Trial Protocol

Hypothermia for Acute Ischaemic Stroke Trial – Pilot Phase

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SUMMARY

Background: Animal studies strongly suggest that cooling improves outcome after ischaemic stroke. Cooling is probably most efficacious with temperatures of 34°C or below, but such temperatures may not be tolerated well by awake patients on a stroke unit. Cooling to 35°C may have a smaller but still substantial effect on outcome and may be achievable for large numbers of patients with ischaemic stroke. Large randomised clinical trials testing whether cooling improves outcome in patients with acute ischaemic stroke are warranted, but the optimal strategies to achieve hypothermia are uncertain. The aim of this pilot phase is to compare the feasibility and safety of surface cooling to 35°C, started within 4.5 hours after the onset of acute ischaemic stroke and maintained for 12 hours, with strategies aimed at reaching a temperature of 33°C and/or maintaining hypothermia for 24 hours.

Methods: This is a pilot phase for a randomised, open, multi-centre, phase III international clinical trial with masked outcome assessment, comparing four different surface cooling strategies with standard treatment in awake adult patients with acute ischaemic stroke. A total of 24 patients will be randomised in the Edinburgh pilot, with a further 2-3 pilots planned elsewhere in Europe. Patients will be randomised to conventional treatment (8 patients) or to one of the following four surface cooling strategies (4 patients each): (A) 35°C maintained for 12 hours; (B) 33°C maintained for 12 hours; (C) 35°C maintained for 24 hours or (D) 33°C maintained for 24 hours. Before randomisation begins we will recruit 3 patients to be cooled to 35°C maintained for 12 hours (but without the biomarker component) to streamline the patient pathway. In the randomised pilot phase we will use a dose escalation approach to ensure that the longer cooling duration is only performed once we have gained sufficient experience with shorter duration cooling.

In all patients randomised to hypothermia, cooling will be started within 4.5 hours of the onset of symptoms by means of intravenous infusion of 20 ml/kg cooled normal saline (4°C) over 30 minutes, followed by surface cooling using the Arctic Sun device. Shivering and discomfort will be prevented and if necessary treated with intravenous pethidine. The primary objective is to determine the feasibility, tolerability and safety of the various cooling strategies, as evidenced by the primary endpoint, the proportion of completed interventions. Secondary outcome measures include measures of the safety and tolerability of the intervention.

1. INTRODUCTION

1.1 BACKGROUND

Acute ischaemic stroke is a condition caused by occlusion of one of the cerebral arteries or arterioles and is typically characterised by the sudden onset of a focal neurological deficit. Common deficits include dysphasia, dysarthria, hemianopia, weakness, ataxia, and sensory loss. In Western communities, about 80% of strokes are ischaemic; the other strokes are haemorrhagic.[1,2].

The social and economic burden of stroke is enormous. Stroke is the second cause of lost disability-adjusted life years in high-income countries and the second cause of death world wide.[3] In people aged 55 years or more, the incidence generally ranges from 4.2 to 6.5 per 1,000 person years.[4] The direct lifetime costs per ischaemic stroke in Germany have recently been estimated at € 43,129. Rehabilitation and chronic nursing care account for the largest part of these costs.[5] As stroke incidence rates rise exponentially with age, the social and economic burden of stroke will rise further with the ageing of the population.

1.1.1 The Ischaemic Penumbra

Ischemic brain injury results from a cascade of events running from energy depletion to necrosis or apoptosis.[6] Intermediate factors include excitotoxicity, free radical formation, and inflammation. Initially after arterial occlusion, a central core of very low perfusion is surrounded by an area with dysfunction from metabolic and ionic disturbances, but in which structural integrity is still preserved, the so-called ischemic penumbra. In the first minutes to hours, clinical deficits therefore do not necessarily reflect irreversible damage. For this reason, the penumbra is the target of treatment for acute ischaemic stroke. Depending on residual blood flow and duration of ischemia, the penumbra will eventually be incorporated in the infarct if reperfusion is not achieved.[6]

1.1.2 Current Treatment Options

Based on the concept of a salvageable ischaemic penumbra, about 500 'neuroprotective' treatment strategies have shown to improve outcome in animal models of acute ischaemic stroke.[7] By contrast, only very early intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) and aspirin are incontrovertibly efficacious in patients, despite innumerable clinical trials of other treatment strategies in acute ischaemic stroke.[8-10] Intravenous thrombolysis is currently restricted to a three-hour time window,[11] and even in high-income countries, only a very small minority (generally 3-7%) of patients with acute stroke receive this therapy.[12-14] Aspirin can be given to a broad range of patients with acute ischaemic stroke, but the benefit is small, with a NNT of 77 to prevent poor outcome in a single patient.[9,15] For this reason, there is an obvious need for additional and more effective treatment strategies that are broadly applicable.

In summary, animal studies strongly suggest that cooling improves outcome after ischaemic stroke. Cooling is probably most efficacious with temperatures of 34°C or below, but such temperatures may not be tolerated well by awake patients on a stroke unit. Cooling to 35°C may have a smaller but still substantial effect on outcome and may be achievable for large numbers of patients with ischaemic stroke. Large randomised clinical trials testing whether cooling indeed improves outcome in patients with acute ischaemic stroke are therefore warranted. To inform such trials, the current pilot phase will test and compare the feasibility, tolerability and safety of different depths and durations of hypothermia in awake patients with acute ischaemic stroke.

1.2 RATIONALE FOR TRIAL

1.2.1 Rationale for Hypothermia

One of the reasons for the failure of allegedly neuroprotective compounds in patients may be that most inhibit only a single step in the chain of events leading to cell death.[16,17] By

contrast, hypothermia affects a wide range of cell death mechanisms, including energy depletion, disruption of the blood-brain barrier, free radical formation, excitotoxicity, and inflammation.[18,19] The potential of hypothermia is underlined by randomised clinical trials in patients with global cerebral ischemia after cardiac arrest[20,21] and in infants with moderate or severe hypoxic-ischemic encephalopathy.[22] In addition, several prospective observational studies have shown an association between a raised body temperature and poor outcome after stroke on the one hand, and low body temperature and improved outcome on the other.[23,24] Next to reperfusion strategies, hypothermia therefore is the most promising therapeutic modality for patients with acute ischemic stroke.

1.2.2 Previous and Ongoing Studies

So far, clinical trials of cooling in patients with acute ischemic stroke have been too few and too small to allow any conclusions.[18,19,25] The Cooling for Acute Ischemic Brain Damage (COOL AID) trial is the only published randomised controlled trial and included just 40 patients where cooling to a target temperature of 33°C for 24 hours was initiated within 12 hours of stroke onset using intravascular vascular cooling.[26] The Nordic Cooling Stroke Trial (NOCSS) was a randomised trial which tested the effect of surface cooling to 35°C initiated within 6 hours of stroke. Unfortunately, the trial was recently terminated because of slow recruitment after the inclusion of 44 patients against a target recruitment of 1,000 (U.J. Weber, personal communication). The ongoing Intravascular Cooling for the Treatment of Stroke – Longer window (ICTuS-L) trial is a phase II trial designed to investigate the feasibility and safety of a combination of intravenous thrombolysis and intravascular cooling to 33°C.[27] The only large temperature-driven phase III randomised acute stroke trial is the Paracetamol (Acetaminophen) In Stroke (PAIS) trial, which sought normalisation of temperature rather than hypothermia;[28] overall, this showed no benefit, although in a post hoc analysis there was a suggestion that patients with pyrexia at entry may have benefited.[29]

1.2.3 Depth of Hypothermia

COOL AID,[26] as well as most randomised trials of hypothermia in postanoxic encephalopathy after cardiac arrest,[20,21] perinatal hypoxic-ischemic encephalopathy,[22] and traumatic brain injury[30] have tested cooling to levels of 32°C to 34°C. For patient comfort, monitoring, and the prevention of shivering, hypothermia to these levels generally requires sedation, mechanical ventilation, and therefore admission to an intensive care unit.[18,31] Due to the limited availability of intensive care beds in most countries, treatment of even a minority of acute stroke patients is therefore precluded by substantial practical and logistical problems. The fact that intensive care treatment has long been common clinical practice for patients with severe traumatic brain injury or after cardiac arrest may explain why large and definitive randomised clinical trials of moderate hypothermia have been accomplished in these patient populations, whereas such trials have not even been started in patients with acute ischaemic stroke.

In a recent systematic review and meta-analysis of hypothermia in animal models of acute ischaemic stroke, hypothermia reduced infarct size by more than 40% with temperatures of 34°C or below. However, infarct size was still reduced by 30% (95% confidence interval (CI), 21 to 39%) with cooling to 35°C,[32] suggesting that even very modest cooling has considerable potential as a neuroprotective strategy. Temperature reductions to 35.5°C or 35°C have been shown feasible and safe in awake patients with acute ischaemic stroke by surface cooling, in combination with pethidine (meperidine) to treat shivering.[33] With a similar strategy, body temperature could be reduced to 34.5°C in awake patients with acute myocardial infarction.[34]

1.2.4 Time to Start of Treatment

Based on preclinical studies, time is the most critical factor in the treatment of stroke.[6] A pooled analysis of six randomised trials of intravenous thrombolysis with rt-PA has suggested a potential benefit up to six hours after stroke onset, but the benefit was greater the sooner treatment was started.[35] Expediting the delivery of care should therefore be a crucial factor in any acute stroke trial.

In the above-mentioned meta-analysis of animal studies, the effect of hypothermia was most consistent when treatment was started before or at the onset of ischaemia, but the benefit remained substantial with treatment delays of up to six hours.[32] In the European Hypothermia After Cardiac Arrest Trial, cooling improved functional outcome despite a median interval of eight hours between the restoration of spontaneous circulation and the attainment of the target temperature.[21] There are no data on the maximum time to start of cooling in patients with acute ischaemic stroke. However, it is expected that a potential benefit will be greater the earlier cooling is started.

1.2.5 Reperfusion

On the first day after stroke onset, spontaneous reperfusion occurs in only a minority of the patients.[36,37] Even after intravenous thrombolysis, complete recanalization of an occluded middle cerebral artery (MCA) two hours after start of treatment is found only in up to one third of patients.[38,39] In the first hours after stroke onset, most infarcts will therefore still lack adequate perfusion. In animal models of focal cerebral ischaemia, efficacy was higher in temporary rather than permanent MCA occlusion, but the reduction in the latter was still substantial (37%; 95% CI, 30 to 43%).[32] This suggests that hypothermia may be efficacious irrespective of the occurrence of reperfusion.

1.2.6 Thrombolysis

Together with aspirin, intravenous thrombolysis with rt-PA is the only pharmacological treatment of acute ischaemic stroke of proven benefit. With the exclusion of a small subgroup of patients in the COOLAID-studies, there is no substantial patient data on the combination of hypothermia and thrombolysis. In vitro studies have shown that the fibrinolytic activity of rt-PA is reduced at lower temperatures.[40,41] However, the effect appears to be small: for each degree decrease in temperature the amount of in vitro clot lysis decreased by about 0.5%.[40] Data from animal models are limited. In older studies, hypothermia appeared to have no effect on vessel opening, and to augment the protective effect of rt-PA. However, these results may be confounded by an increase in mortality in animals receiving both rt- PA and hypothermia. Recent experimental data indicate that in comparison to thrombolysis alone, a combination of cooling to 34°C and thrombolysis by rt-PA reduces both infarct size and parameters associated with the disruption of the blood brain barrier. Combination therapy did not change perfusion parameters as measured by perfusion weighted imaging (PWI).[42]

1.2.7 Duration of Hypothermia

Adequate information on the optimal duration of hypothermia in patients with ischaemic stroke is lacking. In the above-mentioned systematic review of hypothermia in animal studies of focal cerebral ischaemia, cooling for more than six hours was slightly less efficacious than cooling for two hours or less.[32] However, as the analyses were not adjusted for potential confounders, this finding should be interpreted with caution. In animal models of focal cerebral ischaemia, the diverse pathophysiological processes which are invoked exert their deleterious effects over different timecourses extending from the first hours to several days after vessel occlusion.[6] Such observations would suggest that hypothermia should be more efficacious if prolonged. In clinical trials of cardiac arrest, hypothermia has been proven efficacious if maintained for 12 or 24 hours.[20,21]

1.2.8 Modes of Hypothermia

Two major methods of inducing hypothermia in stroke patients can be distinguished: surface cooling and endovascular cooling.[18,19,43] Surface cooling methods include convective air blankets, water mattresses, alcohol bathing, and ice packing. These methods have the advantage of being non-invasive, cheaper than endovascular cooling, and are probably applicable on a larger scale as experience with introducing catheters in large veins is not required. Disadvantages include a slower rate of temperature reduction, a more difficult control at the target temperature, and patient discomfort. Endovascular cooling is generally faster and patient comfort may be greater if warming blankets are applied.[44,45] Disadvantages are its invasive nature, its preventing hypothermia concurrent with thrombolysis, and the

required experience with endovascular techniques, thus preventing an easy wide-spread application.

Surface cooling has been shown feasible and appears appropriate for temperature reductions in awake patients to about 35°C if intravenous pethidine is administered to prevent shivering and for patient comfort; [33,34,46] in animal studies pethidine has no impact on the neuroprotective effects of hypothermia.[47] For a more rapid induction of hypothermia, chilled intravenous fluids may be infused at the onset of surface cooling.[48-50]

1.2.9 Temperature Measurements

Common temperature measurements include those in the rectum, bladder, tympanum, oesophagus, or arteries. It is not known which of these reflect temperature in ischaemic brain tissue best. In trials of hypothermia in cardiac arrest, target temperatures were measured in the bladder[20,21] or in the pulmonary artery.[20,21]

2. TRIAL OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

To compare the feasibility, tolerability and safety of surface cooling to 35°C, started within 4.5 hours after the onset of acute ischaemic stroke and maintained for 12 hours with similar strategies aimed at reaching a temperature of 33°C and/or maintaining hypothermia for 24 hours.

2.1.2 Secondary Objectives

To identify which peripheral temperature measurement (oesophageal, tympanic) best reflects temperature in ischaemic brain tissue; to determine the feasibility of collecting serum and DNA samples in a larger trial; and to identify which panel of biomarkers might best be taken forward to that trial.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

- Proportion of patients completing the intervention per protocol.

2.2.2 Secondary Endpoints

- Feasibility (recruitment rate; time to target temperature; stability at target; control of temperature during warming period)
- Tolerability (Columbia Shivering Score; patient questionnaire)
- Safety (deaths; adverse events including infections, DVT or coagulopathy; pethidine dose required)
- Oesophageal temperatures compared with tympanic, and bladder and/or rectal where available, at baseline, every 15 minutes in the first three hours after start of cooling and every 30 minutes thereafter until 48 hours after stroke onset
- Penumbral temperature 3 hours after initiation of cooling
- National Institutes of Health Stroke Scale (NIHSS) score, the Barthel Index (BI)[51] and the modified Rankin scale (mRS) at three months
- Infarct volume on CT or MRI 7 days after the induction of hypothermia[52,53]
- Temperature in ischaemic core, surrounding brain, and contralateral hemisphere determined using MR spectroscopy initiated 2-3 hours after the commencement of cooling
- Feasibility of collecting and processing samples for future biomarker study.

3. TRIAL DESIGN

This is a randomised, open, multi-centre, pilot phase trial for a phase III international clinical trial with masked outcome assessment, comparing the combination of cooling and best medical treatment with best medical treatment alone in patients with acute ischaemic stroke. 24 patients will be recruited in Edinburgh. Other European centres plan to conduct similar pilot studies (involving around 100 patients over 4 centres) and we will align our study protocols to allow pre-planned meta-analysis of feasibility, safety, tolerability and efficacy data. The trial will be approved by appropriate review boards in each participating centre. The University of Edinburgh will act as trial sponsor within the EU.

Outcome measures to assess feasibility, tolerability, and safety include the following:

Feasibility

- Compliance: the proportion of completed interventions (completed = a treatment that is continued until the end of the predefined time period, or earlier in cases where the patient has fully recovered)
- Time to first reaching target oesophageal temperature
- Stability at target temperature (time spent with oesophageal temperature within 0.7°C of target)
- Control of warming (per-protocol rewarming to 36°C taking at least 3 hours 20 minutes (35°C group) or 10 hours (33°C group).

Tolerability

- Columbia Shivering Score (measured every 15 minutes during the cooling and rewarming period)
- Patient questionnaire and interview with trial nurse (performed at 7 days or hospital discharge).

Safety

- Neurological deterioration, defined as an increase of more than 4 points on the NIHSS at day 7 after the induction of hypothermia
- Hypotension, defined as a mean arterial pressure of less than 70mmHg sustained for 10 minutes or more
- Haemorrhagic complications, i.e. symptomatic intracranial haemorrhage or any other haemorrhage requiring blood transfusion
- Infections, i.e. pneumonia, urinary tract infection, and other infections, defined according to the modified Centre for Diseases Control criteria
- Reduction in level of consciousness requiring Intensive Care Unit admission
- Any skin injury or reaction at the cooling site
- Gastrointestinal haemorrhage.

In this trial the primary temperature measurement is oesophageal. This will be monitored continuously and compared with tympanic temperature measurement every 15 minutes during cooling and hourly thereafter until 48 hours after stroke onset; and with penumbral temperature (using MR spectroscopy) at 3 hours after the start of cooling.

Other outcome measures will include the scores on the NIHSS, the Barthel Index (BI)[51] and the modified Rankin scale at three months, and infarct volume on CT or MRI at day 7 [53,54].

4. TRIAL POPULATION

4.1 NUMBER OF PARTICIPANTS

A total of 24 patients will be included in Edinburgh. Patients will be randomised to conventional treatment (8 patients) or to one of the following four surface cooling strategies (4 patients each): (A) 35°C maintained for 12 hours; (B) 33°C maintained for 12 hours; (C) 35°C maintained for 24 hours or (D) 33°C maintained for 24 hours.

4.2 INCLUSION CRITERIA

Patients may be enrolled in the trial if all of the following criteria have been met:

1. A clinical diagnosis of acute ischaemic stroke in accordance with WHO criteria;
2. Arrival at the hospital within 3 hours of symptom onset and a possibility to initiate cooling within 90 minutes of hospital admission. Onset time for patients who awoke with symptoms is defined as the last time the patient was awake without symptoms of stroke;
3. Score on the National Institutes of Health Stroke Scale (NIHSS)[54] ≥ 4;
4. Age ≥ 18 years;

4.3 EXCLUSION CRITERIA

Patients will be excluded from the trial for any of the following reasons:

1. Evidence from a CT or MRI scan or from other pre-randomisation investigations of an intracranial haemorrhage, a tumour, encephalitis, or any diagnosis other than acute ischaemic stroke likely to be the cause of present symptoms. (Mild haemorrhagic transformation of the infarct, defined as petechial haemorrhage, is not an exclusion criterion);
2. Conditions that may be exacerbated by hypothermia, such as haematological dyscrasias, oral anticoagulant treatment with INR >1.5, severe pulmonary disease, severe heart failure (defined as a New York Heart Association (NYHA) score of III or IV), history of myocardial infarction within the previous three months, angina pectoris in the previous three months, severe infection with a leukocyte count >15/ml and a CRP >50mg/dl, or a clinical diagnosis of sepsis;
3. Contraindication to MR scanning;
4. Oxygen saturation below 92% without use of oxygen therapy or below 94% with a maximum of 2 L/min oxygen delivered nasally;
5. Bradycardia (<40 beats/min);
6. Body weight > 120 kg;
7. Pre-stroke score on the modified Rankin Scale (mRS)[55] > 2;
8. Allergy to pethidine, use of a monoamine oxidase inhibitor such as selegiline in the previous 14 days, severe hepatic dysfunction, or severe renal dysfunction;
9. Pregnancy. Women of childbearing potential are excluded unless a negative test for pregnancy has been obtained prior to randomisation;
10. Other serious illness that may confound treatment assessment or increase the risks of cooling;
11. Previous participation in this trial;
12. Social or other conditions that according to the investigators judgement might be a major problem for follow-up.

Note: Treatment with intravenous rt-PA is not an exclusion criterion.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Potential patients will be screened by the receiving stroke team on referral.

5.2 CONSENTING PARTICIPANTS

Informed consent for this trial will be obtained from the patient prior to the performance of any protocol-specific procedure. Assessments or tests described in the protocol which would have been performed as part of the patient's routine clinical evaluation (i.e. not specifically performed for this trial) do not require consent. The patient may withdraw consent at any time.

If potential patients are unable to provide written informed consent or witnessed verbal consent, the patient's relative or welfare guardian can agree to their participation. In this case a consent form needs to be completed. The relative or welfare guardian can withdraw their consent at any time.

If a patient with mental incapacity has been enrolled but then regains mental capacity the team should ensure that the patient is informed about the trial and should confirm that the patient is willing to continue to participate. Where practical the patient should be given the appropriate patient information brochure and sign a consent form.

5.3 SCREENING FOR ELIGIBILITY

Acute stroke referrals in Lothian are triaged through an on call consultant to determine eligibility for thrombolytic treatment with intravenous tPA. The eligibility of these patients for the current trial will be assessed at that time.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

A screening log will collect data on ineligible and non-recruited patients at each centre, with reasons for non-recruitment where these are known.

5.5 RUN IN PERIOD

The protocol requires that randomised patients be transferred for MR scanning three hours after the initiation of cooling. While we expect that this will be feasible, we will first cool 3 non-randomised patients to 35°C in the High Dependency Unit setting so that we may focus on streamlining that part of the trial. These patients will be given a separate patient information leaflet and informed consent form, and these are shown in Appendix 5.

5.6 RANDOMISATION

5.6.1 Randomisation

After written informed consent has been obtained, patients will be randomised to conventional treatment or to one of the following four surface cooling strategies: (A) 35°C maintained for 12 hours; (B) 33°C maintained for 12 hours: (C) 35°C maintained for 24 hours or (D) 33°C maintained for 24 hours, using a length-of-time escalation design (see next paragraph). Randomisation will be stratified for the intention to perform intravenous thrombolysis with rt-PA and for stroke severity (dichotomised between NIHSS scores of 13 and 14). The choice to perform intravenous thrombolysis is left at the discretion of the local investigator. Allocation to treatment will be through a web-based randomisation service hosted at the University of Edinburgh. Each active treatment arm will consist of 4 patients and the control group of 8 patients.

5.6.2 Treatment Allocation

All patients will be managed in the High Dependency Unit at the Western General Hospital. Because of the potential discomfort of prolonged cooling to low temperatures, and the learning required efficiently to deliver cooling to awake patients, we will randomise in blocks of 12, each block including 4 patients allocated to standard care. The first 12 patients will be randomised 1:1:1 to 35°C for 12 hours; 33°C for 12 hours; or standard care (Groups A and B). Patients 13-24 will be randomised 1:1:1 to 35°C for 24 hours; 33°C for 24 hours; or standard care (Groups C and D).

In all patients randomised to hypothermia, cooling will be started within 4.5 hours after the onset of symptoms and within 90 minutes of hospital admission by means of intravenous infusion of 25ml/kg refrigerated normal saline (4°C) over 30 minutes.

In patients randomised to hypothermia, surface cooling will be applied to the thighs and chest immediately after the start of the saline infusion using five Arctic Sun Energy Transfer Pads, connected to an Arctic Sun temperature control module with integrated chiller (Medivance, Inc). Inlet water temperature will be automatically controlled to achieve a target oesophageal temperature of 35°C or 33°C.

Start of treatment will be defined as the start of cooling, i.e. start of infusion of refrigerated saline. Active cooling will be continued for 12 or 24 hours. Thereafter, patients will be passively warmed at a rate controlled by the cooling device to be at most 0.3ºC per hour until the oesophageal temperature is 36°C; the cooling device will then be disconnected.

Oesophageal temperature will be measured with probes providing feedback to the Arctic Sun. In addition to the continuous oesophageal recordings, tympanic temperature will be recorded before cooling is started and subsequently at 15-minute intervals with a standard tympanic thermometer. Where other temperature measurements are made as part of standard care, these data will also be recorded. Level of consciousness, presence or absence of shivering, blood pressure and heart rate will be recorded every 15 min for the whole cooling and warming phase.

To prevent shivering and discomfort in patients randomised to hypothermia, a protocol similar to that used in ICTuS-L will be applied.[27] However, pethidine starting doses will be lower because of higher target temperatures in the current trial than in ICTuS-L. Patients randomised to hypothermia will receive a loading dose of pethidine 0.5 mg/kg intravenously over 5 minutes, followed by a pethidine dose of 0.25 mg/kg/h intravenously, which may be adjusted over time on the basis of a published four point shivering scale.[27] If shivering does occur, the patient will be given a bolus of 10 to 25 mg pethidine intravenously, followed by an increase in the continuous infusion of 5 mg/h. If at any time significant sedation begins to develop, the pethidine maintenance dose will be lowered. To mitigate any possible narcotic-related emesis, the patient is fasted, and a nasogastric tube is inserted and attached to continuous low wall-suction. In addition, patients randomised to hypothermia will wear gloves and socks to reduce the sensation of cold.

5.6.3 Control Group and Concurrent Treatments

Except for additional treatment during the cooling period, all patients will be treated according to published guidelines for the treatment of acute ischaemic stroke[11,43] and for secondary prevention.[56] Participation in the trial will therefore not preclude early start of oral acetyl salicylic acid or other treatments. However, patients allocated to cooling will not be able to equally participate in early mobilization exercise during the period of active cooling.

5.6.4 Premature Withdrawal

Participation in any research trial is voluntary and therefore the participant or their relative or welfare guardian 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 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 from the intervention – 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 (normal care).

If the patient wishes to withdraw from the trial or their relative or welfare guardian 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. If however the patient is withdrawn from the trial 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. DATA COLLECTION

All patient data will be recorded in the case record file by the local investigator assisted by a trial co-ordinator. Safety and other data from all European pilot studies will be collated in Edinburgh by the Chief Investigator assisted by a trial co-ordinator and a statistician. The following data will be collected:

6.0.1 Baseline

1. Date of birth, sex, date and time of stroke onset
2. Medical history and vascular risk factors
3. Oesophageal, tympanic, and rectal and bladder temperatures where available, blood pressure, and heart rate
4. Pre-stroke scores on the mRS and BI
5. NIHSS
6. Laboratory tests, including full blood count, serum glucose, electrolytes, PTT, aPTT, and C-reactive protein
7. Blood samples for analysis of biomarkers of brain injury and for genetic studies
8. 12-lead electrocardiogram
9. CT or MRI scan of the brain, depending on local preference

6.0.2 2-3 hours after randomisation

1. MRI with structural imaging, diffusion imaging and MR spectroscopy with measurement of brain temperature.

6.0.3 Randomisation Through to Day 7 (± 1 day; or discharge, if earlier)

1. Date and time of randomisation
2. Date and time of start of cooling
3. Level of consciousness, presence of shivering, rectal, bladder, and tympanic temperatures, blood pressure, and heart rate every 15 minutes in the first three hours after start of cooling, every 30 minutes thereafter until 12 hours after start of warming, and every 6 hours until day 7 (or discharge, if earlier)
4. Laboratory tests, including full blood count, serum glucose, electrolytes, PTT, aPTT, C-reactive protein, blood samples for biomarker and genetic studies. 12-lead electrocardiogram 6 and 12 hours after randomisation, and at 48 hours
5. NIHSS at 24 and 48 hours and at 7 days (or discharge, if earlier)
6. mRS and BI at day 7 (or discharge, if earlier)
7. Concurrent medication
8. Neurological and systemic adverse events
9. CT or MRI scan at day 7 ± 2 days

6.0.4 1 Month and 3 Months (± 14 days)

Scores on the mRS, BI and NIHSS. To promote objective outcome assessment, a trial nurse will perform a standardised evaluation of each patient, including functional status, and will include the obtained information in an essay. Based on this essay, the members of the trial

steering committee who are blinded to treatment allocation, will determine the scores on the mRS and BI.

Serious adverse events (definition: see 8.1) during the trial period 7 days (or discharge, if earlier) through 3 months.

7. STATISTICS AND DATA ANALYSIS

7.1 SAMPLE SIZE CALCULATION

This is a pilot phase trial of the safety, feasibility and tolerability of a physical intervention. Cooling of 16 patients will allow us to establish whether these target temperatures are feasible; whether further measures are required to increase the tolerability of the treatment. Comparison with the outcome in 8 untreated patients will allow us to make broad inferences about safety. Combining these data with those from other centres will give us better estimates of safety and will inform the design of and sample size calculations for a large-scale clinical trial.

7.2 PROPOSED ANALYSES

As this is a pilot phase, we are as interested in whether the treatment can work in theory as whether it will work in practice. We will therefore perform both intention-to-treat and per-protocol analyses, and examine non-compliance to see whether compliance can be improved in the main trial. Statistical analyses will primarily be descriptive, as this is an exploratory study. Continuous outcomes will be presented using means and 95% confidence intervals. Binary outcomes will be presented as proportions with 95% confidence intervals.

If there are no clear problems with the tolerability, feasibility, and safety of cooling to 33°C or of 24 hours cooling, the potentially greater efficacy of cooling to 33°C rather than 35°C and 24 hours rather than 12 hours cooling is likely to lead to consideration of surface cooling to 33°C for 24 hours as the optimum intervention for a phase III trial. However, if there are concerns about tolerability feasibility, and safety of cooling to 33°C and/or of 24 hours cooling, a target temperature of 35°C and/or duration of 12 hours might be selected.

8. ADVERSE EVENTS

8.0.1 Safety

In non-randomised case series of patients with acute ischaemic stroke who were intubated and mechanically ventilated for cooling to 32°C or 33°C, pneumonia, arrhythmias, arterial hypotension, and thrombocytopenia were frequent complications.[57-60] However, some of these complications may be attributed to the infarcts under trial, which were generally severe. In randomised trials of cooling to 32°C to 34ºC after cardiac arrest, no differences in adverse effects were observed between the hypothermia and control groups.[20,21] In a case-control trial of cooling to 35.5°C involving 17 patients, a mild decrease in blood pressure and heart rate were observed during hypothermia, as well as mild increases in haematocrit and the concentrations of haemoglobin, potassium, creatinin, albumin, and C-reactive protein. No serious adverse events were observed.[33]

Reported side effects of pethidine include nausea, vomiting, constipation, drowsiness, and confusion. At higher doses, respiratory depression, arterial hypotension, and reduced level of consciousness have been reported.

8.0.2 Adverse Event Reporting

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Participants or their relative or welfare guardian will be instructed to contact their hospital doctor at any time after consenting to join the trial if any unexpected symptoms develop. All adverse events (AEs) that occur after joining the trial will be reported in detail in the CRF. In the case of an AE, the hospital doctor will initiate the appropriate treatment according to their medical judgment. Participants with AEs present at the last visit will be followed up until resolution of the event.

8.1 DEFINITIONS

An adverse event (AE) is any untoward medical occurrence in a clinical trial subject.

A serious adverse event (SAE) is defined by the National Research Ethics Service in the UK 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 anomaly or birth defect.

8.2 DETECTING AND RECORDING AEs AND SAEs

All AEs and SAEs will be recorded from the time a participant consents to join the trial until the last trial visit. When an AE/SAE occurs, the Investigator will review all documentation (e.g. hospital notes) related to the event. The Investigator will then record all relevant information in the CRF and on the SAE form (if the AE meets the criteria of serious).

8.3 EVALUATION OF AEs AND 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

8.3.1 Assessment of Severity

The Investigator should make an assessment of severity for each AE/SAE and record this on the CRF according to one of the following categories:

Mild an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe an event that prevents normal everyday activities.

Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

8.4 REPORTING OF SAEs

As soon as the investigator becomes aware that an SAE has occurred in a trial 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 0131 242 9447.

8.5 FOLLOW UP PROCEDURES

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

AEs still present in participants at the last trial visit should be monitored until resolution of the event or until no longer medically indicated.

9. PREGNANCY

Pregnancy. Women of childbearing potential are excluded unless a negative test for pregnancy has been obtained prior to randomisation.

10. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

10.1 PROJECT MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grantholders, Chief Investigator and a Trial Co-ordinator. Coordination of the trial across European centres will be through the European Stroke Research Network for Hypothermia (ESRNH), who will appoint an International Trial Steering Committee.

10.2 TRIAL MANAGEMENT

A Trial Co-ordinator will oversee the trial and will be accountable to the Chief Investigator. The Trial Co-ordinator will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Chief Investigator or delegated member of the trial team.

A Delegation Log will be prepared, detailing the responsibilities of each member of staff working on the trial.

10.3 CENTRAL TRIAL OFFICE

The Central Trial Office is based in the University of Edinburgh. The office will be responsible for randomisation, collection of data, data processing and analysis.

Publication and dissemination of the trial results will be coordinated by ESRNH in collaboration with the Chief Investigator and Investigators.

10.4 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The names or the TSC members and their roles are detailed in Appendix 1.

10.5 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of subjects in the trial. The DMC will oversee the pilot studies in all centres, not just in Edinburgh. The names of the DMC members are detailed in Appendix 2.

10.6 INSPECTION OF RECORDS

Principal Investigators and institutions involved in the trial 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 trial records and source documentation.

11. GOOD CLINICAL PRACTICE MODULE

11.1 ETHICAL CONDUCT OF THE TRIAL

The trial will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

A favourable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the trial.

11.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the trial at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of trial site staff. Delegated tasks will be documented on a Delegation Log and signed by all those named on the list.

11.2.1 Informed Consent

Written informed consent for this trial must be obtained from the patient or their nearest relative or welfare guardian (if the patient is not capable of giving consent) prior to the performance of any protocol-specific procedure. However, several assessments or tests described in the protocol may have been performed as part of the patient's routine clinical evaluation (i.e. not specifically performed for this trial). A copy of the written informed consent must be given to the subject, their family doctor and a copy held in the trial patient file.

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant, or their relative or welfare guardian, to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants will receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant should be performed by the Investigator or designated person, and must cover all the elements specified in the participant Information Sheet/Informed Consent.

The participant will be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant will be given sufficient time to consider the information provided. Because of the short time window for trial inclusion and treatment, this will be in the order of 10 to 15 minutes. It will be emphasised to the participant or their relative or welfare guardian that they may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

11.2.2 Trial Site Staff

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

11.2.3 Data Recording

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

11.2.4 Investigator Documentation

The Trial Office will ensure all other documents required by the principles of ICH GCP are retained in a Trial Master File and that appropriate documentation is available in a local Investigator Site File.

11.2.5 GCP Training

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

11.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written

permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, or the REC. The Investigator and trial site staff involved with this trial will not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

11.2.7 Data Protection

All UK Investigators and trial site staff involved with this trial will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians treating the participants.

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 participants.

12. TRIAL CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS

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

12.2 PROTOCOL VIOLATIONS AND DEVIATIONS

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

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

12.3 TRIAL RECORD RETENTION

All trial documentation will be kept for 15 years.

12.4 END OF TRIAL

The end of trial is defined as the last participant's last assessment.

The Investigators and/or the Trial Steering Committee have the right at any time to terminate the trial for clinical or administrative reasons.

The end of the trial will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the trial is terminated prematurely. The Investigators will inform participants and ensure that the appropriate follow up is arranged according to this protocol for all involved.

A summary report of the trial will be provided to the REC and Regulatory Authority within one year of the end of the trial.

13. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

Reporting of trial progress to the relevant regulatory authorities is the responsibility of the Chief Investigator. Publications are the responsibility of the Chief Investigator.

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this trial resides with the trial team. On completion of the trial, the trial data will be analysed and tabulated, and a clinical trial report will be prepared in accordance with the principles of ICH guidelines.

13.2 PUBLICATION

The trial results will be published by the members of the Executive Committee. Additional analyses and substudies may be approved by the Steering Committee, and may also be published on behalf of all participating investigators.

Before submission of any manuscript all investigators will have the opportunity to comment on the manuscript.

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

Summaries of results will also be made available to Investigators for dissemination within their clinical workplace (where appropriate and according to their discretion).

13.3 PEER REVIEW

This application has undergone peer review by Chest Heart and Stroke Scotland as part of their grant awarding process.

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APPENDIX 1: TRIAL STEERING COMMITTEE

Member	**Role**
Dr Malcolm Macleod	Stroke Neurologist (Chair)
Prof Peter Andrews	Honorary Professor Department of Anaesthetics, Critical Care and Pain Medicine and Critical Care Consultant
Prof Martin Dennis	Professor of Stroke Medicine
Prof Peter Sandercock	Professor of Medical Neurology
Prof Joanna Wardlaw	Professor and Honorary Consultant Neuroradiologist
Prof. Ian Marshall	Head of Medical Physics and Medical Engineering
Dr H Bart van der Worp (Utrecht)	Stroke Neurologist

APPENDIX 2: DATA MONITORING COMMITTEE

Prof Philip Bath, Nottingham (Chair)

OTHERS (to be confirmed)

APPENDIX 3: INFORMATION LEAFLETS

APPENDIX 4: CONSENT FORMS

APPENDIX 5: RUN IN PERIOD INFORMATION LEAFLET AND CONSENT FORM