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European Society of Intensive Care Medicine study of therapeutic hypo**therm**ia (32-35℃) for ICP reduction after traumatic brain injury

Eurotherm3235Trial PROTOCOL

VERSION 8 9th May 2012

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Sponsored by: The University of Edinburgh and NHS Lothian

Protocol Index

APPENDIX LIST

1.0 Introduction

1.1 Background

Traumatic brain injury (TBI) is a major cause of death and severe disability throughout the world. TBI leads to 1,000,000 hospital admissions per annum throughout the European Union (EU). It causes the majority of the 50,000 deaths from road traffic accidents and leaves 10,000 patients severely handicapped: three quarters of these victims are young people [1]. Additionally, TBI causes 290 000 hospital admissions, 51 000 deaths and leaves 80 000 patients with permanent neurological disabilities in the United States annually [2]. The consequence of this is both a devastating emotional and physical impact and an enormous financial burden [3].

Therapeutic hypothermia has been shown to improve outcome after cardiac arrest [3], consequently the European Resuscitation Council and American Heart Association guidelines [4;5] recommend the use of hypothermia in these patients. Hypothermia is also thought to improve neurological outcome after neonatal birth asphyxia [6]. Cardiac arrest and neonatal asphyxia patient populations present to health care services rapidly and without posing a diagnostic dilemma therefore, therapeutic systemic hypothermia may be implemented relatively quickly. As a result of this, hypothermia in these two populations is similar to the laboratory models wherein systemic therapeutic hypothermia is commenced very soon after the injury and has shown so much promise [7].

The need for resuscitation and Computerised Tomography (CT) imaging to confirm the diagnosis in patients with TBI, are factors which delay intervention with temperature reduction strategies. Treatments in TBI have traditionally focussed on restoring and maintaining adequate brain perfusion, surgically evacuating large haematomas where necessary, and preventing or promptly treating oedema [3]. Brain swelling can be monitored by measuring intracranial pressure (ICP), and in most centres ICP is used to guide treatments and to monitor their success. The use of hypothermia in TBI should be regarded in this context.

<u>Pathophysiology</u>

Ischaemia has a key role in all forms of brain injury and preventing ischaemic (or secondary) injury is at the core of all neuroprotective strategies [3]. A complex cascade of processes ensues at the cellular level after a period of ischaemia beginning from minutes to hours after injury and continuing for up to 72 hours or longer. Thus, there may be a

window of opportunity of several hours, or even days, during which injury can be mitigated by treatments such as hypothermia [3].

Review of Clinical Evidence

In total, 29 clinical studies have been performed to assess the effects of hypothermia in TBI. Twenty-seven of these were performed in adult patients, 18 of which included control groups. Data from one pilot study were subsequently included in a larger study, therefore leaving 17 studies. As outlined above, study protocols have differed considerably, and not all studies were (properly) randomised [3]. A total of 131 patients were enrolled into two studies undertaken in patients with normal ICP. Only one of these studies reported outcome data (at 3 months) and the results showed no significant difference between groups (good outcome in 21/45 (hypothermia) vs. 27/46 patients (controls), p=0.251) [8].

Eighteen studies, with outcome data available for 2096 patients, used hypothermia in patients with high ICP that was refractory to "conventional" treatments (usually sedation/analgesia, paralysis, osmotic therapy, and sometimes barbiturates) [9-26].The results are summarised in Figure 1 overleaf. All observed decreases in ICP during cooling. Thirteen of these studies reported significant improvements in outcome associated with hypothermia [10;12-14;16;17;19-25]. All of these were performed in specialised neurotrauma centres, with experience in applying hypothermia and managing its side effects. Ten were single centre studies [10;12;14;16;17;20;22-25], three (all performed in China) [14,20,22] were multi-centre. Four additional studies [11;15;18;21] observed a trend to improved outcome, but these differences were not statistically significant.

Interpretation of these results is complicated by the fact that these studies have enrolled different categories of patients, with different types of injuries, and have used widely diverging treatment protocols [27]. Most have used elevated ICP as an inclusion criterion although some have used CT-scan criteria. The duration of cooling varied from 24 hours to more than five days and re-warming rates have also varied. Some studies have used ICP to guide depth and duration of treatment although responses to rebound intracranial hypertension have differed [3]. Use of co-interventions such as osmotic therapy, sedation, analgesia, paralysis, targets for mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) have also varied considerably [3]. All of these factors can affect outcome

after TBI in general, and the potential efficacy of cooling in particular. Thus interpreting, comparing and aggregating the results of these studies presents a number of complex challenges.

In contrast, one of the two largest multi-centre randomised controlled trials (RCTs) failed to show that therapeutic hypothermia improved outcome at 6 months after TBI (RR of a poor outcome 1; 95% CI 0.8-1.2; p=0.99) [9]. Significantly more of the patients admitted to hospital with hypothermia who were randomised to normothermia, and consequently re-warmed, had a poor outcome (78% n=31). Compared to patients admitted with hypothermia and treated with hypothermia (61% n=38) (p=0.09).

On subsequent analysis, it became clear that although this study was methodologically well designed, there was marked inter-centre variance in the treatment effect of hypothermia, age of participants, severity of illness scoring between groups, management of intracranial hypertension and haemodynamic and fluid management [28]. Therapeutic hypothermia in the hypothermia group was started relatively late with a slow speed of cooling (average time to target temperature >8 hours) in all centres.

Hypotension (lasting >2 hours) and hypovolaemia occurred three times more frequently in the hypothermia group. Bradycardia associated with hypotension also occurred four times more frequently in this group, electrolyte disorders and hyperglycaemia were also found more frequently in the hypothermia group [9]. All of these complications are known side effects of hypothermia. Most are easily preventable with good intensive care and should not be regarded as inevitable consequences of hypothermia treatment. Since even very brief episodes of hypotension or hypovolaemia can adversely affect outcome in TBI, these and other issues may have significantly affected the results of this trial [29-31]. One possible problem was that some of the participating centres had little or no previous experience in using hypothermia. Large centres, familiar with cooling showed apparently favourable neurological outcomes whereas smaller centres showed poor outcomes.

Induction of Hypothermia

The most widely accepted use of hypothermia is after cardiac arrest. Two RCTs in this patient group have shown significant neurological improvements in patients treated with hypothermia many hours after injury, whose initial cardiac rhythm was ventricular fibrillation or ventricular tachycardia [32;33]. Subsequent data from a large study of

patients after myocardial infarction suggest that infarct size was reduced in patients who were cooled to <35°C before coronary intervention [34]. Thus, suggesting that faster cooling rates may be beneficial to patient outcome.

Methods of cooling can be broadly divided into surface and core cooling techniques [35]. The above study used surface cooling devices alone and found that large numbers of patients did not reach target temperature quickly enough before the start of the coronary intervention [34]. Despite advancing technology in surface cooling devices and the introduction of endovascular catheters for core cooling, average periods of 2-3 hours are still required to reach temperatures of 32-34°C [35]. The currently available surface cooling devices are also relatively large and cumbersome. This coupled with the need for staff with specialist knowledge of the management of therapeutic hypothermia may prevent its use outside of the Intensive Care Unit [35].

A recent study examined the feasibility, speed and complication rates of infusing refrigerated fluids intravenously to quickly induce hypothermia in patients with various neurological injuries [35]. Results showed that a 1500ml infusion of 0.9% saline, administered over 30 minutes, in patients without cardiac shock, reduced core temperature from 36.9 ± 1.9°C to 34.6 ± 1.5°C at 30 minutes and to 32.9 ± 0.9°C at 60 minutes. Continuous monitoring of arterial blood pressure, heart rhythm, central venous pressure, arterial blood gasses and serum levels of electrolytes, platelets and white blood cells showed no significant adverse events [35].

When hypothermia develops, the body will immediately try to counteract the temperature drop to maintain homeostasis [36]. One of the key mechanisms of heat production is shivering which can lead to an increased oxygen consumption of 40%-100% which may be detrimental in this patient population. Sedation drugs are known to increase peripheral blood flow which, in turn, will increase the transfer of heat from the core to the peripheries, thus reducing core temperature [36]. Therefore shivering may be counteracted by the administration of sedatives, anaesthetic agents, opiates and/or paralysing agents [36].

It should be noted however, that the capacity and effectiveness of the mechanisms of controlling body temperature decrease with age. Younger patients will therefore react earlier and with greater intensity than older patients. For this reason, induction of

hypothermia in younger patients often requires high doses of sedation drugs to counteract the counter-regulatory mechanisms [36].

Meta Analyses

Six meta-analyses have been published between the years 2000 and 2008 [37-42]. These include various numbers of trials, with varying quality of randomisation and blinding procedures. All have found a trend to positive effects of hypothermia on neurological outcome, although statistical significance was reached in only two reviews: RR of improved neurological outcome 0.78 (95% CI 0.63-0.98) [37] and RR 0.68 (95% CI 0.52-0.89) [38].

The most recent meta-analysis [42] included 8 trials which studied comparable patient groups at baseline. Hypothermia was shown to reduce mortality by 20% although this was not statistically significant (RR 0.80; 95% CI 0.59-1.09). Subgroup analysis showed that this effect was significantly greatest when hypothermia was maintained for >48 hours (RR 0.51; 95% CI 0.33-0.79). Hypothermia was also associated with a non-significant increase of 25% in neurological outcome when measured by the Glasgow Outcome Scale at 6 months (RR 1.25; 95% CI 0.96-1.62). Despite not reaching statistical significance, results showed an increased likelihood of improved neurological outcome when cooling was maintained for >48 hours (RR 1.91; 95% CI 1.28-2.85). Another key finding of this meta-analysis is that hypothermia was only of significant benefit to those patients who had not received barbiturate therapy (RR 0.58 95% CI 0.40-0.85).

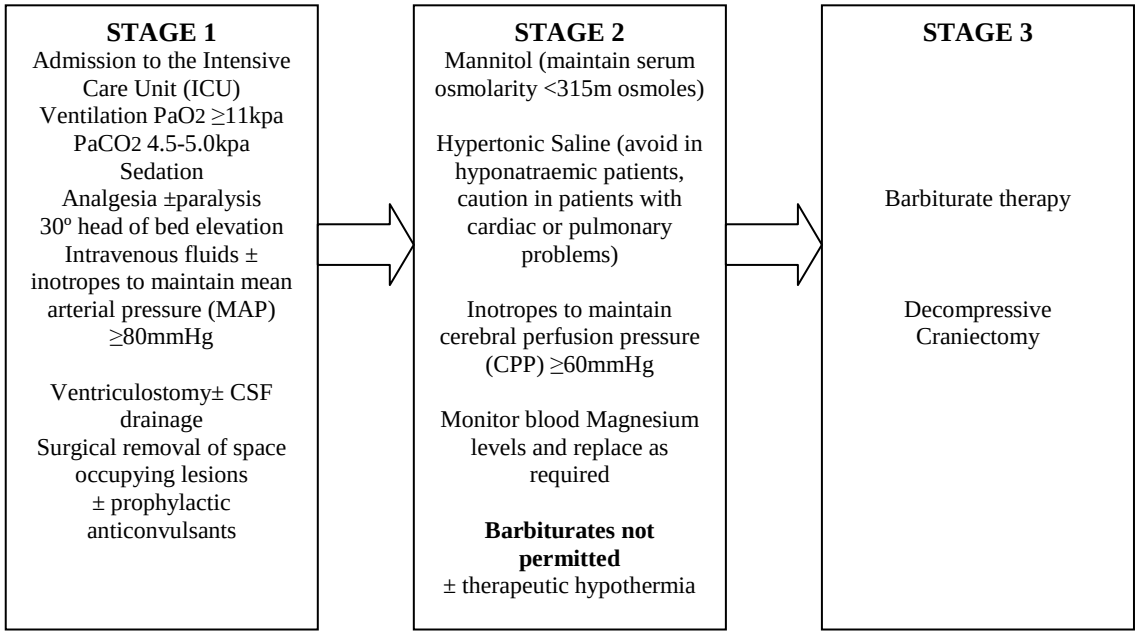
A criticism of these analyses is that most failed to take account of important differences in patient groups (such as those with or without intracranial hypertension) and of differences in treatment protocols, except the use of hypothermia. Only one differentiated between studies that enrolled patients with normal ICP and those that enrolled patients with intracranial hypertension and found no neurological improvement associated with hypothermia [41]. Two assessed effects of treatment duration and speed of re-warming [37;38], concluding that cooling for >48 hours and re-warming rates of 24 hours, or 1°C/4 hours, were both key factors in reducing mortality (RR 0.70; 95% CI, 0.56-0.87) and improving neurological outcome (RR, 0.79; 95% CI 0.63-0.98) respectively.

1.2 Rationale for Study

The evidence from previous research shows that treatment with therapeutic hypothermia to reduce intracranial hypertension may improve patient outcome after TBI. A recent meta-analysis has shown key relationships between the duration of hypothermia treatment and speed of re-warming with patient outcome. Improved patient outcome was found when hypothermia was continued for between 48 hours and 5 days and patients were re-warmed slowly (1°C/4 hours). Experience with cooling also appears to be important if complications which may outweigh the benefits of hypothermia are to be avoided.

The Eurotherm3235trial will examine the relationship between therapeutic hypothermia for ICP reduction after TBI and patient outcome. The trial will enrol patients with TBI who have ICP >20mmHg that is resistant to stage 1 therapy (see Figure 1).

Figure 1: Stages of therapeutic management after traumatic brain injury [37;43]



The Brain Trauma Foundation's recommended treatment threshold for treatment of ICP is 20mmHg [37]. Although early cooling after injury is considered to be beneficial, this is offset by failure to show benefit from hypothermia in the absence of raised ICP. Enrolment to the trial will therefore be allowed for up to 10 days following injury. This potential delay in cooling will be compensated for, to an extent, by inducing hypothermia with 20-30ml/kg of refrigerated 0.9% saline given intravenously over 20-30 minutes. No maximum duration of cooling is specified and hypothermia will continue until ICP is no longer dependent on

temperature reduction to remain below 20mmHg. Patients will then be slowly re-warmed at a rate of 0.25°C per hour (1°C/4 hours).

The Extended Glasgow Outcome Scale will be used to assess patient outcome at 6 months. Many patients with severe TBI are expected to have poor outcome. This outcome questionnaire will therefore be used as it is more sensitive to differentiate between poorer outcome categories after TBI.

2 Study Objectives

2.1 Hypothesis

Patients treated with therapeutic hypothermia (32-35°C) will have reduced morbidity and mortality rates compared to those receiving standard care alone after TBI.

2.2 Research Questions

Does therapeutic hypothermia (32-35°C) reduce morbidity and mortality rates at 6 months after TBI assessed by the extended Glasgow Outcome Scale questionnaire?

Does therapeutic hypothermia (32-35°C) reduce intracranial hypertension?

Is therapeutic hypothermia a cost effective treatment to improve outcome after TBI?

2.3 Study Endpoints

2.3.1 Primary

- Outcome at 6 months using the extended Glasgow Outcome Score (GOSE) questionnaire

2.3.2 Secondary

- 6 month mortality rate
- Intracranial pressure (ICP) control
- Incidence of Pneumonia across both groups
- Length of stay in the Intensive Care Unit (ICU) and Hospital
- Modified Oxford Handicap Scale score at one month, discharge from the randomising hospital or death, whichever occurs first
- Correlation between the predicted outcome using the modified Oxford handicap scale at hospital discharge and the GOSE Score at 6 months post injury

- Health economics (dependent on additional external funding)

3. Trial Design

3.1 Trial Design

This is a pragmatic, multi-centre randomised controlled trial to examine the effects of hypothermia (32-35ºC) on outcome after traumatic brain injury. The study will recruit for 41 months. Participants will be randomised to either the control or intervention group (Figure 3). Participants allocated to the control group will receive standard care without therapeutic hypothermia. Participants randomised to the intervention group will receive standard care with therapeutic hypothermia. Hypothermia will be initiated with 20-30mls per Kilogram (Kg) of refrigerated 0.9% saline given intravenously and maintained using the cooling technique available at that centre. A flowchart has been designed for the induction and maintenance of therapeutic hypothermia in the intervention group (Appendix 1). The depth of hypothermia (range: 32-35°C) will be guided by ICP with a higher pressure level warranting a cooler target temperature. A guideline has been designed for the detection and treatment of shivering in the intervention group (Appendix 2). This has been designed specifically for this trial drawing on;

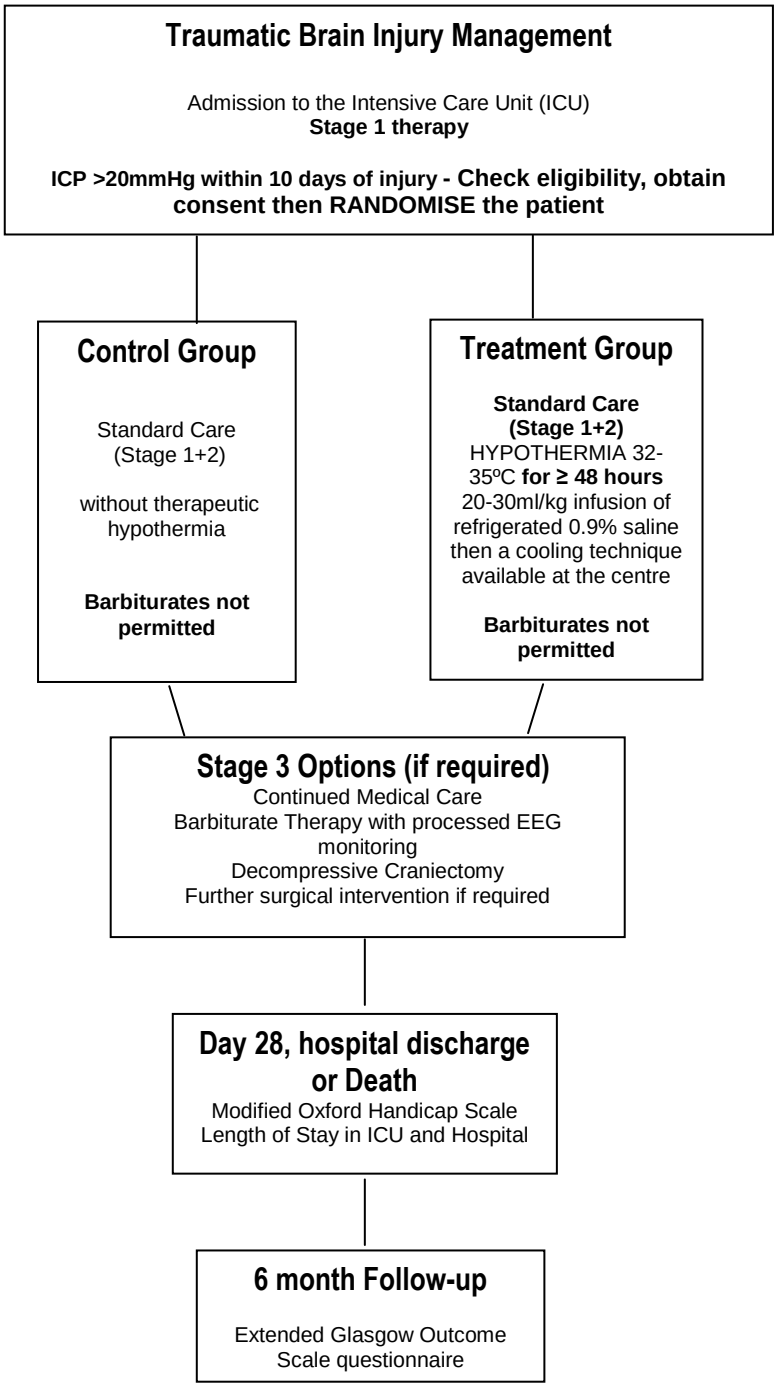
- the hospital protocol of the Mission Hospital, Orange County California (permission given by Mary Kay Bader, Neuro CNS, Mission Hospital, Orange County Ca)
- The hospital protocol of the University Medical Centre, Utrecht , The Netherlands (permission given by Dr Kees Polderman, UMC, Utrecht, The Netherlands)
- The Bedside Shivering Assessment Scale [44]

Therapeutic hypothermia of 32-35°C will be maintained for at least 48 hours in the treatment group. Previous studies have shown that therapeutic hypothermia which lasts for at least 48 hours shows a trend to reduction in mortality and improved neurological function after TBI [42]. Hypothermia will be continued for as long as is necessary to reduce and maintain ICP <20mmHg. Intracranial hypertension is defined as an ICP >20mmHg by the Brain Trauma Foundation Guidelines, 2007 [37]. Together with therapeutic hypothermia therapy, all patients in the intervention group will continue to be treated with stage 1 and 2 therapies as required to reduce intracranial hypertension [37;38]. If raised ICP becomes resistant to these therapies and despite increasing the depth of hypothermia, care may be escalated to include stage 3 interventions. If this is required, therapeutic hypothermia treatment should be terminated for patients allocated to

the treatment group and the patient re-warmed using the re-warming guideline. The reason for treatment escalation should be documented on the daily data collection form.

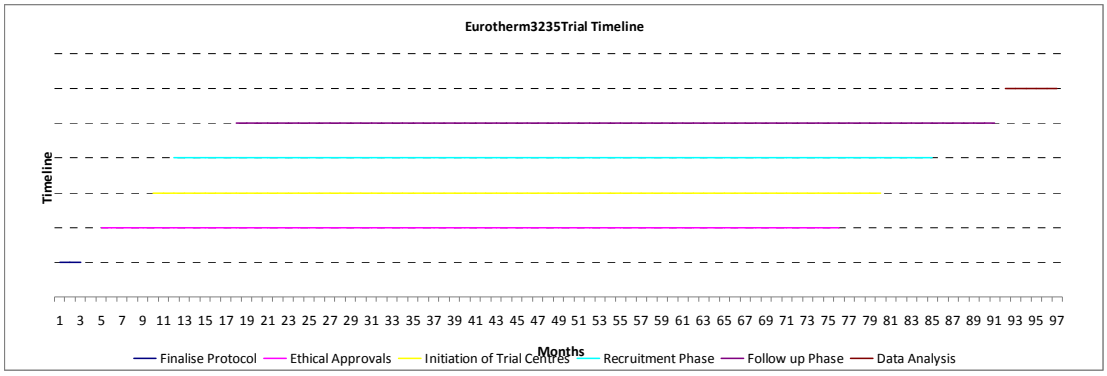
The primary endpoint of the Eurotherm3235trial is outcome 6 months after traumatic brain injury using the GOSE questionnaire (Appendix 3). Participants will be sent the GOSE questionnaire with a covering letter (Appendix 4) by post 6 months after randomisation by the coordinating centre.

Figure 3: Study Flowchart



3.2 Project Timeline

Date	Months	Total number of months	Action
Jan 09-Mar 09	1-3	3	Finalise Protocol
Apr 09-Nov 15	4-83	79	Obtain ethical and hospital approvals
Sept 09-Mar 16	9-86	77	Initiation of trial centres and staff
Nov 09-Jul 16	11-91	80	Recruitment of patients
May 10-Jan 17	17-97	80	Follow up of patients
Feb 17-Jul 17	98-103	6	Analysis and Reporting



4. Study Population

4.1 Sample Size

A total of 600 patients (300 per treatment group) will be enrolled. At least 70 hospitals specialising in the care of TBI patients will be initiated worldwide including centres in Belgium, Germany, Italy, Netherlands, Spain, Sweden and the United Kingdom.

4.2 Inclusion Criteria

1) Believed to be legal age for consent to take part in research
2) Primary closed Traumatic brain injury
3) Raised ICP >20mmHg for ≥ 5 minutes after first line treatments with no obvious reversible cause e.g. patient position, coughing, inadequate sedation
4) ≤10 days from the initial head injury
5) Cooling device or technique available for > 48 hours
6) Core temperature ≥ 36°C (at the time of randomisation)

7) An abnormal CT scan of the brain. This is defined as one that shows haematoma, contusion, swelling, herniation or compressed basal cisterns.

4.3 Exclusion Criteria

1) Patient already receiving therapeutic hypothermia treatment
2) Administration of barbiturate infusion prior to randomisation
3) Unlikely to survive for the next 24 hours in the opinion of the ICU Consultant or Consultant Neurosurgeon treating the patient
4) Temperature ≤34°C at hospital admission
5) Pregnancy

* All female patients of child bearing age who meet the Inclusion Criteria will undergo a urine pregnancy test. This will be performed as part of the screening for eligibility procedure by the investigator or research nurse in the ICU.

5.0 Participant Selection and Enrolment

5.1 Identifying Participants

Eligible participants will be identified by nursing and medical staff on the ICU.

5.2 Consenting Participants

Eligible patients for this study must have raised ICP despite stage 1 treatment options for the management of head injury. Stage 1 treatment options include sedation and ventilation therefore participants will not be able to give informed consent themselves.

See Appendix 5 for consenting procedure, Appendix 6 for Information Sheets and Appendix 7 for Consent Forms. The Patient and Relative Information Sheets have been designed in consultation with patients who have suffered a TBI and their relatives. Consultations took place at the drop-in centre for the Edinburgh Headway Group, a registered charity for brain injured patients. Details of the charity can be found at http://www.edinburghheadway.org.uk

5.3 Screening for Eligibility

A screening log will be completed for all eligible patients (Appendix 8). Data including inclusion criteria met, exclusion criteria not met and date consent obtained will be collected on this form. It will be kept in a locked cabinet at the centre. This data will also be entered in the trial database via the electronic CRF in order for the trial office to monitor recruitment and/or refusal rates at each site.

5.4 Randomisation

5.4.1 Randomisation

Patients should be randomised as soon as possible after meeting the inclusion criteria. The randomisation of participants to hypothermia or standard care will be undertaken using either a central internet based randomisation service or a telephone randomisation service depending on the available technology at each site (Appendix 9).

Treatment allocation will be minimised using the following baseline covariates;

1. Trial Centre
2. Age < or ≥ 45 years
3. Post-resuscitation Glasgow Coma Score motor component 1-2 or 3-6
4. Time from injury < or ≥ 12 hours
5. Pupils; Both reacting or 1 or neither reacting

5.4.2 Treatment Allocation

It is not possible to blind local investigators to allocation as it will be obvious clinically which patients are receiving hypothermia e.g. equipment required, patient temperature, blood results, fluid requirements. Blinding of outcome data assessment will however be ensured as the GOSE questionnaire will be posted to participants by the coordinating centre.

5.4.3 Premature Withdrawal

Participation in any research trial is voluntary and therefore the participant or their legal representative may wish to withdraw from the trial at any point. If this is the case, it should be made clear on a Premature Withdrawal Form (Appendix 10) whether any previously collected data may still be used for the analysis and which part of the trial the patient is being withdrawn from;

1. Withdraw entirely - the hypothermia intervention will be safely terminated, no further data will be collected and previous data collected will not be used in the analysis.
2. Withdraw entirely – no further data will be collected and the intervention will be safely terminated but data previously collected may be used in the analysis.
3. Withdraw from the intervention but be willing to be followed up
4. Withdraw from being followed up only

If the patient wishes to withdraw from the trial or their legal representative wishes to withdraw them, they are free to do so without giving a reason and without the patient's medical care or legal rights being affected [45]. If however the patient is withdrawn from the study by the doctor in charge of their care on medical grounds, the reason for this withdrawal must be clearly documented in the data collection form and a serious adverse event (SAE) form completed if appropriate.

6.0 Data Collection and Checking

Daily data collection will start on the day of randomisation (baseline) for all patients and will continue until the ICP monitor has been removed. Data will be collected using an electronic case report form (eCRF) (Appendix 11). This will include the Modified Oxford Handicap Scale (Appendix 12) which will be completed at hospital discharge. Paper copies of all CRFs will be available to centres with little or no access to the internet. All CRFs must be completed in English and will be managed by Lincoln, Paris. Blinded and patient identifiable data will be stored separately in secure databases. All patient identifiable data will be stored by the coordinating centre.

For those centres using paper CRFs, all forms must be completed in English using black ball-point pen. The correction of data can only be made by drawing a line through the incorrect data and writing the correct data next to those data that were incorrect. Correction fluids are not allowed. All changes to data must be dated and initialled by the investigator or his/her delegate. The paper CRFs should then be faxed to the coordinating centre where the data will be entered into the secure database.

<u>Follow up Data</u>

The patient's General Practitioner (GP)/Family Doctor will be sent a letter by post to inform them of the patient's involvement in the Eurotherm3235Trial (Appendix 13).

Patient outcome will be assessed 6 months after injury using the GOSE questionnaire (Appendix 3). As this is the primary endpoint of the study, it is vital that this information is obtained. If the patient is still in hospital 6 months after the injury, an independent staff member may visit the patient on the ward to go through the questionnaire with them if this is appropriate. If however the patient has been discharged from hospital, the questionnaire will be sent to their residing address. A member of the trial team will

telephone the patient's family doctor/GP to find out their vital status before any questionnaires are sent to the patient.

It is likely that the patient will be unable to complete the questionnaire by themselves due to the nature of their injury. Therefore a letter will also be sent to the person who gave consent for the patient inviting them to help the patient to complete the form and remind them of the study (Appendix 14). This will be sent at the same time as the GOSE questionnaire is sent to the patient. If we do not receive a response from the patient within 3 weeks, we will send them the shorter GOS questionnaire (Appendix 15) with a covering letter (Appendix 16).

If there is still no response, and the patient has been discharged from hospital, we will attempt to contact them directly by telephone. If the patient lacked capacity at hospital discharge and we cannot contact them directly by telephone, we will telephone the person who consented for the patient to be enrolled in the study and will complete the shorter GOS questionnaire with them over the telephone.

If however the patient regained capacity before hospital discharge and has given consent to continue to be involved in the follow-up phase of the study, yet we cannot contact them directly by telephone, no further contact will be made. This process will be discussed during the consent procedure.

Staff in Edinburgh will work closely with local investigators to obtain data that are as complete and accurate as possible. Key data, such as outcome measures, will be 100% double entered into the trial database. Extensive range and consistency checks will further enhance the quality of the data.

7.0 Statistics and Data Analysis

7.1 Sample Size Calculation

The primary endpoint for this trial is outcome at 6 months measured by the GOSE questionnaire. The main evidence has been gathered by six meta-analyses published between the years 2000 and 2008. These included varying numbers of clinical trials and examined each trial based on an assessment of the quality of randomisation and blinding procedures. All meta-analyses found a trend to positive effects of hypothermia on neurological outcome, but statistical significance was reached in only two [37;38].

With a conventional dichotomous analysis of the eGOS, comparing the proportions of patients with an unfavourable outcome in the two groups, a 600 patient trial has 81% power at the 5% significance level (2-sided) to detect an absolute reduction of 12% (60% reducing to 48%). There is 87% power to detect an absolute reduction of 13% (60% reducing to 47%).

This is conservative compared with the Peterson et al (42) systematic review of optimised therapeutic cooling.

Using an ordinal analysis of the eGOS together with covariate adjustment then there is the potential to increase the statistical efficiency of the analysis. If we achieve the efficiency gains suggested by simulations run by the IMPACT investigators (46) and demonstrated in a reanalysis of the CRASH trial (47), then a trial of 600 patients would have equivalent power to a trial of 1000 patients.

This would give 80% power at the 5% significance level (2-sided) to detect an absolute reduction of 9% (60% reducing to 51%).

7.2 Proposed Primary Analysis

A detailed Statistical Analysis Plan (SAP) setting out full details of the proposed analyses will be finalised before the trial database is locked for analysis. The primary analysis will follow these principles:

- The analysis will be undertaken on the 'intention-to-treat' principle.
- The estimated treatment effect will be presented along with its corresponding 95% confidence interval.
- The analysis of the primary outcome measure, the 6 month GOSE, will exploit the ordinal nature of the outcome scale. It is currently an active research question in both TBI and stroke trial methodology which approach to use to analyse such ordinal outcome scales, the two main options being 'shift analysis' and the 'sliding dichotomy'. The preferred approach will be declared in the SAP, taking into account the results of current on-going methodological research.
- The primary analysis will be adjusted for key baseline covariates, to be specified in the SAP. The unadjusted analysis will also be presented as a sensitivity analysis.

- All interim efficacy analyses reviewed by the independent Data and Safety Monitoring Committee will be interpreted according to the strict Peto-Haybittle guideline so that no adjustment is required to the final p-value to allow for the multiple testing.

7.3 Other Planned Analyses

A *priori* sub group analysis will be presented testing the relationship between minimisation factors including; age < 45 years, admission post resuscitation GCS motor score <2, time from injury <12 hours and outcome. The analysis will test for interaction effects, and stricter levels of statistical significance ($p<0.01$) will be sought, reflecting the exploratory nature of these subgroup analyses. Only the primary outcome measure will be used in these analyses.

Other exploratory and observational studies will be conducted by some centres. These sub-studies will be run by local Investigators and will require approval by the trial management and steering committees together with further ethical approval. All sub-studies must also have secured external funding.

7.3 Economic Analysis

The undertaking of economic data collection and analysis will be dependent on obtaining external funding. Details of this analysis will be added when external funding is obtained.

8.0 Adverse Events

The local investigator is responsible for the detection and documentation of events that meet the criteria and definitions detailed below.

8.1 Definitions

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial subject. Many untoward events are expected in patients admitted to the Intensive Care Unit due to the severity of their illness and/or injury.

The treatment of any untoward medical occurrence is part of the standard care for patients admitted to the Intensive Care Unit. Therefore ***no*** adverse events will be collected in this study.

A **serious adverse event** (SAE) is defined by the National Research Ethics Service in the UK [46] as any adverse event that:

- Results in death
- Is life threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect

Death is an expected outcome in approximately 25% of all critically ill patients with severe TBI and will not be reported as an SAE in this study.

The ***specific*** SAEs to be collected are;

- Bleeding – defined as a new haemorrhage requiring ≥2 units of packed red cells
- Cardiovascular instability – defined as a systolic blood pressure <90mmHg for ≥30 minutes [37;37]. Terminal hypotension will not be collected.
- Thermal burns >5% of body surface area using the Lund-Browder Chart (Appendix 17)
- Cerebral perfusion pressure (CPP) <50mmHg for ≥ 15 minutes

Unexpected events considered to be SAEs that are not described above, can also be collected by using the 'Other' option on the SAE form. Events collected using this option will be at the discretion of the Principal Investigator and must be clearly described in the 'Circumstances of Event' section of the form.

8.2 Detecting and Recording SAEs

All SAEs must be recorded from the time a patient is randomised until 24 hours after the ICP pressure monitor is removed.

When an SAE occurs, it is the responsibility of the local investigator to review all documentation (for example hospital notes) related to this event. The investigator should

then report all relevant information on the CRF. All SAEs should also be documented on an SAE form (Appendix 18).

8.3 Evaluation of SAEs

The investigator must make an assessment of whether the SAE is likely to be related to the treatment according to the following definitions:

Unrelated where an event is not considered to be related to the treatment

Possibly although the relationship to the treatment cannot be ruled out, the nature of the event and/or underlying disease make other definitions possible

Probably the relationship and absence of a more likely explanation suggest the event could be related to the intervention

Definitely the known effects of therapeutic hypothermia suggest that this is the most likely case of the event

8.4 Reporting of SAEs

As soon as the investigator becomes aware that an SAE has occurred in a study participant, they must report the information to the Academic and Clinical Central Office for Research & Development (ACCORD) office in Edinburgh within 24 hours. The SAE form must be completed as thoroughly as possible with all available details of the event and must be signed by the investigator. If the investigator does not have all the information regarding an SAE, they should not wait for this additional information before notifying the ACCORD office. The form can be updated when additional information is received. The SAE report must contain details of the causality and expectedness at the time of initial report to the ACCORD office.

The SAE form should be transmitted by fax to the ACCORD office central office on 00 44 131 242 9447.

8.5 Follow up Procedures

After initially recording and reporting an SAE, the investigator is required to follow each participant until resolution of symptoms. Follow up information of an SAE should be reported to the ACCORD office on resolution.

9.0 Trial Management and oversight arrangements

9.1 Project Management Group

The trial will be coordinated by a project management group, consisting of the grant-holder and Chief Investigator in Edinburgh, Trial Managers and advisers.

9.2 Trial Management

The trial office is associated with the Edinburgh Clinical Trials Unit (ECTU) in the University of Edinburgh and gives day to day support to the clinical centres. Trial office staff are responsible for all aspects of trial management. These responsibilities include providing research advice and support to all centres, ensuring the timely completion of CRFs in collaboration with all centres, data checking and analysis. The trial office staff will also be responsible for the production of progress reports for the Data and Safety Monitoring Committee (DSMC), Trial Steering Committee, Ethics committees and the European Society of Intensive Care Medicine who are funding the study. Publication and dissemination of the study results will be coordinated by ECTU in collaboration with the Chief Investigator and Principle Investigators.

A *senior trial manager* will oversee the study and will be accountable to the Chief Investigator. Two *Trial Managers* will supervise the day to day conduct of the trial, including: initiation of trial centres, ensuring training records are maintained and updated, supervision and support of all trial staff, site visits to all participating centres, regularly liaising with all trial investigators, monitoring of centres and site closures. The *Secretary*/D*ata Clerk* will be responsible for all administrative responsibilities of the trial, including: manual data entering from paper CRFs, monitoring response to follow up questionnaires, following up missing data queries and non responses to questionnaires with the local investigators.

The statistical and scientific integrity of a major clinical trial is enhanced by incorporating three distinct *statistician* roles: the Study Statistician who will undertake all statistical tasks including formal analysis and reporting of data, the Data and Safety Monitoring Committee (DSMC) and an Independent Statistician. This Statistician will be truly independent having no trial involvement except producing unblinded interim reports for the DSMC at specified time periods.

Subject to additional funding being obtained, a *health economist* will be responsible for the development of the data collection forms required for the economic evaluation, the

analysis of economic data and the preparation of the economic evaluation component of the final report.

An *IT programmer* will establish a database management system for efficient conduct of the trial including the randomisation, timely despatch of questionnaires, automatic form monitoring, data validation and cleaning.

9.3 Trial Steering Committee

A trial steering committee (TSC) will establish and oversee the conduct and progress of the trial. Other members of the trial management group may attend as observers at the invitation of the Chair of the Steering Committee.

9.4 Data and Safety Monitoring Committee

An independent data and safety monitoring committee (DSMC) will be established to oversee the safety of the trial participants. During the period of recruitment to the trial, interim analyses will be supplied, in strictest confidence, to the DSMC together with any other analyses that the committee may request.

In the light of these analyses, the DSMC will inform the TSC if, in the opinion of the committee, the randomised comparison in the trial has provided either

- **a)** proof beyond reasonable doubt[1] that for all or some types of patients, the intervention is clearly indicated.(or contraindicated) in terms of a net reduction in morbidity and mortality across groups.
- **b)** evidence that might reasonably be expected to influence materially the care of people who require ICP management in ICU by clinicians who know the results of this and comparable trials.
- **c)** Futility of enrolment

The TSC will then decide whether or not to modify recruitment to the trial. Unless this happens, the TSC, project management group, clinical collaborators and trial office staff

[1] Appropriate criteria for proof beyond reasonable doubt cannot be specified precisely. A difference of at least three standard deviations in the interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule is proposed (Peto R et al *Br J Cancer* 1976; 34: 584-612).

will remain blinded to the interim results. The conduct of the DSMC will be according to the DAMOCLES principles [47].

9.5 Inspection of Records

Principal investigators and institutions involved in the study will permit trial related monitoring, audits, Regional Ethics Committee (REC) review and regulatory inspection(s). In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor or regulatory authorities direct access to all study records and source documentation.

9.6 Study Monitoring

The study will be monitored on behalf of the Co-Sponsors by the Trial Managers. Site staff should be available to facilitate the monitoring visits and must ensure that all required documentation is available for review.

Study initiation visits will be carried out at all sites before recruitment commences at that site. Site monitoring will be carried out in sites that recruit more than 10 patients throughout the duration of the trial. During these monitoring visits, the Trial Manager(s) will carry out Source Data Verification (SDV) of trial data, verification of informed consent forms and ensure the completeness of the Investigator Site File (ISF). Site monitoring will not be carried out routinely for sites recruiting small numbers of patients. Central quality control checks (QC) of trial data will however be carried out as described in section 6.0. Where central QC of data identifies a problem with data collection at any site, or if the Chief Investigator and/or Co-Sponsors have concerns surrounding the quality or validity of the trial data at any site, a site monitoring visit will be conducted.

Serious breaches in the study protocol and/or GCP identified through trial monitoring will be notified immediately to the Co-Sponsors and appropriate corrective action will be taken and documented.

10. GOOD CLINICAL PRACTICE MODULE

10.1 Ethical Conduct of the Study

This is not a clinical trial of an Investigational Medicinal Product (CTIMP) therefore the study will be conducted in accordance with the Principles of GCP.

A favourable ethical opinion will be obtained from the appropriate Research Ethics Committees (RECs) and local Research and Development (R&D) approval will be obtained prior to commencement of the study.

10.2 Investigator Responsibilities

Each local Investigator is responsible for the overall conduct of the study at their site and compliance with the protocol and any protocol amendments. In accordance with the principles of GCP, the duties listed in this section are also the responsibility of the Investigators. Responsibilities may be delegated to an appropriate member of the study site staff. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list.

10.2.1 Informed Consent

The local Investigator is responsible for ensuring that informed consent is obtained before any protocol specific procedures are carried out.

See Appendix 4 for consenting procedure, Appendix 5 for Information sheets and Appendix 6 for Assent/Consent Forms.

10.2.2 Study Site Staff

The Investigator must be familiar with the study protocol and study requirements. It is also the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the Protocol and their trial related duties.

10.2.3 Data Recording

The Investigator is responsible for the quality of the data recorded in the CRF.

10.2.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the Trial Office in Edinburgh, including, but not limited to:

- An original signed Investigator's Declaration
- Curriculum Vitae (CV), signed and dated by the Investigator indicating that it is accurate and current

The trial office will ensure that all other documents required by the principles of GCP are retained in a Trial Master File and that appropriate information is available in local Study Site Files.

10.2.5 GCP Training

All study staff must hold evidence of appropriate Principles of GCP training or undergo this training. This should be updated every two years throughout the trial.

10.2.6 Confidentiality

All evaluation forms, reports and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the person giving consent for the patient to be enrolled in the trial except as necessary for monitoring and auditing by the sponsor, its designee, or the REC. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than the performance of the study, any data, record or unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsors or their designee must be obtained for the disclosure of any said confidential information to other parties.

10.2.7 Data Protection

All Investigators and study site staff involved with the study must comply with the requirements of local laws on Data Protection with regard to the collection, storage, processing and disclosure of personal information. Access to collated patient data will be restricted to those clinicians treating the patients.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual patients.

11. STUDY CONDUCT REPONSIBILITIES

11.1 Protocol Amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed by the Chief Investigator. Amendments to the protocol must then be submitted to the appropriate REC and local R&D department for approval by the Chief Investigator prior to patients being enrolled into an amended protocol.

11.2 Protocol Violations and Deviations

The Investigator should not implement any deviation from the protocol without agreement from the Chief Investigator and appropriate REC and R&D approval except where necessary to eliminate an immediate hazard to the trial patients.

In the event that an Investigator needs to deviate from the protocol, the nature of and reason for the deviation should be recorded in the CRF. If this requires a subsequent protocol amendment, this should be submitted by the Chief Investigator, to the REC and local R&D department for review and approval if appropriate.

11.3 Study Record Retention

All study documentation will be kept for 5 years from the end of the study.

11.4 End of Study

The end of study is defined as the receipt of the last participant's 6 month GOSE questionnaire.
The Investigators, Trial Management Committee or Trial Steering Committee have the right, at any time, to terminate the study for either clinical or administrative reasons.

The end of the study will be reported to the appropriate RECs within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants and will ensure that the appropriate follow up is arranged for all enrolled patients.

A summary report of the study will be provided to the appropriate RECs within 1 year of the end of the study.

12. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

12.1 Authorship Policy

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with the CONSORT Statement [48].

12.2 Publication

The clinical study report will be used for publication and presentation at scientific meetings. The trial team have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to investigators for dissemination within their countries.

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