Cooling in Mild Encephalopathy Trial (COMET)

Feasibility study

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Protocol authorised by:
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Date: 06.08.2018

Signature:

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

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Cooling in Mild Encephalopathy Trial

1. STUDY SUMMARY

TITLE
Cooling in Mild Encephalopathy Trial (COMET) – Feasibility study

BACKGROUND
Although cooling the body to 33.5°C for 72 hours benefits babies who have severe forms of hypoxic-ischaemic brain injury, most babies have milder forms of brain injury (i.e. mild encephalopathy). Approximately 20% of the babies with mild encephalopathy have adverse long term neurodevelopmental outcomes, particularly in the cognitive domain. Pre-clinical data suggest that therapeutic hypothermia is remarkably neuroprotective in milder brain insults and reduces white matter injury. Hence, a shorter duration of cooling may be sufficient to provide neuroprotection.

COMET is a sequential study that includes a ***feasibility phase*** *(current protocol)*, ***phase II randomised controlled trial*** to identify the 'optimal cooling duration', and then a ***final confirmatory phase III clinical trial*** to examine if cooling therapy at this optimal duration improves neurodevelopmental outcomes after mild encephalopathy.

AIMS
1. To examine the feasibility of recruiting and randomising babies with mild neonatal encephalopathy to multiple treatment durations.
2. To examine the feasibility of obtaining adequate quality data on the primary outcome for the phase II trial (i.e. thalamic N-acetylaspartate concentration) in the recruited babies
3. To examine the feasibility of collecting adequate quality data for exploratory sub-studies on heart rate variability and gene expression profile

METHODS
A total of 32 babies with mild neonatal encephalopathy will be recruited from several large hospitals in the UK over a one year period. The eligible babies will be randomised to normothermia (36.0°C to 36.5°C) or whole-body cooling for one of three durations: 24h, 48h, or 72h followed by rewarming at 0.5°C per hour.

We will collect 0.5 ml of venous or arterial blood at the time of recruitment (aged <6 hours) and again at 80 hours of age for gene expression profiling. Continuous ECG data and aEEG data will be collected from all babies from the time of recruitment (aged <6h) for at least 24 hours. The thalamic concentration of N-acetyl-aspartate, [NAA], will be measured using 3 Tesla magnetic resonance (MR) spectroscopy performed between 4 and 7 days after birth.

DATA ANALYSIS AND OUTCOME MEASURES
- Proportion of the eligible babies recruited and the realistic recruitment rates per centre
- Number of babies with adequate quality data on thalamic NAA levels.

POPULATION AND DESIGN
32 newborn babies with mild encephalopathy randomised to 4 different intervention arms.

BENEFITS
These data will eventually inform national and international guidelines on management of babies with mild neonatal encephalopathy. If cooling reduces the brain injury, and improves neurodevelopmental outcomes, it will have a substantial health and economic impact in the UK and other high-income countries.

2. BACKGROUND

Birth asphyxia related brain injury (neonatal encephalopathy, NE) occurs in 4 to 6 per 1000 live births, and is the most common cause of death and neuro-disability in term babies in the UK [1,2]. Moderate whole-body cooling, to a core temperature of 33.5°C for 72 hours, reduces death and disability after moderate or severe NE, and is used as the standard of care treatment for these babies across the NHS, and in other high-income countries. However, these babies only form the tip of the iceberg – for the vast majority of babies, perinatal asphyxia results in mild NE. As most of the major cooling trials only recruited babies with moderate or severe NE, who also have the worst outcomes (i.e. death or severe cerebral palsy), it is unknown whether such cooling is beneficial for babies with mild NE [3].

Although most of the cooling trials excluded babies with mild NE, it is no longer considered a 'mild disease' [4]. Up to 50% of affected babies have brain injury on magnetic resonance (MR) imaging [5-8], and one third are reported to have an adverse long term neurodevelopmental outcome. Jacobs et al. (2011) reported adverse neurodevelopmental outcomes at two years of age in 8/24 (33%) children who had mild NE at birth and were not cooled [9]. Murray et al. (2016) reported significantly lower full scale IQ, verbal IQ and performance IQ in 22 children following mild NE, when compared with 30 healthy controls, assessed at five years of age ($p<0.005$) [10]. Lally et al. (2014) have reported neurodevelopmental delays at 3.5 years of age in 8/24 (33%) south Indian babies with mild NE [11]. Such neurodevelopmental impairments will have a profound lifelong impact, including an increased risk of autism [12], attention deficit disorders [13] and learning difficulties [14-16].

Despite a lack of evidence, there has been a worrying therapeutic creep of cooling for mild NE throughout the NHS, and worldwide [17,18]. We recently conducted a survey of 54 of the 68 UK cooling centres, of which 36 (67%) stated that they routinely cool mild NE babies (who by definition do not meet the NICE cooling criteria)[19]. Although all centres used the same depth of cooling (33 to 34°C), the duration of cooling therapy varied widely – 39% discontinued cooling by 24h if there was a clinical improvement, and 61% cooled for the full 72h irrespective of clinical improvement [20].

Separately, a recent audit of the London Neonatal Transport Service (NTS) reported a similar therapeutic drift, as 41% (59/145) of babies transported for cooling therapy in London had only mild or no NE [21].

This practice has largely been driven by a fear of litigation in case an infant with moderate or severe NE is misclassified as having mild NE on examination at 6h. Given this lack of evidence and widespread variation in practice, there is an urgent need to investigate the impact of whole-body cooling in mild NE.

<u>Preclinical data and the optimal duration of cooling therapy for mild encephalopathy</u>
Preclinical models have consistently shown effective neuroprotection with cooling after moderate or severe NE [22], and more recently after mild NE [23]. The brain injury evolves slowly after mild NE [24], and hypothermia is remarkably neuroprotective in such cases [25], when compared with severe brain injury [22]. Hence it is possible that a shorter duration of cooling therapy would be sufficient to provide neuroprotection in mild NE.

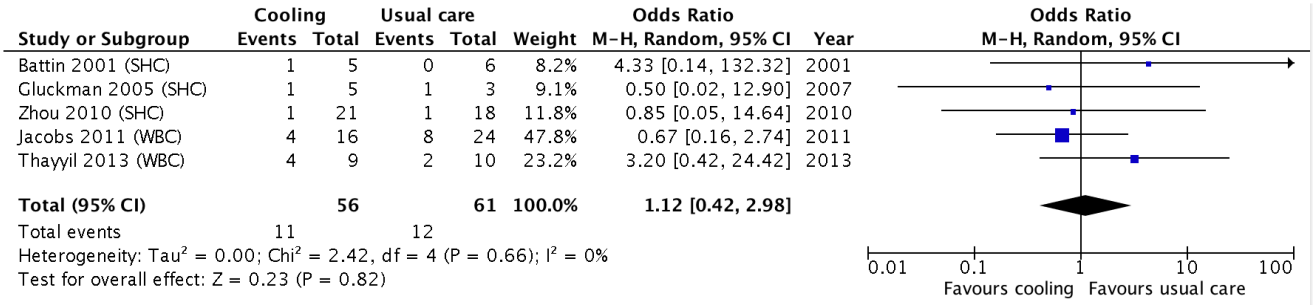
However, the minimal duration of cooling for neuroprotection is species-dependent. Hence the optimal durations of therapeutic hypothermia in animal models and humans are different. For example, small animal models of NE (mice, rats) require shorter cooling durations and large animal models (pig, sheep) require longer cooling durations. Hence, most preclinical

studies have observed neuroprotection with 24h to 48 h of cooling, while very short periods or very long periods of cooling are not neuroprotective [26].

Considering the rapid clinical recovery that occurs in mild NE, and the potential for over-ventilation and hypocarbia which could worsen brain injury, it is likely that these babies may benefit from a duration of cooling that is shorter than the full 72 hours. Such an approach would also reduce the length of intensive care stays and the need for prolonged sedation. Nevertheless, cooling for less than 24 hours is unlikely to be beneficial, and we have found MRI evidence of residual brain injury in 50% of the babies with mild encephalopathy who were cooled for less than 24, and long term adverse outcomes in 20% [27].

Safety and efficacy of cooling therapy in mild encephalopathy: meta-analysis.
We conducted a systematic review and meta-analysis of all cooling trials involving babies with mild neonatal encephalopathy (Figure 1). The pooled data including 117 babies with mild encephalopathy showed an odd ratio of 1.12 (95% CI 0.42 to 2.98), and hence we need further evidence before recommending cooling as a standard therapy for these babies. Adverse neurodevelopmental outcomes at 18 months were seen in 20% of the babies with mild encephalopathy.

Figure 1. The effect of cooling on adverse outcomes (death, moderate or severe disability) after mild neonatal encephalopathy[28]



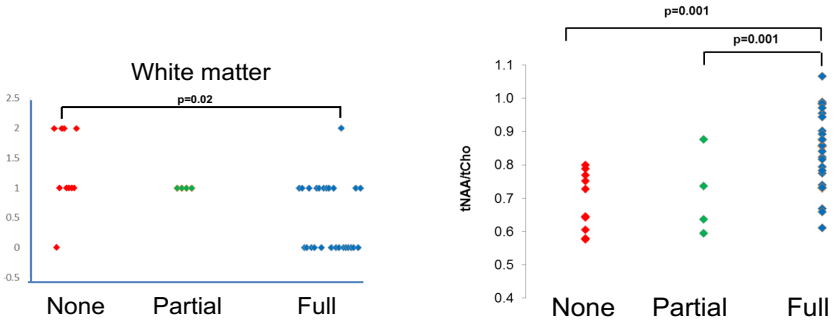
Surrogate MR biomarkers of long term outcome in neonatal encephalopathy
An extensive systematic review and meta-analysis of the published literature suggested that MR spectroscopy biomarkers, measured shortly after birth, have the highest accuracy in predicting adverse outcomes years after neonatal encephalopathy [29]. However, the published studies were based on single centre studies which are of limited use for multi-centre trials.

As a part of the MARBLE study we developed cross-platform MR spectroscopy techniques and prospectively examined the prognostic accuracy of various MR biomarkers in a multi-country setting. We found that the absolute concentration of thalamic N-acetylaspartate, [NAA], measured within two weeks of birth, had a near perfect 97% specificity and 100% sensitivity in predicting an adverse neurological outcome at 2 years after neonatal encephalopathy[30 31]. Thalamic [NAA] at two weeks accounted for 40% of the variance observed in cognitive performance scores at two years of age, and significantly out-performed metabolite peak area ratios such as lactate/NAA, and other MR biomarkers including fractional anisotropy measurements (unpublished data).

Brain injury after cooling therapy in babies with mild neonatal encephalopathy

We examined the brain injury in 41 babies with mild neonatal encephalopathy recruited into the MARBLE study. Of these, 27 babies were cooled for 72 hours ('full') and 14 were not cooled ('none') or were cooled for less than 6 hours ('partial'). Although the cooled babies were sicker, they had less white matter injury on conventional MR imaging and higher NAA/choline levels on MR spectroscopy[32].

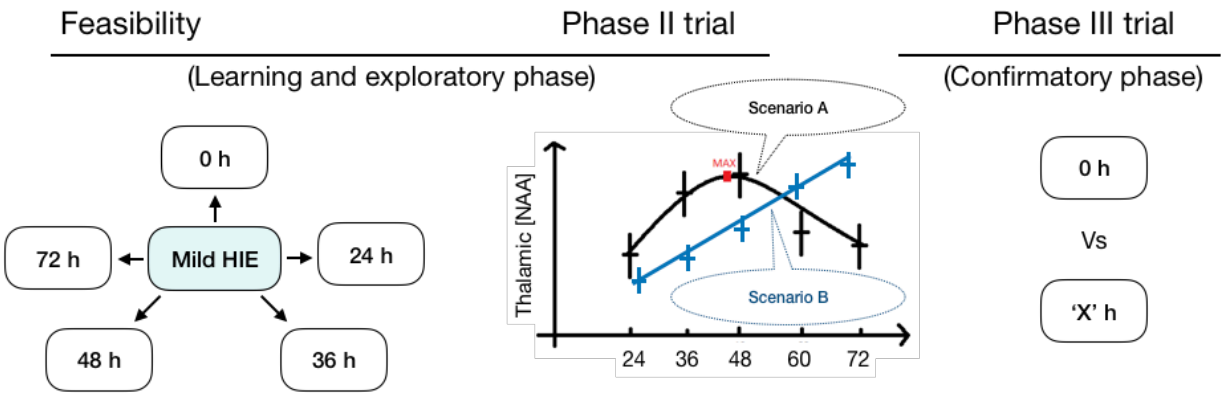
Figure 2. White matter injury scores on conventional MRI (left) and thalamic NAA/choline (right)



Justification of the COMET trial design

Given that the duration of cooling is species-dependent, it is unlikely that the optimal duration of cooling in animal models can be directly extrapolated to humans. The conventional approach of evaluating neuroprotective interventions in phase III trials is challenging in mild encephalopathy due to several reasons. For example, approximately 760 babies with mild encephalopathy need to be recruited per arm to detect a 30% reduction in the adverse outcomes (moderate or severe disability or death) at 80% power and 0.05% significance, given a control event rate of 20%. This requires a massive international effort and resources, and treatment failures at phase III trials are catastrophic. An alternative approach is to examine the mean differences in cognitive scores as an outcome measure. Such trials would still require large sample sizes, and may not provide adequate information for health policy changes and the NICE guidelines.

In the COMET trial, we will use thalamic [NAA] as a screening test to examine the treatment effect of cooling, and to optimise the cooling duration before proceeding on to a phase III trial. If there is no difference in [NAA] in the usual care and cooled babies in the phase II trial, it is unlikely that there would be a clinically important difference in a phase III trial, and such a



trial would not be warranted. In this scenario, the standard care for babies with mild encephalopathy would continue as normothermia.

On the other hand, if a significant improvement in [NAA] is found with cooling in the phase II trial, this would merit continuation to phase III, including an evaluation of the cost-benefits of the intervention.

The COMET trial design is based on a novel clinical trial methadology recently developed by the MRC Clinical Trial Unit (London) and the London School of Hygeine and Tropical Medicine[33].

3. AIMS

1. To examine the feasibility of recruiting and randomising babies with mild neonatal encephalopathy to multiple treatment durations.
2. To examine the feasibility of obtaining adequate quality data on the primary outcome for the phase II trial (i.e. thalamic N-acetylaspartate concentration) in the recruited babies
3. To examine the feasibility of collecting adequate quality data for exploratory sub-studies on heart rate variability and gene expression profile.

4. PATIENTS AND METHODS

All tertiary neonatal centres providing therapeutic hypothermia and with facilities for 3 Tesla MRI scanning and spectroscopy are eligible to participate in the COMET trial.

4.1 Study participants

Babies (>35 weeks gestation and birth weight >1.8kg) requiring resuscitation at birth will be screened for eligibility and recruited if they meet the inclusion criteria. We will recruit a total of 32 term or near term (>35 weeks) babies (8 per arm) with mild neonatal encephalopathy over a 12 month period.

4.2 Inclusion criteria

All of the following three criteria should be met:

1. Age less than six hours.

AND

2. Evidence of acute perinatal asphyxia
    a. Metabolic acidosis (pH <7.0 and/or BE >-16) in cord gas or a blood gas within one hour of birth.

OR

    b. If the pH or BE is borderline (pH<7.15 to 7.0) and/or BE >-10 to -16) in cord and/or blood gas within 1h of birth, or no blood gas available, additional evidence of perinatal asphyxia is required, which includes either an acute obstetric event (e.g. cord prolapse, abruption, shoulder dystocia) OR Need for continued resuscitation or ventilation at 10 minutes and/or a 10 min Apgar score <6

AND

3. Evidence of mild NE (at-least two abnormalities) on an NICHD neurological examination performed between 1 and 6h of birth.

The NICHD neurological examination has been extensively validated in multiple large multi-country trials in babies with moderate and severe encephalopathy, and more recently in mild encephalopathy as part of the MARBLE study and the PRIME study[34,35] (extended classification).

At-least 2 items should be present under the mild encephalopathy criteria for the baby to be eligible, and this is expected to identify babies with mild encephalopathy who have a 20% risk of moderate or severe adverse neurodevelopmental outcome at 2 years. The details of the examination are given in Appendix 1.

All the examiners will be trained and certified in the NICHD examination prior to recruitment.

4.3 Exclusion criteria
The following group of babies will be excluded prior to randomisation

1. Babies without encephalopathy
2. Babies with moderate or severe encephalopathy who meet the current NICE/AAP guidelines for cooling therapy.
3. Babies with seizures (clinical and/or aEEG/EEG)
4. Babies with moderate or severe abnormalities on aEEG voltage criteria.
5. Babies with life threatening congenital malformations

4.4 Study procedures
After informed parental consent a total of 32 babies with mild encephalopathy will be randomised to one of the four arms (8 per arm)

(i) Normothermia (36.5°C ± 0.5C) for 24 hours and then usual care for a further 48h.
(ii) Whole body cooling (33.5°C ± 0.5°C) for 24 h followed by rewarming at 0.5°C per hour.
(iii) Whole body cooling (33.5°C ± 0.5°C) for 48 h followed by rewarming at 0.5°C per hour.
(iv) Whole body cooling (33.5°C ± 0.5°C) for 72 h followed by rewarming at 0.5°C per hour.

Randomisation (web-based) will be performed at the cooling centre for all babies. The standard clinical referral pathway will be followed for out-born babies with mild NE, and the clinical assessment and randomisation will happen only at the cooling centre. However, the transport teams will provide the information leaflets and discuss the study with the parents prior to retrieval, so that the babies can be randomised immediately on admission.

Supportive treatment will be the same for all groups, as per the unit protocol. All babies will have amplitude integrated EEG within six hours of birth, for a minimum period of 72 hours, as part of standard clinical care. Following completion of cooling therapy in the respective trial arms, babies will be rewarmed at a rate of 0.5°C per hour to eventually reach normothermia.

Use of sedation during cooling
Although sedation is often used during cooling in the UK, there is little evidence based to support this. In a non-randomised study, Thoresen et al. (2001) compared the brain injury in 18 piglets kept normothermic (39°C) with 21 piglets who were cooled to 35°C for 24 hours [36]. The piglets were not given general anaesthesia, and no difference in brain injury was seen. The cooled piglets shivered and had elevated cortisol levels. The lack of neuroprotection was attributed to stress, possibly due to inadequate sedation, although the study examined anaesthetics rather than sedatives. Unlike piglets, newborn babies have brown fat and hence non-shivering thermogenesis occurs in response to cooling. Thus, the clinical implications of these data are unclear [36].

Furthermore, neuroprotection is observed in other animal models without sedation [37]. More recent data from the sub-analysis of the NICHD cooling trial suggest that sedation had no effect on the neurodevelopmental outcomes [38]. Hence, routine sedation will not be mandated in the COMET trial, and babies would be extubated whenever clinically stable.

Babies developing seizures after randomisation
A small number of babies (less than 5% in the PRIME study and MARBLE study) with mild encephalopathy during the initial assessment, may develop seizures and progress to moderate encephalopathy.

Recent evidence from delayed cooling trial suggests possibility of some neuroprotection even up to 24 hours of age[39]. Hence, any baby developing seizures or progressing to moderate encephalopathy will receive cooling therapy for at least 72 hours as per the unit protocol. The data from these babies will be analysed as per the original allocation (Intention to treat).

aEEG and ECG
All babies will have aEEG as a part of the routine clinical care for the first 24 hours. In addition, 2 channel ECG data from the first 24 hours will be stored on a small portable device for analysis of heart rate variability.

Blood samples
We will collect 1 ml of blood at the time of randomisation and again at 80 hours from randomisation from all recruited babies. The blood (venous or arterial) will be collected, at the time of routine clinical sampling, whenever possible.

MR imaging and spectroscopy
All recruited babies will have 3 Tesla MR imaging and spectroscopy acquired between 4 and 7 days of age (prior to hospital discharge whenever possible). In addition to conventional T_1 and T_2, and diffusion tensor imaging, a series of spectroscopy data will be acquired in a $15x15x15mm^3$ voxel centred on the thalamus to quantify NAA concentration [40]. Due to the variance arising from inter-site scanner differences, an MR spectroscopy phantom will be used for calibration across all sites prior to starting the study. In the absence of a comprehensive diffusion phantom, inter-site diffusion data will be corrected post-hoc using ComBat [41]. The results of the MR scans including any incidental findings will be fed back to the clinical teams for appropriate counselling of the parents.

4.5 Withdrawal criteria
Withdrawal should occur only upon parental or clinician request. Recent data from the NICHD delayed cooling trial suggests potential benefits of cooling therapy for up to 24 hours of age in babies with moderate or severe encephalopathy. Hence, any baby who develops documented seizures (clinical and/or aEEG) between the age of 6 to 24 hours (i.e. after randomisation) will be considered to have moderate or severe encephalopathy, and will receive full cooling therapy for at least 72 hours, at the discretion of attending clinical teams [39]. These babies will not be excluded from the study, and will be analysed in the originally allocated group (intention to treat).

4.7 Outcome measures
- Proportion of the eligible babies recruited
- Proportion of the recruited babies from whom sufficient quality data for thalamic [NAA] estimation was obtained
- Number of recruited babies from whom adequate quality RNA was extracted for gene expression studies
- Number of recruited babies from whom adequate quality ECG was obtained for heart rate variability analysis.
- Number of babies with mild encephalopathy progressing to moderate or severe encephalopathy.

- Number of babies crossing over between the allocation groups.

5. STATISTICS AND DATA ANALYSIS

As this is a feasibility study formal power calculations have not been performed. We expect to recruit at least 60% of the eligible population and to have adequate quality data on the primary outcome for the main trial (i.e. thalamic N-acetylaspartate concentration) in >95% of the recruited babies.

6. ADVERSE EVENTS

All known adverse events relating to neonatal encephalopathy and whole-body cooling are described in the parent information leaflet and will be discussed at the point of obtaining the informed research consent, prior to the start of cooling. The following clinical events occur due to the underlying disease (neonatal encephalopathy) although these are less likely in babies with mild neonatal encephalopathy. Previous data from cooling trials on babies with moderate and severe encephalopathy suggest that these adverse outcomes are reduced by cooling.

1. Brain injury on magnetic resonance imaging
2. Death during the neonatal period or during infancy
3. Adverse neurodevelopmental outcome at 18 months and at childhood
4. Persistent pulmonary hypertension
5. Metabolic imbalances
6. Cardiac arrhythmia
7. Thrombocytopenia
8. Renal failure
9. Coagulopathy

Whole-body cooling may increase the risk of the following adverse events.

1. Thrombocytopenia and an increased need for platelet transfusions
2. Subcutaneous fat necrosis

All adverse events are expected to occur within the cooling period (first 72 hours) or within 72 hours of re-warming. Adverse reactions occurring subsequently (after 1 week of life), except subcutaneous fat necrosis, will not be considered as relating to the intervention. Subcutaneous fat necrosis may occur several weeks after the intervention.

Serious adverse events that may be due to hypothermia are:

- Cardiac arrhythmia.
- Life-threatening bleeds
- Major venous thrombosis not related to an infusion line

6.1 DEFINITIONS

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

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

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

6.2 REPORTING PROCEDURES

All adverse events will be recorded during hospitalisation using the case report form. Babies who suffer neonatal encephalopathy are expected to have higher mortality and morbidity up to two years of age. If an UNEXPECTED serious adverse event occurs (i.e. an event not mentioned in the above list in 6.), it should be reported to the COMET trial manager at the Centre for Perinatal Neuroscience (CPN) at Imperial College London within 24 hours, using one of the Serious Adverse Event report forms. The COMET trial manager will ensure that the COMET Independent Data Monitoring Committee and the Research Ethics Committee are informed accordingly.

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

7. REGULATORY ISSUES

7.1 Regulatory & ethics approval

This study has been reviewed and approved by the Health Research Authority and the West of Scotland Research Ethics Committee. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. The study will also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study.

7.2 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.

Whether or not the parent(s) decide to take part in the study shall not affect the clinical decisions made during the care of the baby, nor the quality of care provided. All participants are free to withdraw from the study at any time without giving any reason and without prejudicing further treatment.

7.3 Confidentiality

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

All personal data will be stored for a period of 10 years, 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.

All MR data will be stripped of identifying information upon export from the scanner, and all other records only reference study numbers. Any remaining potentially sensitive data which are necessary to know for the purposes of study (e.g. date of birth) will be kept on a central, backed-up and encrypted drive on the Imperial College London network, which is only accessible from a separate physical location. Access to each of these areas is tightly controlled, and new users requiring access to these data will require formal authorisation from the Chief Investigator.

MR data will be again anonymised using the study number, and encrypted with a password prior to transfer. Imperial College London file transfer protocols will be used for data transfer. All research data will be stored at Imperial College London, for a period of 10 years.

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

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

7.6 Funding
The National Institute for Health Research, UK and Garfield Weston Foundation funds this study. There are no payments offered to the study participants.

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

8. STUDY MANAGEMENT
The day-to-day management of the study will be co-ordinated through the Centre for Perinatal Neuroscience, Imperial College London.

The Project Management Group (PMG) will oversee all aspects of the day-to-day running of the study, and will consist of the investigators and the COMET trial staff, based at the Centre for Perinatal Neuroscience, Imperial College London. PMG 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 PMG 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

9. 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.

10. Publications policy

Ownership of the data arising from this trial resides with the trial team. On completion of the trial the data will be analysed and tabulated and a final study report prepared. Consort guidelines and checklists are 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. This 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 or the decision to submit the report for publication.

Appendix 1. NICHD Examination for neonatal encephalopathy

Eligibility criteria require ≥ 2 abnormal categories in mild and NOT ≥3 moderate or severe.

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

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