

These blood samples will be used for:

- **Blood Melatonin, Ethanol (alcohol) and Acetaldehyde Levels**: these tests are important to measure whether we have achieved the melatonin target levels, ensure the blood alcohol levels remain below our safety limit and monitor levels of acetaldehyde, a by-product of alcohol for additional safety information. *Please note that acetaldehyde levels will only be checked in the first baby of each dose level.*
- **Biomarker Samples:** these are five small (1mL) blood samples taken and analysed later to help us understand HIE better, develop new tests for HIE and find better ways to predict how babies will develop in future. Participation in this exploratory biomarker research is optional. You may choose to opt out of this part of the study, and your decision will not affect your baby's participation in the rest of the study or the standard of care they receive.
- **Future Research:** We will also ask your permission to use any remaining blood samples for future research related to early brain development either at academic sites nationally or internationally or in academic collaborations with commercial partners. Data will only be shared with approved researchers who have obtained ethics approval for these further studies. These samples will be stored in laboratories labelled with a unique study number and *partial* date of birth, therefore your baby's identifiable information will not be disclosed. We are not able to disclose the individual results of these analyses to participants.
- Following testing outlined within the study, all samples will be disposed of in accordance with Human Tissue Act (HTA) regulations, unless you have explicitly consented to their retention for future research. Any samples not required for further ethically approved studies will be safely and securely destroyed.

| **Study Blood Samples** | **T0** (before 1st dose) | **T0+2h** (After 1st dose) | **T0+ 24h** (before 2nd dose) | **T0+ 26h** (after 2nd dose) | **T0+48h** (before 3rd dose) | **T0+72h** (before 4th dose) | **T0+96h** (24h after final dose) |
|---|---|---|---|---|---|---|---|
| Melatonin, Alcohol and Acetaldehyde* levels (0.5mL) | X | X | X | X | X | | X |
| Biomarker Blood Sample (1mL) | X | | X | | X | X | X |

**Acetaldehyde measurements in only the first baby at each dose level.*

If your baby stops receiving the trial treatment early for any reason, whether due to your decision to withdraw consent or a clinical decision made by the medical team, we would like to take a blood sample at the time of stopping the treatment and, if feasible, another sample 24 hours later. These samples are important for understanding how the trial medication behaves in the body and ensuring the safety of the treatment.

The scans (MRI/MRS, NIRS and aEEG/EEG) will be pseudonymised which means that they will only contain your baby's unique ACUMEN Participant Identification Number (PIN) and date of birth (and not their name, address, or other personal information). These pseudonymised scans will be stored and transferred for analysis to the following places:

- MRI and MRS Data: These scans will be uploaded from your scanning centre to secure servers (Bioxydyn servers based in the UK) and analysed by external radiologists based in the UK and EU. These scans will be uploaded to a secure data system (UCL Data Safe Haven, UK) at the end of the study.
- NIRS Data: This will be stored on a NIRS device at your site called Maximo, uploaded to a secure data system (UCL Data Safe Haven, UK), and then analysed by study personnel at UCL, UK.
- aEEG/EEG Recordings: These recordings will be stored on the Nervus server (UK) and accessed by a team at University College Cork, Republic of Ireland to assess brain activity and check for seizures. These recordings will be uploaded to a secure data system (UCL Data Safe Haven, UK) at the end of the study.
- Video for Assessment of Movement & Behaviours: As part of the study, a video of your baby will be recorded during aEEG/EEG monitoring. This video will also be used for a second centralised review of the neurological examination by the research team at UCL. The video may contain identifiable features, such as your baby's face.. The video will be securely stored on the Nervus server and UCL Data Safe Haven and accessed only by authorised researchers at UCL for this purpose. These recordings will be uploaded to a secure data system (UCL Data Safe Haven, UK) at the end of the study.
- All study data will be archived for 33 years after the end of the study.

When your baby is discharged, they will receive a full neurological exam (Hammersmith Neonatal Neurological Examination) as part of standard care. Your baby will also have a standard hearing test, and a video recording will be taken of your baby's general movements for assessment. The results of these assessment will be collected in the study database together with key discharge details (e.g. head circumference, feeding, weight, length of stay).

**Follow Up:** At 3 months, your baby will have a follow-up visit with a member of the ACUMEN research team. **This is an additional follow-up to the standard care of babies with HIE.** At this visit, we will check on your baby's progress and developmental

milestones using the Ages and Stages Questionnaire. We will also ask for another video of your baby's general movements and perform a neurological exam (Hammersmith Infant Neurological Examination) to assess their current development. The results of these assessments will be inputted into the study database.

Some of the tests in this study are part of standard care for babies with HIE, while others are only being done for the ACUMEN study. The table below explains which tests are standard and which are additional for research.

| **Type of Assessment** |
|---|
| Assessments done as part of **standard care** at all recruiting hospitals |
| Cooling Therapy (Therapeutic Hypothermia) |
| Blood Tests for Routine Monitoring |
| Cranial Ultrasound |
| Modified Sarnat Neurological Examination |
| Hearing Test |
| Assessments done only as part of the **ACUMEN trial** |
| Melatonin Treatment |
| Additional blood tests to measure melatonin, ethanol and acetaldehyde* levels |
| Additional blood tests for exploratory biomarkers and future research |
| Hammersmith Infant Neurological Examination at 3 months |
| Ages and Stages Questionnaire |
| Assessments that **may** be standard care at some hospitals |
| Hammersmith Neonatal Neurological Examination |
| General Movement Assessment |
| aEEG/EEG (Brain Activity Monitoring) |
| NIRS Monitoring |
| MRI/MRS Brain Scan |

**Acetaldehyde levels will only be measured in the sentinel baby of each dose level cohort.*

# 5 What are the possible benefits of taking part?

By taking part in the ACUMEN study, your baby will receive a potential new therapy (melatonin) to help protect their brain. The lowest dose we give has been shown to have some benefit in a small group of babies.

Babies will be cared for with the highest level of neonatal care, including continuous brain wave monitoring and expert analysis of any seizures that occur. Additionally, they will be closely monitored for brain oxygen levels and blood flow, which will help improve their breathing support. This level of monitoring may not yet be standard of care in all hospitals. Babies in the ACUMEN study may receive more detailed monitoring, which can help identify health problems earlier than in some other units.

As part of this study, babies will receive one of several possible dose levels of melatonin. The research team will inform you about the dose level your baby will be given. It is important to know that, because we are testing different dose levels, we do not yet know which dose is most effective.
While we hope the information from this study will help improve treatments for future babies with HIE, it is important to understand that the main purpose of this research is to assess safety rather than to test how well the treatment works at this stage.

# 6 What are the possible side effects?

## What are the most common side effects?

Current research suggests that melatonin is safe: doses of up to 5mg/kg have been given through the vein and up to 25mg/kg via the mouth in newborn babies.

Some studies have suggested melatonin might lower blood pressure, but our research has not raised this concern. Since this will be the first time we will give this melatonin preparation to babies with HIE, we will closely monitor your baby for side-effects. These include (but are not limited to):

1. Drowsiness: most babies will be sedated for their ventilation support
2. Blood pressure changes: monitored through a line placed in the artery or an external blood pressure cuff. Babies may need slight increase in the dose of blood pressure medicines

Melatonin is still being researched as a potential treatment for newborns with HIE, and while early studies suggest it may help protect the brain, its long-term effects in babies are not yet fully understood. This means that there may be long-term risks that we do not

yet know about. The purpose of this study is to gather more information about the safety of melatonin in newborns.

## 7 What are the possible disadvantages and risks of taking part?

The ACUMEN study is a dose finding safety study. The medicine is unlicensed and has not yet been administered to humans in this preparation but has been extensively studied in preclinical studies on animals in the laboratory. The Medicines Health Regulatory Body (MHRA) has reviewed this medication and, as it is specifically intended for use in babies with HIE—a condition that does not occur in adults—they have authorised its first use in babies without requiring prior studies in adult patients.

All medical procedures involve the risk of harm. There might be risks associated with this study that we do not yet know about as this is a safety study. Animal toxicology studies were done using this drug and no toxic effects were found at the doses that we are using or at higher doses. If you have questions about side-effects, please ask your study doctor.

New information about the treatment being studied may become available while the study is running. We will tell you about any new findings that might affect your decision about your baby's continuation in the study.

## 8 More information about taking part

### Does my baby have to take part in the ACUMEN study?

It is up to you to decide whether or not to take part. If you decide to take part, you will be given this information sheet to keep and you will be asked to sign a consent form.

A decision not to take part will not affect the standard of care you receive.

The Patient Advice and Liaison Service (PALS) offers confidential advice, support, and information on health-related matters. You have the opportunity to discuss any concerns about the study or the care of your baby with a PALS officer in your hospital.

### Will my GP be informed?

Yes, if you decide for your baby to take part in this study, your GP will be informed of your baby's participation. This is to ensure that your GP is aware of your baby's involvement in the study and can provide any necessary follow-up care if needed.

## What happens after the study has finished?

Once your baby has had all 6 doses of the study drug at the 72-hour timepoint, the treatment is considered complete and no further drug will be given. The information collected during the study will help researchers understand whether melatonin is safe and whether it may be beneficial for babies with HIE in the future. Your baby's routine medical care will continue as usual, and no further study-related procedures will take place after your baby has been followed up for 90 days.

## Expenses and Payments

These are not met by the study as we would not require either you or your baby to visit us beyond the time that your baby needs to recover after birth until the 3-month study visit.

Please note that all discoveries (intellectual property) are a gift to UCL and that you will not benefit financially if the research leads to a new treatment.

## Can I change my mind after my baby has joined the study?

You can change your mind about your baby's participation in the study at any time and without giving a reason. Your study doctor can advise you about any concerns you may have.

A decision to stop taking part at any time will not affect the standard of care your baby receives.

If you withdraw your baby early from the study during the study treatment period (i.e when the drug is still being given to your baby), we would like to take a blood sample at the time of stopping the treatment and, if feasible, another sample 24 hours later. These samples are important for understanding how the study medication behaves in the body and ensuring the safety of the treatment.

Taking these additional samples is entirely optional and will only be done if you consent to it. You are under no obligation to allow these additional samples to be taken, and your decision will not affect your baby's care in any way.

## What will happen to the information collected about me and my baby during the study?

**How will we use information about you?**

We will need to use information from your baby from their medical records for this research project.

This information will include your baby's date and time of birth, and your name and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Once we finish the study, we will carefully review and anonymise the data before any analysis or sharing to ensure that no combination of information can lead to identifying you or your baby. Published reports will be written in a way that ensures your baby's identity remains protected, and we have taken steps to prevent re-identification.

The hospital will keep identifiable information about you for a minimum of 33 years after the study has finished.

The type of information collected about you and your baby are demographics (such as date/time of birth, birth weight etc.), pregnancy and delivery history, and any clinical assessments that are performed during the trial. If your baby's care is transferred to another hospital, we may need to contact this hospital so that we can continue to collect data and monitor your baby.

The hospital will keep your name and contact details confidential and will not pass this information to UCL. We will use this information as needed, 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. Certain individuals from UCL and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The people who analyse the information will not be able to identify you or your baby and will not be able to find out your name or contact details.

## What are your choices about how your information is used?

You can discuss any concerns you may have with your doctor at any time.

If you choose for your baby to stop taking part in the study, we would like to continue collecting information about your baby's health from you and your baby's hospital medical records. If you do not want this to happen, tell us and we will stop.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about your baby.

Your pseudonymised information could be used for future related research with your permission. This future related research may be but not limited to early brain injury and development, and any related research to melatonin.. However, ethics approval will be sought prior to use of this information, and no one will be able to identify you or your baby from the data.

The ACUMEN trial may use the collected data for marketing authorisation to develop melatonin as a licensed and commercial product to be used in the future in other babies; however, only anonymised data will be provided to the regulatory bodies.

The CCTU is registered under the provisions of the UK 2018 Data Protection Act (DPA) to store this information. There is a question about this on the consent form that we will ask you to sign before you begin the study.

## Where can you find out more about how your information is used?

You can find out more about how we use your information:

- at www.hra.nhs.uk/information-about-patients/
- our leaflet 'How health researchers use information from participants in clinical trials' available from https://www.ucl.ac.uk/comprehensive-clinical-trials-unit/use-data
- https://www.ucl.ac.uk/legal-services/privacy/ucl-general-privacy-notice-participants-and-researchers-health-and-care-research-studies
- by asking one of the research team
- by sending an email to the UCL Data Protection Officer on data-protection@ucl.ac.uk
- by emailing us on cctu-enquiries@ucl.ac.uk

## What will happen to the results of the ACUMEN study?

We will publish the results of the ACUMEN study in a medical journal so that other doctors and researchers can learn from them. The results may also be presented at medical conferences, shared during invited talks, or publicised through appropriate media channels such as newspaper articles or online platforms. Any publicity surrounding the study will ensure your and your baby's anonymity is protected. We also work closely with patient groups to advertise the results of the study in an easy-to-read format for patients. You can ask your study team or usual doctor for a copy of any publication or link to patient websites when the study is published. Your and your baby's identity and any personal details will be kept confidential. No named information about you or your baby will be published in any report relating to this trial.

## Who is organising and funding the trial?

This study is organised by the Comprehensive Clinical Trial Unit (CCTU) in University College London (UCL), which has run trials for many years. The study coordination, data collection and analysis and administration will be provided by the CCTU. You can find out more about us at https://www.ucl.ac.uk/cctu.

UCL is the sponsor and data controller for this study and has overall responsibility for the conduct of the study. They are responsible for ensuring the study is carried out ethically and in the best interests of the study participants.

This study is funded by the UKRI Medical Research Council Developmental Pathway Funding scheme.

## Who has reviewed the ACUMEN study?

The study has been reviewed and authorised by the Medicines and Healthcare products Regulatory Agency (MHRA), as well as a Research Ethics Committee, the Health Research Authority (HRA), and the Research and Development Office at all participating hospitals. As well as by the Comprehensive Clinical Trials Unit Protocol Review Committee.

The study has obtained ethics approval from the UCL Life and Medical Sciences Research Ethics Committee ID: 0112.

## What if new information becomes available during the trial?

Sometimes during a study, new information becomes available about the treatment options being studied. If this happens, the study doctor will tell you about it and discuss with you whether you wish for your baby to continue the study. If you decide that your baby should stop taking part in the study, your doctor will arrange for your baby's care to continue outside of the study. However, if you decide that your baby should continue, you might be asked to sign an updated consent form.

Your doctor might also suggest that it is in your baby's best interest to stop taking part in the study. Your doctor will explain the reasons and arrange for your baby's care to continue outside the study. Your baby will continue to receive standard medical care.

## What happens if the ACUMEN study stops early?

Very occasionally a study is stopped early. If this happens, the reasons will be explained to you. Your study doctor will arrange for your baby's care to continue outside of the study. Your baby will resume standard medical care.

## What if something goes wrong?

Every care will be taken in the course of this clinical study.

**Complaints**

In the event that something does go wrong, and your baby is harmed during the research, and this is due to someone's negligence, then you may have grounds for a legal action for compensation against UCL/ [Insert Trust Name] but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Alternatively, you can contact the Patient and Advice Liaison Service at the hospital:

**Hospital Patient Advice & Liaison Service (PALS)**

**Address**: [insert Trust PALS address]

**Email**: [insert Trust PALS email address]

**Tel**: [insert PALS telephone number]

## 9 Contacts for further information

If you want further information about the ACUMEN study, please contact the study doctor using the details provided on the front page of this Participant Information Sheet.

## 10 Glossary

**Cooling or Therapeutic Hypothermia (HT):** Therapeutic hypothermia is a medical treatment that involves cooling a baby's body temperature to 33.5C for 72 hours to help protect the brain. By reducing the body's temperature, it can help slow down harmful processes and reduce the risk of further brain injury.

**Dose-escalation Study**: A study that determines the best dose of a new drug or treatment. In a dose-escalation study, the dose of the test drug is increased a little at a time in different groups of people until the highest dose that does not cause harmful side effects is found. A dose-escalation study may also measure ways that the drug is used by the body and is often done as part of a phase I clinical trial. These trials usually include a small number of patients and may include healthy volunteers.

**Excipient**: Chemicals used in medicines to help keep them in soluble (liquid form)

**Electroencephalography (aEEG/EEG):** a painless test that measures electrical brain activity, giving the clinician an idea of the baby's brain function and allows monitoring of seizures (fits)

**MRI**: a non-invasive medical imaging technique using magnetic fields to create detailed picture of tissues and structures. In HIE, it is used to give clinicians information of areas of injury and possible long-term prognosis

**MRS:** is a non-invasive imagining technique performed during MRI to measure the chemical properties of tissues. In HIE, research has shown that it can accurately predict 2-year developmental outcomes (language, cognitive and motor).

**NIRS**: Near infrared spectroscopy is a painless test that uses light to measure the oxygen level of tissues.

**Phase 1 trial:** A Phase 1 trial is usually the first time that a medicine is tested in a certain human population and so it will usually investigate the safe dose range and potential side effects.

**Preclinical Research**: Research done in a laboratory and/or using animal models to test a treatment before it is studied in humans.

# THANK YOU FOR TAKING THE TIME TO CONSIDER TAKING PART IN THE ACUMEN TRIAL.