COMET

Cooling in Mild Encephalopathy

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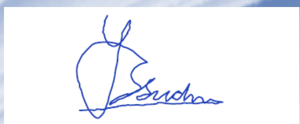
Prof. Sudhin Thayyil Chief Investigator	06/02/2024	

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Sponsor

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

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National Institute for Health Research Health Technology Assessment

This protocol describes the COMET 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 UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

NHS	National Health System
CBCL	Preschool Child Behaviour Checklist
SD	Standard deviation
IQ	Intelligence quotient
HI	Hypoxia-ischemia
MARBLE	Magnetic Resonance Biomarkers in Neonatal Encephalopathy
PRIME	Prospective Research in Infants with Mild Encephalopathy
MRI	Magnetic resonance imaging
NICHD	National Institute of Child Health and Human Development
aEEG	Amplitude-integrated electroencephalography
BPAM	The British Association of Perinatal Medicine
HELIX	Hypothermia for Encephalopathy in low and middle-income countries
HEAL	High dose Erythropoietin for Asphyxia and Encephalopathy
ILAE	International League Against Epilepsy
EEG	Electroencephalography
TOBY	Total Body Hypothermia
PSS	Personal social services
PARCA-R	Parent report of Children's abilities- Revised
ODN	Operational delivery network
NICU	Neonatal intensive care unit
LNU	Local neonatal unit
SCBU	Special care baby unit
ICH GCP	International Conference on Harmonization of Good Clinical Practice
eCRF	Electronic case report form
GP	General practice
DICOM	Digital imaging and communications in medicine
GSE	Gold standard examiner
PI	Principal investigator
AE	Adverse event
SAE	Serious adverse event
IDMC	Independent Data safety and Monitoring Committee
NEC	Necrotising enterocolitis
PPHN	Persistent pulmonary hypertension of the newborn
ECMO	Extra-corporeal membrane oxygenation
GMFCS	Gross motor function classification system
mITT	Modified intention to treat
MOP	Manual of procedures
LCRN	Local clinical research network
REC	Research ethics committee
HRA	Health research authority
GDPR	General data protection regulation
HTA	Health technology assessment
TMG	Team management group
ICMJE	International committee of medical journal editors

STUDY SUMMARY

Trial Title	Cooling in Mild Encephalopathy (COMET) trial
Internal ref. no. (or short title)	COMET Trial
Clinical Phase	Phase III
Trial Design	Prospective multi-centre open label two-arm randomised controlled trial with masked outcome assessments.
Trial Participants	Babies with mild hypoxic ischaemic encephalopathy born at or after 36 weeks of gestation and admitted to neonatal units within six hours of birth
Sample Size	426 babies
Treatment duration	72 hours
Follow up duration	24 (±2) months of age
Trial Period	5.5 years
Research questions	1) Does whole-body cooling (33.5±0.5^{0}C) initiated within six hours of birth and continued for 72 hours, improve cognitive development at 24 (±2) months of age after mild neonatal encephalopathy compared with normothermia (37±0.5^{0}C)? 2) Does a prospective trial-based economic evaluation support the provision of cooling therapy for mild encephalopathy in the NHS on cost-effectiveness grounds?
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.
Secondary outcomes	Secondary outcomes during neonatal hospitalisation 1. Neonatal seizures 2. Duration of intensive care 3. Duration of hospital stay. 4. Duration of mechanical ventilation 5. Duration of inotropic support 6. Bloodstream or cerebrospinal fluid positive infection 7. Thrombocytopenia or coagulopathy 8. Any breastfeeding at hospital discharge. 9. Brain injury scores on conventional magnetic resonance imaging Secondary outcomes assessed at 24 (±2) months of age. • 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. • Internalising and externalising behaviour problems, and Total Problems Scale score on Preschool Child Behaviour Checklist (CBCL)
Exclusion criteria	• Infants who meet the criteria for whole-body hypothermia. • 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 have already 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.
Investigational Medicinal Product(s)	• 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^{0}C per hour to attain normothermia. • Targeted normothermia group: core body temperature will be maintained at 37°C±0.5°C using servo-controlled incubators or warmers for the first 88h.
Formulation, Dose, Route of Administration	To administer this intervention newborn babies will be kept on a cooling mattress or blanket circulating a coolant, a rectal temperature probe will be inserted, and overhead radiant warmer will be switched off. Core body temperature will be rapidly reduced and then maintained at 33.5±0.5°C for 72 hours, followed by rewarming over 6 to 8 hours (0.5°C per hour) to attain normothermia (37°C±0.5°C). Rectal temperature will be continuously monitored for 88 hours. In case of randomization to the control group, the rectal temperature will be maintained at 37°C±0.5°C for first 88 hours.

INTRODUCTION

In the UK approximately 1400 babies are admitted to neonatal units with hypoxic ischaemic encephalopathy every year; of these about 600 have moderate or severe hypoxic ischaemic encephalopathy and 800 have mild hypoxic ischaemic encephalopathy[1]. The incidence of mild hypoxic ischaemic encephalopathy is estimated to be 0.8 to 1 per 1000 livebirths[2].

Whole-body hypothermia, an evidence-based therapy for babies with moderate or severe encephalopathy in high income countries, is increasingly used for babies with mild hypoxic ischaemic encephalopathy in the NHS without an adequate evaluation of safety and efficacy[3]. Although in-hospital morbidity data on over 3000 babies with mild hypoxic ischaemic encephalopathy who received whole-body hypothermia have been reported, limited data exist on later neurodevelopment. Hence, the impact of whole-body hypothermia in babies with mild hypoxic ischaemic encephalopathy on longer-term outcomes remains unknown[1]. Without rigorous evaluation of safety and efficacy, whole-body hypothermia will become embedded in NHS clinical care without parents (and clinicians) knowing if it benefits or harms the babies[1].

Whole-body hypothermia

Several well conducted clinical trials[4-6] in the past decade, including seminal trials led by investigators of the COMET trial, reported that a controlled reduction of core body temperature by 3 to 4°C within 6 hours of birth and continued for 72 hours (Risk Ratio; 95% Confidence intervals) reduces: the combined outcome of death or major neurodevelopmental disability at 18-24 months of age (0.75; 0.68 to 0.83; 8 studies, 1344 infants); death alone (0.75; 0.64 to 0.88; 11 studies; 1468 infants) and disability among survivors (0.77; 0.63 to 0.94; 8 studies, 917 infants) after moderate or severe encephalopathy[7]. Whole-body hypothermia is therefore the standard treatment for babies with moderate or severe hypoxic ischaemic encephalopathy and is recommended by the National Institute for Health and Care Excellence[8].

Therapeutic drift

Whole-body hypothermia is a significant intensive care treatment and poses discomfort for the baby (e.g., intravenous lines, ventilatory support, sedation with narcotic drugs, delayed/reduced enteral feeding, and separation of mother and baby). This is a major intervention to undertake without knowing whether there are long-term benefits of offering it to babies with mild hypoxic ischaemic encephalopathy.

Despite the lack of evidence on safety or efficacy, 1050 (30%) of 3511 babies with mild hypoxic ischaemic encephalopathy admitted to the UK neonatal units between 2011 to 2016 received whole-body hypothermia[9]. More importantly, 830 infants without encephalopathy were also cooled. Furthermore, the number of babies with moderate encephalopathy doubled from 141 to 293 during this time period, while severe encephalopathy numbers remained the same. These data indicate that many babies who do not meet the criteria of the original clinical trials are being offered whole-body hypothermia in the NHS. Moreover, many babies with mild hypoxic ischaemic encephalopathy are being incorrectly classified as having moderate hypoxic ischaemic encephalopathy.

Separately, a London neonatal transport audit reported that of the 170 babies transported for whole-body hypothermia between 2017 and 2019, 45% had mild hypoxic ischaemic encephalopathy or birth acidosis without encephalopathy and did not meet the current criteria for whole-body hypothermia. Structured neurological examination prior to initiation of whole-body hypothermia was either not performed or not documented in most babies[10,11] These data indicate an urgent need for a standardised approach to the clinical assessment of babies with hypoxic ischemic encephalopathy in the NHS, so that the babies receive optimal clinical care and are not harmed by unnecessary treatments.

A national survey of all cooling centres in the UK in 2017 reported that 75% of the NHS cooling centres were offering whole-body hypothermia to babies with mild hypoxic ischaemic encephalopathy[3]. Therapeutic drift is also a major concern for obstetricians as whole-body hypothermia accounts for 71% of the maternity cases investigated by the Healthcare Safety Investigation Branch (HSIB) and could increase the chances of obstetric litigations[12].

Therapeutic drift has major resource implications for the NHS as the incidence of mild hypoxic ischaemic encephalopathy (0.8 per 1000 livebirths) and severe birth acidosis (8 per 1000 livebirths) without encephalopathy is 1.3 and 10 times higher than that of moderate or severe encephalopathy (0.6 per 1000 livebirths), respectively[13]. Furthermore, lack of evidence and variations in clinical practice across the NHS leads to sub-optimal care[1]. Therapeutic drift of offering whole-body hypothermia to babies with mild or no encephalopathy in Canada and the United States of America has been even greater[14,15].

Neurodevelopmental outcomes

Reports published in the pre-hypothermic era (before 2005) are challenging to evaluate due to small sample sizes, diagnosis not limited to encephalopathy due to hypoxia-ischemia alone or made at varying times during neonatal hospitalisation, differences in psychometric measures used to test the children, and low follow-up rates (often less than 70%). More recent reports include the following studies.

The PRIME (Prospective Research in Mild Encephalopathy) study recruited 63 un-cooled babies with mild hypoxic ischaemic encephalopathy from Canada, US, UK (Imperial College London), and Thailand, of which 43 (68%) had Bayley assessments at 2 years; Seven (16%) had a Bayley Cognitive Scale Composite score of less than 85 points[16], indicating at least mild cognitive impairment. Only one baby (1.6%) developed seizures after six hours and progressed to moderate hypoxic ischaemic encephalopathy.

Finder et al reported that the mean (SD) Bayley-III Cognitive Scale Composite score of 55 non-cooled babies with mild hypoxic ischaemic encephalopathy was 6 points lower than 152 healthy peers mean (SD) 98 versus 104 (15)[17] when assessed between 18 to 42 months of age (68% follow-up rate). Murray et al reported that the mean IQ of 22 babies with mild hypoxic ischaemic encephalopathy was 18 points lower than 30 healthy peers (99 versus 117; p<0.001) at 5 years of age[18].

Pre-clinical evidence

Hypothermic neuroprotection has been reported in a mild hypoxia-ischemia (HI) rat model in some regions of the brain although this protection was not seen in hippocampal areas – the region associated with later memory problems after HI injury[19]. In another preclinical model of mild HI involving fetal lambs, 72 hours of hypothermia provided more neuroprotection than 24 hours[20].

On the other hand, two preclinical studies involving piglet models reported that hypothermia without HI increases neuronal cell death and apoptosis[21,22]. Hypothermia activated microglial unfolded protein response and thereby induced apoptosis and subsequent glial cell death, independent of the anaesthesia or hypoxic injury[21,22]. These data raise concerns about potential harm in a clinical scenario as well, as many babies without encephalopathy are being offered whole-body hypothermia in the NHS.

Clinical evidence

In a subgroup analysis of 47 babies with mild hypoxic ischaemic encephalopathy in the MARBLE (Magnetic resonance biomarkers in neonatal encephalopathy) study conducted by the COMET investigators, babies who received whole-body hypothermia had reduced white matter injury on magnetic resonance imaging (MRI) (50% versus 87%; p=0.02) and higher thalamic N-Acetyl Aspartate/Creatine (1.6 (0.21) vs 1.4 (0.1)); p<0.001) peak area metabolite ratios compared with those who did not receive cooling. At 2 years of age, none of the whole-body hypothermia group had adverse neurodevelopmental outcomes, while 2 (14.3%) non-cooled babies did. (p=0.09)[23].

Magnetic resonance imaging (MRI) data on 960 of 1857 babies (784 cooled vs 1073 non-cooled) with mild hypoxic ischaemic encephalopathy from 9 studies reported atypical white matter injury (40% to 86%) and punctate white matter lesions as the predominant abnormality and the injury to deep brain nuclei was uncommon. No difference in brain injury or seizures after 6 hours were apparent in babies who had hypothermia and those who did not, although significant selection bias existed[14,24-31].

Two metanalyses, extracting the data from babies with mild hypoxic ischaemic encephalopathy inadvertently recruited to clinical trials of moderate or severe hypoxic ischaemic encephalopathy have been reported; one included 91[32] and the other, led by the investigators of the COMET trial included 117 babies[33]. The confidence intervals for the pooled risk ratio (0.67 and 1.1 respectively) for reducing death or neurodisability at 18 months (Figure 1) ranged from 0.3 to 2.3, indicating that significant benefit or harm from hypothermia cannot be excluded[33].

Study or Subgroup	Cooling Events	Cooling Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Battin 2001	1	5	0	6	4.2%	3.50 [0.17, 70.94]
Gluckman 2005	1	5	1	3	11.3%	0.60 [0.06, 6.44]
Jacobs 2011	4	16	8	24	57.7%	0.75 [0.27, 2.08]
Thayyil 2013	4	9	2	10	17.1%	2.22 [0.53, 9.37]
Zhou 2010	1	21	1	18	9.7%	0.86 [0.06, 12.75]
Total (95% CI)		**56**		**61**	**100.0%**	**1.11 [0.55, 2.25]**
Total events	11		12			

Heterogeneity: $Chi^2 = 2.31$, df = 4 (P = 0.68); $I^2 = 0\%$
Test for overall effect: Z = 0.29 (P = 0.77)

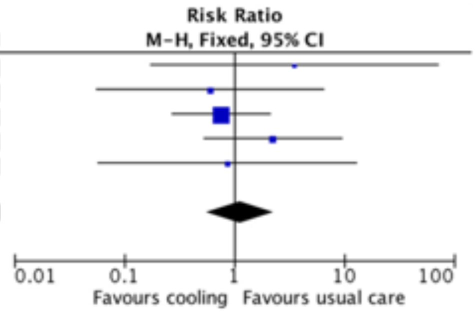

Figure 1: Effect of cooling on death or disability after mild encephalopathy.

Registry based data.
Short term outcomes on 7181 babies with mild hypoxic ischaemic encephalopathy are available from the Canadian (n=1089; cooled 36%)[14], Californian (n=1364; cooled 71%)[15], Children's Hospital Neonatal Consortium (n= 272; cooled 95%)[34]; US Children's Hospitals National Database (n=945; cooled 13%) [35] and the UK (n=3511; cooled 30%)[36] registries. These data show that whole-body hypothermia significantly increased the duration of ventilatory support (2 days versus 1 day), intensive care stay (9 days versus 6 days), need for invasive ventilation (60% versus 45%), use of opioid infusion (67% versus 12%), disseminated intravascular coagulation (8% versus 2%), hepatic dysfunction (23% versus 11%), cardiac dysfunction (8% versus 2%), discharge home on oxygen (26% vs 15%), and tube feeding at hospital discharge (22% versus 13%) compared to usual care. Other adverse short-term outcomes noted only in babies with mild hypoxic ischaemic encephalopathy who underwent whole-body hypothermia include hypotension (16%), thrombocytopenia (10%), coagulopathy (17%), persistent metabolic acidosis (8%), and subcutaneous fat necrosis (1%). No neurodevelopmental outcome data are available from any of these registries, so the long-term impact is unknown.

Pre-emptive use of narcotic infusions, a common practice during whole-body hypothermia, is often a major concern for parents[37,38]. Secondary analysis of the NICHD Neonatal Research Network hypothermia trial and the MARBLE study have reported opioid sedation increased hospital stay and duration of ventilation and had no relation with neurodevelopment[37,39].

Clinical staging of encephalopathy
The original Sarnat staging for neonatal encephalopathy was based on evolution of encephalopathy over the first three days and hence cannot be used for staging within six hours of birth. These criteria were modified for the first National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) hypothermia trial [4]so that the neurological assessment can be performed within six hours of age to classify encephalopathy. The clinical assessment when performed by certified examiners, had similar accuracy of aEEG in identifying babies with moderate or severe hypoxic encephalopathy, and predicted later adverse outcomes with similar accuracy. This assessment (modified Sarnat stage) has been effectively used in the NICHD NRN Optimising Cooling Strategies hypothermia trial[40], NICHD NRN delayed

hypothermia trial[41], and Hypothermia for Encephalopathy in Low and Middle-income countries (HELIX) trial[42] and has been extensively validated.

The modified Sarnat criteria were expanded to include babies with mild hypoxic ischemic encephalopathy for the PRIME study and were validated further in the COMET pilot randomised controlled trial. Details of the assessment are given in the appendix.

Diagnosis of neonatal seizures

Seizures in hypoxic ischemic encephalopathy are provoked and hence do not fit into the traditional seizure classification that are designed for infants, children, and adults. Seizures typically appear 6 to 12 hours after the hypoxic-ischemic insult and then peak over 24 to 48 hours before spontaneously decreasing. The recent International League Against Epilepsy (ILAE) neonatal classification framework emphasizes the role of electroencephalography (EEG) and amplitude integrated EEG (aEEG) in the diagnosis of seizures in neonates and includes a classification of seizure types relevant to this age group. Many neonatal seizures are electrographic-only with no evident clinical features; therefore, EEG seizures are included in the COMET RCT. Clinical events without an EEG or aEEG correlate are not considered as seizures. The ILAE neonatal seizure classification allows the users to categorise neonatal seizures based on the level of diagnostic certainty. A flow chart of seizure diagnosis is provided in the Appendix.

Level		
1	Definite seizures	Seizures confirmed on conventional EEG with clinical (electro-clinical seizure) or without (electro-graphic only) clinical manifestations.
2a	Probable seizures	Seizures confirmed on aEEG with (electro-clinical seizure) or without clinical manifestations (electro-graphic only)
2b	Probable seizures	Clinically assessed focal clonic or focal tonic seizure directly witnessed or reviewed on video by experienced medical personnel when EEG or aEEG was not available.
3	Possible seizure	Clinical events suggestive of epileptic seizures other than focal clonic or focal tonic seizures, directly witnessed or reviewed on video by experienced medical personnel.
4	Not seizure	Reported seizure event (as previously defined) but insufficient evidence to meet the case definition.
5	Not seizure	Reported seizure event (as previously defined), documented or witnessed by experienced medical personnel and evaluated by simultaneous conventional EEG or aEEG and determined NOT to be a case of neonatal seizure.

As both neonatal seizures and anti-seizure medications may be associated with adverse neurodevelopmental outcomes, a diagnostic certainty of level 1 or 2 is required in most cases to instigate anti-seizure therapy. Neonatal seizures should also be examined in the context of the clinical setting – for example in a baby with birth depression from a short hypoxia-ischemic episode occurring during the birth process and mild hypoxic ischemic encephalopathy, lip smacking or staring episodes occurring within couple of hours of birth is unlikely to be seizures. Hence, it is electrographic evidence on EEG or aEEG is suggested before administering anti-seizure medications in such babies.

COMET pilot randomised control trial

We conducted a three-arm pilot randomised controlled trial of whole-body hypothermia at six tertiary neonatal intensive care units in the UK and Italy between 01/10/2019 to 30/04/2023. The neonates were randomly allocated to one of the three groups (1:1:1) based on the age at recruitment – those aged less than 6 hours were randomized to normothermia or 72 hours hypothermia (33.5°C), and those aged more than 6 hours who had whole-body hypothermia initiated within six hours of birth were randomised to hypothermia for 48 or 72 hours. Neurological examination from two of the sites were also video recorded to examine the feasibility of using video recordings for quality assurance and ongoing training.

All neonates had cerebral magnetic resonance (MR) imaging and spectroscopy between 4 and 7 days after birth using harmonised sequences. Due to therapeutic drift (i.e. clinicians treating babies with mild HIE using whole body hypothermia), only 101 (45%) of the 225 eligible neonates during the trial period could be recruited.

Table 1: Short term morbidity of the 101 neonates with mild hypoxic ischaemic encephalopathy recruited to the COMET pilot trial.

	Normothermia (n=34)	**Hypothermia 48 hours (n=31)**	**Hypothermia 72 hours (n=36)**
Invasive ventilation	3 (8.8%)	14 (45.1%)	16 (44.4%)
Non-invasive ventilation	8 (23.5%)	1 (3.2%)	5 (13.8%)
Opioid use	0 (0.0%)	26/31(83%)	29 (80.5%)
Hypotension requiring inotropes	1 (2.9%)	0 (0.0%)	4 (11.1%)
Persistent metabolic acidosis	0 (0.0%)	0 (0.0%)	1 (2.7%)
Subcutaneous fat necrosis	0 (0.0%)	1 (0.0%)	0 (0.0%)
Thrombocytopenia requiring platelets	1 (2.9%)	1 (3.2%)	2 (5.5%)
Coagulopathy requiring blood products	1 (2.9%)	0 (0.0%)	4 (11.1%)
Blood stream positive sepsis	1 (2.9%)	1 (3.2%)	1 (2.7%)
Seizures after 6 hours of age	1 (2.9%)	1 (3.2%)	2 (5.5%)
Median (IQR) age at MRI (days)	5.3 (4.8-6.5)	4 (3.5-7.3)	7 (5.5-8.4)
Median (IQR), hospital stay (days)	5.8 (5-7)	4.8 (4.4-9.1)	8.8 (7.2-11.6)
Death	0 (0.0%)	0 (0.0%)	1 (2.7%)

Seizures occurred after six hours of birth in 2.9%, 3.2% and 5.5% in the normothermic, 48 h and 72 h hypothermia groups. Injury scores on conventional MR were similar across the groups (P=0.87). Thalamic lactate/N-acetyl aspartate and NAA/Creatinine peak area metabolite ratios were not different in the three groups.

The COMET pilot randomised control trial data reaffirms the need for a definitive clinical trial before whole-body hypothermia is offered to babies with mild hypoxic ischemic encephalopathy, and therapeutic drift should not be continued. Accurate clinical and aEEG assessment is mandatory to ensure that only neonates meeting the BAPM (TOBY) criteria for moderate or severe encephalopathy are offered whole-body hypothermia as a standard treatment.

BENEFITS OF THE COMET TRIAL

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.

An additional downstream effect of the proposed COMET trial is a national standardisation of neurological and amplitude-integrated electroencephalography (aEEG) assessment of babies. Given that almost 17% of the babies who receive whole-body hypothermia in the NHS do not even have encephalopathy, such standardisation would reduce incorrect use of this expensive treatment that may cause harm[36].

The British Association of Perinatal Medicine (BAPM)[43] and several international expert groups[36,44,45] have called for an urgent clinical trial of whole-body hypothermia for babies with mild hypoxic ischaemic encephalopathy. BAPM framework for practice for whole-body hypothermia recommended that hypothermia should no longer be offered to babies with mild hypoxic ischaemic encephalopathy, outside the setting of a clinical trial as safety and efficacy is unknown. The proposed trial is also well aligned with the current national ambition of reducing birth related brain injuries in the NHS[46].

HYPOTHESES

Whole-body hypothermia improves cognitive development at two years of age in babies with mild hypoxic ischaemic encephalopathy.

Research Question

- Does whole-body hypothermia to 33.5 $\pm$0.5°C, initiated within six hours of birth and continued for 72 hours, improve cognitive development at two years of age after mild neonatal encephalopathy when compared with routine care (targeted normothermia at 37.0 $\pm$0.5^{0}C)?

- Does a prospective trial-based economic evaluation support the provision of whole-body hypothermia therapy for mild encephalopathy in the NHS on cost-effectiveness grounds?

STUDY OBJECTIVES

The goal of this randomised control trial is to evaluate the safety, efficacy, and cost-effectiveness of whole-body hypothermia as a therapy for babies with mild hypoxic ischaemic encephalopathy.

Primary objective

To examine if whole-body hypothermia to 33.5 $\pm$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 $\pm$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

The primary outcome is the mean Cognitive Composite Scale score from the Bayley IV examination at 24 ($\pm$2) months of age. The trials of hypothermia for moderate or severe encephalopathy have used the composite outcome of death or disability because of high mortality rates, whereas mortality is expected to be low in mild encephalopathy and therefore outcome among survivors was selected as the primary outcome.

Babies who die or who cannot be assessed with the Bayley-IV due to severe disability will be allocated a Cognitive Scale Composite score one point below the basal test score (i.e., score of 54). The mortality rate is expected to be around 1% in mild hypoxic ischaemic encephalopathy. If the child is too tired to co-operate with the Bayley assessment at the time of the original appointment, the assessment will be re-scheduled and performed at a place more suitable for the child, for example at home, within the window period of assessment.

Secondary outcomes

Outcomes assessed during neonatal hospitalisation:

1. Neonatal seizures – Level 1 (Definite seizures: seizures confirmed on EEG with or without clinical manifestations) or Level 2 (Probable seizure:

clinically assessed focal clonic/ focal tonic seizure or seizures confirmed on aEEG) or Level 3 (Possible seizure) – Clinical events suggestive of epileptic seizures other than focal clonic or focal tonic seizures, directly witnessed or reviewed on video by experienced medical personnel.

2. Duration of intensive care defined as number of days of neonatal intensive care.
3. Duration of hospital stay defined as the total number of days of inpatient care in a neonatal unit.
4. Duration of mechanical ventilation defined as number of hours on invasive ventilation through an endotracheal tube.
5. Duration of inotropic support defined as total number of hours on inotropic support.
6. Bloodstream or cerebrospinal fluid positive infection defined as isolation of a pathogenic organism from blood or cerebrospinal fluid along with a clinical diagnosis of sepsis, at any time during neonatal hospitalisation.
7. Thrombocytopenia or coagulopathy requiring transfusion of blood products.
8. Any breastfeeding at hospital discharge.
9. Brain injury scores on conventional magnetic resonance imaging.

Longer term secondary outcomes assessed at 24 (±2) months include:

1) Survival without any neurological impairment defined as a score of ≥85 in all Bayley-IV domains (motor, language, and cognitive), normal neurological examination with no cerebral palsy (Gross motor function classification system score <1), no hearing or visual impairment (as reported by parents), and no seizure disorder.

2) Preschool Child Behaviour Checklist (CBCL 1½-5) will be completed by parents at the 24(±2) month assessment to provide a standardised measure of children's behavioural outcomes on scales that assess internalizing and externalizing behaviour problems and a Total Problems Scale. Mean standardised T-scores on each scale will be compared between groups. The CBCL checklist will be completed after the Bayley IV assessments.

3) Cerebral palsy

4) Microcephaly

Exploratory studies

1. PARCA R: A parent completed questionnaire of the child's development will be collected immediately prior to the neurological assessment between 24 (±2) months from all children. This questionnaire can either be filled in online or in paper prior to the Bayley-IV assessments and takes approximately 10 minutes to complete.
2. Mechanistic studies: Overall, approximately 2.5 ml of blood will be collected for mechanistic studies in all babies: i) 1.0 ml will be collected within 0-6 hours of

age, ii) 0.5 ml will be collected at 48 (±4) hours of age, and iii) 1.0 ml will be collected at around 84 (±4hrs) hours of age.

3. Magnetic resonance spectroscopy: In centres with facilities for undertaking proton magnetic spectroscopy using harmonised sequences, these sequences will be acquired at the time of routine clinical MR scanning.
4. Neurological Examination training and assessment using Sarnat staging: To improve the accuracy of neonatal neurological assessment by expert feedback of video recording. Further details outlined in the 'Patient identification and Screening' and 'Informed Parental Consent' sections.

STUDY DESIGN

COMET is a phase III prospective multi-centre open label two-arm randomised controlled trial with internal pilot and masked outcome assessments. Administration of cooling therapy cannot be masked. The trial will recruit from five operational delivery networks (ODN) involving around 16 hospitals. Any neonatal intensive care unit (NICU, local neonatal unit (LNU), or special care baby unit (SCBU) with facilities for aEEG monitoring and a servo controlled whole-body hypothermia device is eligible to participate. Randomisation will occur at the hospital of birth and the 2-year neurodevelopmental outcome assessments at a suitable location within the same network or at home.

The 24 (±2) months assessments will be performed by a central team of 2 to 4 examiners, masked to the study allocation. Each assessor will be trained and certified against a gold standard examiner prior to the assessments and then recertified annually to reduce interobserver variability. Vision and auditory status of infants will be collected as part of the medical history. The follow up visit will be scheduled in close consultation with the parents, either at the local hospital or at home. Appropriate travel expenses will be provided for families for the visit. Travel expenses will also be provided/reimbursed to research team members who have to travel to perform the 24(±2) months follow up and monitoring visits.

Internal pilot

As whole-body hypothermia is provided only at NICUs, the recruitment monitoring and evaluation of the internal pilot will be based on the number of babies recruited per NICU. We expect a total of 28 NICU to recruit once the trial is set up at all sites. Duration of the internal pilot will be 12 months, following the initial six-month setup period.

As shown in Table 2, If recruitment is 100% (one baby recruited per NICU every 6 weeks), study progression without modifications tackling any potential barriers for successful recruitment (green). If recruitment is below target (100%) but ≥ 50% we will develop a rescue plan (e.g., add additional centres) in conjunction with the Trial Steering Committee and HTA (amber). If recruitment is < 50% (one baby recruited per NICU every 11 weeks) at 12 months post recruitment start, which equates to a total recruitment of less than 86 infants, the trial will be considered unfeasible and will be stopped. This will be subject to a detailed review of project viability by the trial steering committee and HTA (red).

Table 2: Progression Criteria for internal pilot

Progression criteria	Red	Amber	Green
Trial recruitment (of expected)	<50%	50-100%	100%
Number of NICUs opened	<15	15 to 28	28
Number of recruits per NICU per year	<4	4 to 5	>5
Total number of recruits per month	<7	7 to 14	>14
Recruitment rate/NICU/month	<0.25	0.25 to 0.5	>0.5
Total participants	<86	86-172	>172

Patient identification and Screening

All babies born at or after 36 weeks and requiring prolonged resuscitation at birth (defined as continued resuscitation at 10 minutes after birth or 10-minute Apgar score less than 6) or those with severe birth acidosis (defined as any occurrence of: pH ≤7.00 or Base deficit ≥16mmol/l in any cord or baby gas sample within 60 minutes of birth) and admitted to the neonatal unit will be started on aEEG or EEG as a part of standard clinical care.

Neonatal doctors or advanced nurse practitioners (clinical team) will screen these babies for eligibility using a structured neurological examination performed between 1 to 6 hours after birth. In all patient cases, these video recordings are taken as part of routine standard clinical care as all sites. As part of COMET's Neurological Examination training and assessment using Sarnat staging programme, these videos (with parental consent) will be sent to Imperial College for expert assessment and feedback to all sites (further details given in the Informed Parental Section).

As most babies who require resuscitation at birth will appear encephalopathic soon after birth, it is important to perform the assessment only after the initial stabilisation so that the baby has had some time to recover spontaneously. Therefore, the initial assessment will be performed at least 1 hour after birth.

Babies with abnormal neurological assessment will be screened for trial entry by conduct aEEG for at least 30 minutes. Parents of these babies meeting the inclusion criteria will be approached (by either the neonatal doctor, advanced nurse practitioner, or research nurse) for participation and informed consent will be obtained prior to recruitment.

Informed parental consent for COMET trial and neurological examination training and assessment programme

Prior to recruitment, the recruiting team will be trained and certified in the process of informed parental consent using an online program, in addition to completion of the International Conference on Harmonisation Good Clinical Practice (ICH GCP) certification. It would be made explicit that the participation is entirely voluntary, and the trial participation or refusal will not affect the clinical care of the baby. Informed parental consent (in person or over the telephone) will be obtained prior to recruitment. There are two consent processes, involving two different consent forms as described below:

1) <u>COMET trial informed parental consent process (Trial babies only):</u>
   After screening and identifying potential participants for the trial, the clinical or research team at each site will:
   a) Explain the trial to the parents,
   b) Provide a parent information leaflet for the COMET trial,
   c) Play the COMET introductory video to parents using a laptop/tablet,
   d) Seek written parental informed consent for baby to take part in the trial and for their baby's neurological examination video to be sent to Imperial College as part of the Neurological Examination training and assessment programme.

      Parents will be able to opt out of sending the video recordings to Imperial College and still take part in the trial. Parents will also be able to decline taking part in the trial but given consent for video and aEEG to be sent to Imperial College as part of COMET's Neurological Examination training and assessment using Sarnat staging programme (see below).

   Once consent has been given, the baby will be randomised into the study.

   Since the randomisation and intervention need to start within six hours of birth, the parent will have a short time to make the decision. Usually this is between 60 minutes to couple of hours depending on the age of the baby at the time of screening. Telephone consent will be obtained if parents are not available in the neonatal unit at the time of admission; this will be followed by obtaining written consent when parents visit.

   The attending physician and research nurse will regularly meet with parents during the intervention period to ensure that they understand the study procedures. The original copy of each patient's signed informed consent form will be retained in the investigator site file. A copy of the parent information leaflet and signed informed consent form will be given to parents and another copy will be kept in the baby's medical records.

2) <u>Neurological examination training and assessment programme informed parental consent process (All babies admitted to the neonatal following birth depression or acidosis)</u>

   This will involve all babies (≥36 weeks) admitted to the neonatal unit with an Apgar score of <5 at 10 minutes after birth, or continued need for resuscitation at 10 minutes after birth or severe birth acidosis (defined as any occurrence of: pH <7.00 or base deficit >16mmol/l in any cord or baby gas sample within 60 minutes of birth). A structured neurological examination as per the modified Sarnat Staging will be performed soon after admission to the neonatal unit and a video recording of this assessment will be obtained.

   This assessment should be performed only after one hour of birth to allow the baby to recover from initial birth depression and before initiation of whole-body hypothermia, in babies with moderate or severe encephalopathy.

   As parents are likely to be distressed or unavailable at the time of neonatal unit admission, deferred parental consent to use these videos for research will be obtained between 24 to 48 hours after birth, unless the baby is eligible to be randomised to the COMET trial interventions (see above)

   Briefly the clinical or research team at each site will:

   a) Obtain video of the neurological assessment soon after admission to the neonatal unit
   b) If baby meets the trial inclusion criteria, proceed as in the earlier session to obtained informed parental consent for the COMET trial as above.
   c) If the baby does not meet the inclusion criteria for the COMET trial, approach parents around 24 to 48 hours after birth, unless re-direction of care is being considered.
   d) Provide a parent information leaflet for neurological examination training and assessment programme,
   e) Seek written parental informed consent for their baby's neurological examination video to be sent to Imperial College as part of the neurological examination training and assessment programme.

Parents will be able to opt out of sending the video recordings to Imperial College. If parents decline the use of these videos or if the baby is critically unwell i.e. requiring re-direction of intensive care, these videos will be deleted.

The purpose of collating all structured neurological examination videos and aEEG data is to improve quality assurance and training processes. The videos will be reviewed by the neonatal neurology team at Imperial College London, and feedback will be provided to the site teams. This will ensure BAPM criteria for providing whole-body hypothermia is adhered to in all babies. Parents will be given the opportunity to ask questions and given time to consider if they are happy for video and aEEG to be used.

Randomisation and trial intervention

Once parental consent is obtained, babies will be randomised to whole-body hypothermia or targeted normothermia within 6 hours of birth, using a web-based program Sealed Envelope. The randomisation will be performed on a 1:1 basis with stratification for centre and will use blocking to ensure equal allocation to the two groups throughout the trial.

Initial assessment and randomisation (and initiation of whole-body hypothermia or targeted normothermia) will occur at the hospital of birth. The babies in both arms, who are born at a non-cooling centre (LNU or SCBU) will be then transferred to the nearest cooling centre (NICU) within 8 hours of birth for continued care.

Baseline data collection and source data

The data will be collected and entered into the case report form (CRF) and the COMET trial electronic database at the participating sites. The data collection is based on the principles of a minimal and essential data set arranged in a systematic way that enables rapid and non-ambiguous data entry while avoiding duplicate entries and has automated validation checks for data quality. Data will include 1) information obtained during neonatal hospitalisation [ante-natal, birth, and neonatal clinical information including gestational age, birth weight, gender, Apgar scores, pregnancy, labour and birth history, delivery room resuscitation to assess the baseline comparability of the groups, core body temperature for assessment of intervention, details of the hospital course, laboratory investigations and MR imaging for safety monitoring] 2) information collected after hospital discharge from GP records, and parents [subsequent hospitalisations or major illness] and 3) at 24 ($\pm$2) months for primary outcome evaluation.

Source data are hospital electronic records and paper CRFs, where the baby's data will be first recorded. Data contained in the paper CRFs will be transcribed into the eCRFs, which are held within the COMET electronic data capture system (EDC) Weekly data entry will be reviewed for completeness and accuracy by the study nurse or PI. Any queries raised by the central team will be required to be answered within 48 hours.

PATIENT MANAGEMENT

Whole body hypothermia (Intervention group)

Whole-body hypothermia (33.5$\pm$0.5°C) will be initiated within 6 hours of birth and continued for 72 hours using a servo-controlled cooling machine at the nearest available neonatal intensive care unit (cooling centre). Passive cooling methods will not be allowed. Whole-body hypothermia to 33.5$\pm$0.5°C for 72 hours is the duration and depth of cooling that is standard for babies with moderate or severe HIE in the NHS. To administer this intervention babies will be kept on a cooling mattress or blanket circulating a coolant/water, a rectal temperature probe will be inserted, and overhead radiant warmers will be switched off. The cooling device will be set to hypothermia mode and body temperature will be rapidly reduced to 33.5°C from 37°C and maintained within the target range of 33°C to 34°C.

After 72 hours of whole-body hypothermia at 33.5±0.5°C, the baby will be rewarmed at 0.5°C per hour to reach 37.0 ±0.5°C over 8 hours. Rectal temperature data will be collected on the CRF for the first 88 hours and will also be downloaded from the cooling device once the therapy is complete.

Babies with unexplained tachycardia or shivering will have non-pharmacological approaches like swaddling/tucking, pacifiers, rubbing, holding, touch, and massage to make them more comfortable [39,47]. Sedation with narcotic drugs will be used only if the above nonpharmacological approaches are ineffective. Neonatal Pain, Agitation and Sedation Scale (NPASS) score will be recorded every 6 hours during the first 88 hours after birth. Whole-body hypothermia may be discontinued if serious adverse events related to the intervention occur.

Normothermia (Control group)

The rectal temperature will be maintained at 37±0.5°C using servo-controlled incubators for the first 88 hours and any hyperthermia will be treated with a standardised protocol. Rectal temperature will be recorded, as in the whole-body hypothermia group. Continuous axillary temperature will be recorded during the first 88 hours. Previous clinical trials have reported hyperthermia in the non-cooled babies, which adversely affects outcomes.

Babies in the control group who develop seizures (level 1 or level 2) and progress to moderate HIE between 6 to 24 hours may be treated with whole-body cooling for 72 hours as clinical care, although this is expected to occur in less than 5%[48].

Monitoring and care in both groups

Babies with breathing difficulties or apnoea will have appropriate support with non-invasive (CPAP/high flow) or invasive ventilation. All babies will have at least one channel (3 electrodes) aEEG for the first 88 hours after birth. Continuous monitoring using aEEG for the first 88 hours is the current standard care for babies undergoing whole-body hypothermia in the NHS. All infants will have monitoring of physiological and laboratory parameters as clinically indicated. Enteral milk feeds will be administered in both groups and increased as tolerated.

Babies in both groups, born at a Local Neonatal Unit (LNU) or Special Care Baby Unit (SCBU) will be transferred to the nearest available NICU (cooling centre) within around 8 hours of birth for continued care, and aEEG monitoring, following randomisation (and initiation of whole-body hypothermia if in the hypothermia arm). This will allow us to examine the additional benefit (or harm) that is obtained from the randomised treatment above any benefits obtained from being transferred to a tertiary care site.

MR imaging

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. This is the current standard care for all babies treated with whole-body hypothermia in the NHS. The MRI will be reported locally for clinical purposes and a copy will be collected. The MRI DICOM data will also be uploaded onto a central server at Imperial College London and reported by a central reader in batches, masked to the allocation. As there are no definite MRI biomarkers for prognostication in mild HIE, these reports will be used for safety (cerebral bleeds, significant brain injury, major thrombosis) rather than treatment efficacy. MR spectroscopy data will be collected only if the participating site has facilities for performing proton MR spectroscopy using harmonised sequences.

PARTICIPANT ENTRY

Study population

Neonatal care in the UK is currently organised under 13 ODNs. Each ODN has a network of several Neonatal intensive care units (NICUs), Local Neonatal Units (LNUs) and Special Care Baby Units (SCBUs). NICUs offer the most specialised care including whole-body hypothermia therapy and care of extremely premature infants (less than 27 weeks). LNUs care for babies born between 27 to 31 weeks and SCBUs to those born at 32 weeks or later. Currently, if a baby with HIE is born at an LNU or SCBU, the local neonatal clinicians discuss the baby's status immediately with the designated NICU (Cooling centre) and transport teams and initiates whole-body hypothermia prior to transfer to the NICU for continued care. At present, 100% NICUs (and neonatal transport teams), 75% LNUs, and 26% of SCBUs have aEEG devices, although BAPM guidelines recommends that all LNUs and SCBU should have a servo-controlled cooling machine and aEEG. In most cases, the transfer from LNU or SCBU to NICU is made within 6 to 8 hours of birth in routine clinical practice[49].

The COMET trial will recruit from six operational delivery networks (ODN) involving a total of 60 NHS hospitals. Around 28 of these hospitals will have NICUs (cooling centres) and the remaining will be LNUs and SCBUs (non-cooling centres). Only neonatal units with facilities for aEEG monitoring and having a servo-controlled cooling machine to initiate whole-body hypothermia, and an annual delivery rate of at least 3500, will be involved.

LNUs or SCBUs without an aEEG or cooling machine will be provided with a lease machine for recruitment under an agreement with Inspiration Health Care, UK. Involving both cooling and non-cooling centres will ensure that the trial results will be generalisable to all neonatal units in the UK. Furthermore, in the COMET pilot trial, over 60% of babies with mild HIE admitted to NICUs are transferred from LNUs and SCBUs after initiation of whole-body hypothermia and cannot be enrolled into the proposed main COMET trial, unless the randomisation occurs at the birth hospital.

Inclusion criteria

All babies born at or after 36 weeks of gestation with a birth weight of 1800g or more with birth acidosis or requiring resuscitation at birth will be screened for eligibility. Parents will be approached for consent if the baby meets all the three (A + B + C) criteria below:

A) Evidence of intra-partum hypoxia-ischemia defined as any of – (i) Apgar score of ≤5 at 10 minutes after birth, or continued need for resuscitation at 10 minutes after birth or severe birth acidosis defined as any occurrence of: pH ≤7.00 or Base deficit ≥16mmol/l in any cord or baby gas sample within 60 minutes of birth.

B) Evidence of mild hypoxic ischaemic encephalopathy defined as – two or more abnormal findings in any of the six categories of the 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 hypoxic ischaemic encephalopathy on a standardised examination performed by a certified examiner between 1 to 6 hours of age.

C) Normal amplitude on aEEG performed for at least 30 minutes between 1 to 6 hours of age. Normal amplitude will be 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.

The above tiered approach will ensure that only babies with encephalopathy related to a recent intra-partum hypoxic event are enrolled, as hypothermia is likely to be neuroprotective only in this subgroup. Restricting recruitment only to babies having two or more abnormal signs on neurological examination will ensure only those at risk of adverse neurodevelopment will be enrolled.

Exclusion criteria

- Infants who meet the BAPM criteria for whole-body hypothermia
- 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 have already 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.

Standardisation of neurological assessment:

The modified Sarnat stage neurological examination (see appendix) provides a structured and standardised way of assessing babies with encephalopathy between 1 to 6 hours of birth and has been extensively validated in major multicentre clinical trials. Amongst babies born after 35 weeks, this neurological assessment is reported to have an excellent agreement (Kappa 1) between gold standard examiners[50].

The COMET trial will use the well-established training and certification program used in the earlier multicentre NICHD neonatal research network (USA) clinical trials, including the COMET feasibility trial. The standardisation involves three layers:

I. The ODN lead PIs (co-applicants) and the PIs of the participating NICUs will be trained and assigned as the site Gold Standard Examiner (GSE) by Thayyil and Shankaran prior to recruitment and then re-certified annually during recruitment phase. Briefly, this will involve a power-point presentation, joint observation, and assessments of video recordings for concordance. The GSE will then submit a video recording of their assessment on a baby for the annual re-certification.
II. In addition, a critical mass of neonatal doctors at the NICU (and their referral LNUs/SCBUs) involved in recruitment will be trained and certified using a virtual training and certification program based on modified Sarnat staging. Once adequate number of staff required for neurological assessment is certified, green light for recruitment will be given to the site.
III. A neurological assessment video recording (approximately 5 minutes) of babies with birth depression or acidosis will be obtained on admission to NICU, prior to informed parental consent. The consent (i.e. deferred parental consent) for use of this video for quality assurance and sharing with experts to discuss the care of the baby will be obtained alongside consenting for the COMET trial. The video will be reviewed by Thayyil/Shankaran during the monthly PI meeting. Feedback on the video assessments of all sites will be pooled and provided to all recruiting sites every month for continuous quality assurance. The site PI will use these videos for reinforcing local training and encourage junior doctors. Video recordings of neonatal neurological assessments has been previously reported to be an adequate method for classification of encephalopathy stage[51].

Standardisation of aEEG

aEEG will be used as an objective criterion for auditing and quality assurance. This approach has been successfully used in the TOBY trial where only babies with moderate or severe abnormalities on aEEG were eligible and is part of the BAPM framework for whole-body hypothermia[52].
Continuous aEEG monitoring for 88 hours is the current standard of care for all babies undergoing whole-body hypothermia in the UK. While an abnormal aEEG soon after birth has a poor positive predictive value and does not indicate adverse outcomes, a normal aEEG has a high negative predictive value for predicting moderate or severe neurodisability[53]. The basic assessment of aEEG in terms of the amplitude (Kappa

0.93 – 0.98) and seizures (Kappa 0.71-0.85) is widely used in the NHS with a high inter-rater agreement[54]. While full montage EEG and more detailed analysis of the raw EEG patterns may improve seizure detection, it will limit generalisability in the NHS. Hence, the COMET trial will use only a single channel aEEG that can be easily acquired in any NHS hospital.

Standardisation of aEEG acquisition and interpretation across all sites will be led by Pressler. Screen shots (with at least 30 minutes of aEEG trace) of all recruited babies will be obtained at randomisation and will be centrally reviewed. All aEEG recordings will be discussed at the monthly ODN meetings by the site PI to provide additional training and encouragement to junior doctors.

Withdrawal criteria

Infants will be withdrawn from the study if either parents or physicians withdraw consent at any time. Each participant's right to withdraw from the study without giving reasons will be respected at all times. A withdrawal form will be filled in and authorisation will be obtained for use of the previously collected data.

Discontinuation of the study intervention for a serious adverse event will be at the discretion of the attending physician in consultation with the site principal investigator. The infant will continue to be part of the study as per the intent-to-treat principle.

ADVERSE EVENTS

Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward 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. 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.

Recordings and reporting of SAEs, SARs and SUSARS

Monitoring for adverse events of whole-body hypothermia in the intervention group during the intervention period and both groups during the entire length of hospital stay will be conducted by evaluating events described in the secondary outcomes. An additional safety measure will be the appointment of an external Independent Data Monitoring Committee (IDMC) where the progress of the trial and adverse events (AE) will be closely monitored at 4 to 6 monthly intervals, masked to the allocation. The IDMC charter will be finalised and signoff before the start of recruitment.

The adverse events will include persistent metabolic acidosis, thrombosis, major bleeding, perforations/ulcerations/bleeding from the rectal probe, hyperglycaemia, hypoglycaemia, necrotising enterocolitis (NEC), thrombocytopenia requiring platelet transfusions, coagulopathy requiring blood products, loss of skin integrity, and hypotension requiring more than 2 inotropes.

Serious adverse events (SAE) will include mortality, major cerebral bleeds on MRI, pulmonary bleeds, PPHN requiring inhaled nitric oxide or extra-corporeal membrane oxygenator (ECMO), or any other clinical event the investigators deem as life threatening. Additional SAE reports may be requested (e.g., monthly) throughout the course of the study. Safety will be assessed by the frequency of SAE, and total number of events per baby.

The protocol violations that will be noted include 1) study intervention never started, 2) wrong treatment intervention applied, 3) ineligible infant recruited to the trial, 4) neuro exam at eligibility not done 5) recruited to the trial but no consent.

The IDMC will have both Open and Closed sections. The trial statistician, trial manager, PI (Thayyil), and Co PI (Shankaran) will join the Open sessions. This will include the following (i) Brief summary of the trial design including primary and secondary hypotheses and outcomes, study population, inclusion and exclusion criteria, recruitment, screening, randomisation and study intervention procedures, and statistical considerations for trial design and analysis, (ii) Enrolment totals, including screening, consent, randomisation (iii) Safety outcomes, including SAE, death, and abnormal MRIs.

The Closed session will include: 1. Primary and secondary outcomes without formal statistical comparisons, 2. Interim monitoring plan and status (if an interim analysis plan is proposed by the IDMC and approved), and 3. Safety outcomes. As adequate primary outcome data will not be available prior to the completion of recruitment, the trial will not be stopped for efficacy. IDMC will assess adverse events that have only short-term impact separately to those with serious long-term consequences (mortality, major intracranial bleed) before making a recommendation for early discontinuation of the trial. A two-sided significance level of 0.05 will be used for the comparisons of serious adverse events between the two groups.
Interpretation of safety data will require both clinical and statistical experts reviewing the data in concert. If there is a clear benefit or harm of a treatment, clear lack of benefit or external evidence, the decision to stop the trial may be taken by the IDMC and TSC.

Reporting procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

Non serious AEs

All such events, whether expected or not, should be recorded- it should be specified if only some non-serious AEs will be recorded, any reporting should be consistent with the purpose of the trial end points.

Serious AEs

An SAE form should be completed and emailed to the Chief Investigator within 24 hours.

All SAEs should be reported to the London - Bloomsbury Research Ethics Committee (REC) and Health Research Authority (HRA) where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
Email: COMET@imperial.ac.uk
Tel: 020 3313 2473 (Mon to Fri 09.00 – 17.00)

ASSESSMENT AND FOLLOW-UP

The follow-up assessment will be done when the recruited babies are 24 (±2) months of age. The assessment will be carried out using the Bayley Scales of Infant and Toddler Development IV. It is a validated and standardized scoring system that assesses development in three domains, that is cognition, language, and motor development. In addition, all infants will have a detailed neurological examination, including Gross Motor Function Classification System (GMFCS) for cerebral palsy, vision, and hearing assessment. Babies who die (the mortality rate is expected to be less than 1% in mild HIE) or who cannot be assessed with the Bayley-IV due to severe disability will be allocated a Cognitive Scale Composite score one point below the basal test score (i.e., score of 54) [4,55].

All assessments will be performed by a central team of examiners trained by the trial team in Bayley- IV assessment, masked to the allocation. Each assessor will be standardised and certified against a gold standard examiner prior to the assessments and then annually (video recording) to reduce interobserver variability. In all infants, PARCA-R (online or face to face) will be completed by the parents immediately prior to the Bayley IV assessments and CBCL (face to face only) after the Bayley IV assessments.

The follow up visit will be scheduled in close consultation with the parents, either at the local hospital or at home. Appropriate travel expenses will be provided for families for the visit.

Incidental findings

If an incidental finding is observed during a procedure which is carried out as part of the research, and it is considered a significant abnormality then the study team should report these to the PI who should take action accordingly. The incidental finding will be feedback to the participants and to the clinical care team or participants GP in writing.

End of trial

The end of the trial will be notified to the sponsor. The date of the 24 (±2) months follow-up of the last patient undergoing the trial will be considered as the end of the trial.

STATISTICS AND DATA ANALYSIS

The primary outcome is the Cognitive Scale Composite score from the Bayley-IV examination at 24(±2) months. Based on experience the scores are expected to be approximately normally distributed, and thus a two-sample t-test will be used to compare between groups. The mean difference in outcome between groups will be reported, along with a corresponding confidence interval. If the outcome scores are not normally distributed, an appropriate data transformation will be explored, or alternatively a non-parametric test (Mann-Whitney test) may be utilised.

Secondary outcomes are both short term (in hospital) or longer term (at 24 months). Continuous secondary outcomes will be analysed using the unpaired t-test if normally distributed, or the Mann-Whitney otherwise. The Chi-square test or Fisher's exact test will be used to compare categorical outcomes between groups. For each outcome, a point-estimate of difference between groups will be reported, alongside a corresponding confidence interval.

Safety outcomes will consist of measurements of Adverse Events (AEs) and Serious Adverse Events (SAEs). If there are sufficient numbers of AEs and SAEs, the Chi-square test or Fisher's exact test will be used to compare the number of patients with these outcomes between groups. The Mann-Whitney test will be used to compare the number of AEs/SAEs between groups. A list of individual AEs will be reported in each group. All analysis will be performed on a modified Intention to Treat (mITT) basis, using patients with valid outcome data in the analysis. Infants will be analysed in the groups to which they were randomised (intent-to-treat analysis), regardless of the treatment received.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

Sample size calculations

The Bayley-IV Cognitive Scale Composite score has a normative mean of 100 and SD of 15. To detect a clinically important minimum difference of 5 points (0.3 SD), at a 0.05 significance level and 90% power, we would need 191 infants per group, 382 in total. This increases to 426, after allowing for a conservative 10% drop-out rate. The total duration of the trial is 66 months which will include a six-month trial set up period, 30 months of recruitment, and outcome assessments at the age of 24 (±2) months.

The implication of changing the power of the study and the size of outcome differences between groups has been examined and is shown in the subsequent table. This shows the total sample size required in both groups combined, after allowing for a 10% drop-out rate.

Size of group difference	Total study sample size 90% power	80% power
4 points	660	494
5 points	426	318
6 points	296	224
7 points	218	166
8 points	168	128
9 points	134	100
10 points	110	84

The assumed attrition rate of 10% is conservative, as we have consistently obtained >97% follow up at 18 to 22 months in previous trials. The implications of a higher drop-out rate upon the power of the trial are shown below. If the drop-out rate is 20%, the study would still have an 87% power to detect a 5-point difference between groups.

Drop-out rate	Study power
10%	90.0%
12.5%	89.4%
15%	88.5%
17.5%	87.7%
20%	86.5%

DATA MANAGEMENT PLAN

Data collection tools

Prior to the start of recruitment, a Manual of Procedures (MOP) will be developed providing details of the protocol design and procedure and definitions of each data variable, and procedures for data lock. All study personnel entering the data (LCRN funded research nurses and site PI) will be trained and certified during site initiation and names will be documented in the delegation log.

As randomisation is integrated into the trial database, the initial data will be captured electronically and will include date and time of birth (randomisation will be disabled if age > 6 hours), categories of the neurological examination (to avoid errors in categorisation), and aEEG details (to ensure inclusion criteria is met). The central clinical trial team, site PI, lead NICU PI, and regional transport team will be automatically notified of each randomisation, which will enable the trial team and monitor to liaise with the recruiting site to ensure prompt data entry.

The clinical data will be extracted into an electronic database daily before hospital discharge by dedicated LCRN funded research nurses at the NICU. Identifiable data will be stored in a separate administrative database. The trial participants will be identified using a unique ID which will link the clinical and administrative databases. The Imperial clinical trial team will monitor the electronic data quality daily and lock the completed sessions in the database. Weekly data entry will be reviewed for completeness and accuracy by the central team, any queries raised will be required to be answered within 48 hours.

Video recordings of the neurological examination will be reviewed by Thayyil/Shankaran during the monthly PI meeting for quality assurance and screen shots of the aEEG traces will be sent to Imperial College London via secure file transfer protocols soon after randomisation. Appropriate parental consent will be sought for sharing of these data. The whole aEEG data will be transferred to a central repository at the time of discharge. Anonymised MR data (DICOM files) of all babies will also be transferred to the central repository within 1 week of acquisition.

Local radiologists will report each MR for clinical purposes as per the standard clinical protocols. The MR scans will be reviewed by the trial radiologist every 2 to 3 months and appropriate safety data (intracranial bleeds, major thrombosis, significant brain injury) will be included in the Independent Data Safety and Monitoring Committee (IDMC) reports. Data on the primary outcomes (Bayley Scales of Infant Development) and cost evaluation will be captured into the follow up paper CRF. This will then be entered into the follow-up component of the database by the follow-up assessors who are appropriately masked to other clinical data.

Risk assessment

The trial will be conducted in accordance with the approved protocol, governance regulations and manual of operations. A risk assessment and monitoring plan will be prepared prior to the start of the recruitment and will be updated annually.

Trial monitoring

The Principal Investigator (PI) at each site will be responsible for running of the trial at their site including ensuring successful recruitment, staff education and training, data completeness and quality. The monitoring plan will be based on the risk assessment. All sites will be monitored for unexpected patterns, recruitment rates, outliers, inconsistencies hospital records and CRF, and other issues.

The main role of the IDMC will be to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial. The first meeting will be convened at the start of the study and subsequent reviews will be held 2-3 times a year or more frequently as requested by the IDMC. Interim review of the trial's progress will include update on recruitment, data quality, adherence to protocol treatment and follow-up, and main outcomes and safety data.

Access to data

Direct access will be granted to authorised representatives from the Sponsor, host institution, and the regulatory authorities to permit trial-related monitoring, audits, and inspections in line with participant consent.

Archiving

Archiving will be authorised by the Sponsor following submission of the trial report. All essential documents will be archived for 10 years after completion of the trial. Authorisation will be taken regarding the destruction of essential documents.

REGULATORY ISSUES

Ethics approval

The Study Coordination Centre has obtained approval from the London - Bloomsbury Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out.

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.

Consent

The clinical team (including the neonatal transport team) will explain the study to the parents and will provide the parent information leaflet in the first instance. Informed parental consent (in person or over telephone) will be obtained prior to recruitment and randomisation. If parents or surrogate decision-maker are not physically present within 6 hours after birth, telephone consent may be obtained.

The clinician obtaining telephone consent must inform parent(s) about health status of the baby prior to discussing research. Only ICH-GCP trained health care professionals who have been signed off in the delegation log should obtain consent. All aspect of the study mentioned in the parental information sheet should be explained to the parents, prior to obtaining the consent. In addition to the clinician, a healthcare professional must be present to witness the telephone conversation, using a speakerphone option. Other relatives or friends can be present in the room too, according to parent's permission. Interpreters should be used if the parents are unable to speak English. Each point in the telephone consent form should be explained to the parent(s), and the relevant boxes should be initialled by the person taking consent.

The written consent form should then be signed by the parents or surrogate decision-maker at the earliest opportunity once they are present in the neonatal unit. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study, the treating clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Confidentiality

The trial will comply with the confidentiality of participants taking part in the study according to the Data Protection Act, UK, and General Data Protection Regulation (GDPR). Personal identification data including telephone numbers and all contact details will be stored in a separate administrative database at a secure and encrypted server and as hardcopies in a research folder in locked cupboards at Imperial College London. Appropriate parental consent will be sought for sharing and storage of the video recordings of the neurological assessment with the research team. These data will be stored at the site and will be transferred to secure servers at Imperial College London to be shared with central research team as detailed in the consent forms. Access to each of these areas and servers will be tightly controlled, and new users requiring access to these data will require formal authorisation from the Chief Investigator.

All MR, aEEG and axillary temperature data will be pseudoanonymised using the study number and encrypted with a password prior to transfer. The MR and aEEG data will be also uploaded into a secure cloud sever at Imperial College for central reporting.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period and will be destroyed using standard Imperial College London protocols (including removal by specialist software for electronic data), unless parental consent for further research is obtained at that time.

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

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

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.

Funding
The NIHR Health Technology Assessment (HTA) Programme, is funding this study, but will not have any role in the trial design, data analysis, interpretation or reporting of the trial results. Dedicated neonatal research nurses will be appointed at each participating site.

Audits
The study may be subject to audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research.

STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the Centre for Perinatal Neuroscience, Imperial College London. The trial management group (TMG) will oversee all aspects of the day-to-day running of the study, and will consist of the investigators, trial manager, trial research fellow and other COMET trial staff based at the Centre for Perinatal Neuroscience, Imperial College London. TMG will hold a monthly teleconference of all COMET investigators for the entire duration of the trial to discuss the data quality and recruitment.

The responsibilities of the TMG include:

- Appointment and training of the local research staff for the COMET trial
- Case recruitment at participating centres
- Distribution and supply of data collection forms and other appropriate documentation for the trial
- Data collection and management
- Organisation of the follow-up

- Data entry and cleaning
- Collection of adverse event data

PROTOCOL COMPLIANCE AND BREACHES OF GCP

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on clinical trials and must not be used. For example, it is not acceptable to enrol a subject if they do not meet one or more eligibility criteria or restrictions specified in the trial protocol.

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach. Any potential/suspected serious breaches of GCP must be reported immediately to the Sponsor without any delay.

PUBLICATION POLICY

The success of the trial depends on many neonatal nurses, clinicians, and parents. Appropriate credit will be given to the teams at all the collaborating sites, members of trial steering committee, Independent Data Safety and Monitoring Committee and the trial management group. The authorship of the primary paper will be the form of [name], [name], [name] on the behalf of the COMET trial Collaborative group. Upon completion of the trial, the data will be analysed and tabulated, and a final study report prepared. Drafting of the paper will be responsibility of the writing committee. Consort Guidelines and checklist will be reviewed prior to generating any publications for the trial to ensure they meet the standards required for submission to high quality peer reviewed journals etc. http://www.consort-statement.org/.

A copy of the study results will be also given to the parents of all recruited babies if they wish to. The parents' wishes will be recorded at the time of recruitment, and again during follow up. The study sponsor and funders will have no role in the study management, analysis, and interpretation of data, writing of the report, and the decision to submit the report for publication. The COMET trial will follow the ICMJE recommendations for authorship requirements, a complete copy of which is available at http://www.icmje.org/new_recommendations.html. All contributors will be listed at the end of the paper.

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APPENDIX

Appendix 1. Modified Sarnat Staging

CATEGORIES	NORMAL	MILD	MODERATE	SEVERE
1. Level of consciousness	Alert, responsive to external stimuli	Hyper-alert, has a stare, jitteriness, high pitched cry, exaggerated response to minimal stimuli, inconsolable	Lethargic	Stupor, Coma
2. Spontaneous activity	Normal	Decreased, with or without periods of excessive activity	Decreased	No activity
3. Posture	Predominantly flexed when quiet	Mild flexion of distal joints (fingers, wrist)	Strong distal flexion, complete extension	Intermittent decerebration
4. Tone	Strong flexor tone in all extremities	Slightly increased peripheral tone	Hypotonia or Hypertonia	Flaccid or Rigid
5. Reflexes				
Suck	Strong, easy to elicit	Weak, Poor	Weak or has bite	Absent
Moro	Strong, easy to elicit	Low threshold to elicit	Incomplete	Absent
6. Autonomic Nervous System				
Pupils	Normal size	Mydriasis	Miosis	Deviation/Dilated/ Non-reactive
Heart rate	Normal heart rate	Tachycardia (>160)	Bradycardia (<100/minute)	Variable heart rate
Respirations	Normal	Hyperventilation (>80/min)	Periodic breathing	Apnea or on ventilator with or without spontaneous respirations

- The COMET eligibility criteria require one or more abnormal categories under mild, moderate or severe but less than two categories under moderate or severe (i.e. the NICHD NRN criteria for whole-body hypothermia).
- Spontaneous activity and suck in moderate and mild categories are the same, and the assignment should be based on the level of consciousness if the scores are equal.
- Primitive reflexes and autonomic nervous system have more than one category and the allocation is based on the highest grade.
- All infants who require invasive ventilation should be categorised as severe irrespective of the presence or absence of spontaneous respiration.

Appendix 2: Study Flow Diagram