Cooling in Mild Encephalopathy (COMET) trial (NCT05889507)

The Local Principal Investigator is **Julie-Clare Becher** (Office number: 22571; Mobile: 07712150862). Others eligible to recruit: Ben Stenson, Angela McLaren, Gemma Sullivan

Essential links

E-screening assessment for eligibility <3h

1. E-screener QR code:
    - e-screeners must be certified to receive a £25 voucher each time they screen
    - if staff member is uncertified they can still e-screen using code above, but will need to certify within 3 weeks before receiving this voucher. Register here for certification: **https://redcap.link/ems_assessment**
    - please note that this monetary recognition is independent of whether the baby is subsequently recruited to the trial or not- it is for screening and not for recruitment (that is, if you screen such a baby and find a normal exam and this is recorded using the e-screener then you remain eligible for the voucher)
    - If the first exam is normal or shows <2 signs, an automated email requests a repeat exam before 6 hours. If the repeat exam shows ≥2 signs, the baby can be recruited.

Protocol: Full protocol and related documents here

Randomisation: Sealed envelope Sealed Envelope | Access. Consultants should have individual access.

Sponsor Site: A dedicated 24/7 study team at UCL is available to support all sites

- Contact email: comet@imperial.ac.uk
- Contact phone: 020 3313 2473

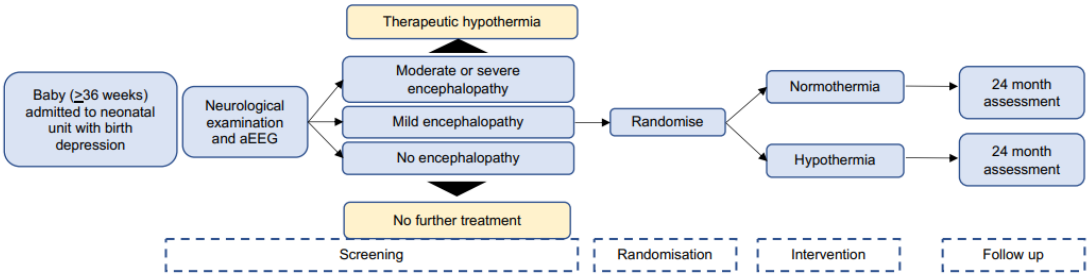
Study Design

COMET is an international multicentre randomised control trial of therapeutic hypothermia for babies with mild hypoxic-ischaemic encephalopathy (HIE) coordinated by Imperial College London. It aims to recruit 426 babies before July 2027.

Intervention

- Whole body hypothermia group: whole body cooling therapy (33.5+0.5°C) for 72 hours using a servo-controlled cooling machine followed by slow rewarming at 0.5°C per hour to attain normothermia.
- Targeted normothermia group: axillary temperature will be maintained at 37°C+0.5°C for the first 88 hours.

Study Flow Diagram



Inclusion criteria

Inborn babies with mild hypoxic ischaemic encephalopathy born at or after 36 weeks of gestation and admitted to neonatal units within six hours of birth:

- Criteria A:
  Evidence of intra-partum hypoxia-ischemia defined as any of:
  - Apgar score of less than six at 10 min after birth
  - Continued need for resuscitation at 10 min after birth
  - Severe birth acidosis defined as any occurrence of: pH less than 7.05 or Base deficit ≥ 16mmol/l in a cord or baby gas sample within 60 min of birth.
- Criteria B:
  Evidence of mild HIE defined as: two or more abnormal findings in any of the six categories of the expanded modified Sarnat examination (level of consciousness, spontaneous activity, posture, tone, primitive reflexes, and autonomic nervous system) but not meeting the diagnosis of moderate or severe HIE, performed by a certified examiner <3h of age. HIE staging here.
- Criteria C:

Normal amplitude, **with or without** sleep wave cycling, on an aEEG performed for at least 30 min between 1 and 6 h of age. Normal amplitude is defined as upper margin of the aEEG activity more than 10 microvolts and the lower margin more than 5 microvolts on *a single channel aEEG.*

AND:

1. can have cooling started within 6 hours of birth

Exclusion criteria

- Outborn babies
- Infants who meet the criteria for whole-body hypothermia (ie those with moderate or severe HIE).
- Infants without encephalopathy defined as less than two abnormalities on structured neurological examination.
- Infants with major congenital or chromosomal anomalies identified prior to randomisation.
- Infants with birthweight <1800g.
- Infants who received muscle relaxation, or anti-seizure medications prior to neurological assessment.
- Infants with moderate or severe background voltage abnormalities or seizures on amplitude integrated electroencephalography (aEEG).
- Infants already enrolled in interventional studies.

How to recruit and randomise

1. Ensure eligibility for Criteria A.

2. Confirm eligibility for Criteria B (as above) using the COMET e-screener qr code (above) at least one hour after birth.

3. Admit to unit if not already admitted, due to presence of mild encephalopathy.

4. Unless the first screener has been certified then a certified person must re-examine to ensure meets mild encephalopathy before obtaining consent.

5. Put on CFM and confirm eligibility after 30 minutes of recording. Ensure that the display is set to cross cerebral single channel. Take anonymous screenshot of CFM on the machine.

6. Obtain parental consent for trial

- Explain the trial to the parents
- Provide parents with the COMET trial parent information sheets
- Show parents the COMET introductory video using a laptop or tablet
- Obtain written parental informed consent for their baby's participation in the trial. They do not consent to video

7. Access Sealed Envelope website to randomise baby Sealed Envelope | Access

What clinicians should know about patient management in each arm:

Hypothermia (Intervention group)

Whole body hypothermia as for moderate or severe HIE except for:

- Sedation with narcotic drugs will be used only if the nonpharmacological approaches like swaddling/tucking, pacifiers, rubbing, holding, touch, and massage) are ineffective.
- A follow-up BSID IV assessment will be done when the recruited babies are 24 months of age by the central Study Team.

Normothermia (Control group)

- The axillary temperature will be maintained at 37+0.5°C, measured every 4 hours and any occurrence of hyperthermia will be managed using a standardised protocol.
- All term babies in the control group will be placed in open cots instead of incubators.
- Babies in the control group who develop seizures and progress to moderate HIE between 6 to 24 hours may be considered for whole-body cooling for 72 hours as clinical care, although this is expected to occur in less than 5%.
- Conventional MRI using standard 3D T1–weighted and 2D T2–weighted sequences and diffusion weighted imaging will be performed in all babies prior to discharge home.
- A follow-up BSID IV assessment will be done when the recruited babies are 24 months of age by the central Study Team.

Background

All references provided in the COMET protocol

The incidence of mild hypoxic ischaemic encephalopathy is estimated to be 0.8 to 1 per 1000 livebirths. While previously it was believed the outcome for babies with mild HIE

was universally good, however recent reports from the cooling data are not as reassuring and indicate an increased risk of cognitive impairment.

Whole body hypothermia has been a standard of care for babies with moderate or severe HIE since 2010 reducing the risk of death or major neurodevelopmental disability at 18-24 months of age. Despite the lack of evidence for safety or efficacy, population data indicates that many babies who do not meet the criteria of the original clinical trials are being offered whole-body hypothermia in the NHS. Between 30-45% of babies being cooled have mild HIE, a proportion of cooled babies have no HIE at all, and three quarters of UK units now offer cooling for babies with mild HIE.

This therapeutic creep indicates an urgent need for a standardised approach to the clinical assessment and treatment of babies with hypoxic ischemic encephalopathy in the NHS, so that the babies receive optimal clinical care and are not harmed by unnecessary treatments.

Pre-clinical models suggest that cooling in the context of a mild ischaemic insult may reduce some but not all markers of brain injury. Other studies have shown that hypothermia in the absence of HIE may in fact increase damage within the brain. This raises concerns about potential harm as many babies without encephalopathy are currently being offered whole-body hypothermia in the NHS.

The COMET trial will establish the safety and efficacy of whole-body hypothermia for mild hypoxic ischaemic encephalopathy, inform national and international guidelines, and will establish uniform practice across the NHS and other high-income countries. It will also provide an economic case for the NHS, if whole-body hypothermia is beneficial. Alternatively, whole-body hypothermia treatment will be discontinued for babies with mild hypoxic ischaemic encephalopathy if it is found to be ineffective or unsafe, again leading to cost savings. In the absence of a clinical trial, whole-body hypothermia will be increasingly used for this population, and safety and efficacy will remain unknown.

Objectives and outcomes

Primary objective: To examine if whole-body hypothermia to 33.5+0.5°C, initiated within 6h of birth and continued for 72h, improves cognitive development at two years of age after mild hypoxic ischaemic encephalopathy compared with targeted normothermia at 37+0.5°C.

Secondary objectives:

1. To compare the adverse events in the whole-body hypothermia and targeted normothermia groups.

2. To estimate the cost-effectiveness and economic value of whole-body hypothermia for mild encephalopathy from an NHS and personal social services (PSS) perspective.

Primary outcome: Cognitive Composite Scale score from the Bayley Scales of Infant and Toddler Development 4th Edition (Bayley-IV) examination at 24 (+2) months of age, performed by the central study team.

Secondary outcomes:

A. Secondary outcomes during neonatal hospitalisation:

1. Neonatal seizures
2. Duration of intensive care
3. Duration of hospital stay.
4. Bloodstream or cerebrospinal fluid positive infection
5. Thrombocytopenia or coagulopathy
6. Any breastfeeding at hospital discharge.
7. Brain injury scores on conventional magnetic resonance imaging

B. Secondary outcomes assessed at 24 (+2) months of age.

1. Survival with no neurological impairment defined as a score of >85 in all Bayley-IV domains (motor, language, and cognitive), no cerebral palsy (Gross motor function classification system score <1), hearing or visual impairment, or seizure disorder.
2. Internalising and externalising behaviour problems, and Total Problems Scale score on Preschool Child Behaviour Checklist (CBCL)