HypOthermia for Patients requiring Evacuation of Subdural Hematoma: a Multicenter, Randomized Clinical Trial
"The HOPES Trial"

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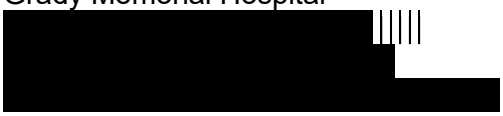

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SYNOPSIS

Study Title

HypOthermia for Patients requiring Evacuation of Subdural Hematoma:
a Multicenter, Randomized Clinical Trial ("The HOPES Trial")

Primary Objective

The objective is to test whether hypothermia improves outcome following TBI with subdural hematoma requiring evacuation. The primary objective is to determine if rapid induction of hypothermia prior to emergent craniotomy for traumatic subdural hematoma (SDH) will improve outcome as measured by Glasgow Outcome Scale-Extended (GOSE) at 6 months.

Secondary Objectives

Safety Objective: To demonstrate the safety of intravascular cooling in the management of acute traumatic SDH.

Exploratory Objective: To determine the effect of hypothermia on TBI biomarkers: glial fibrillary acid protein (GFAP) and ubiquitin C-terminal hydrolase (UCH-L1).

Mechanistic Objective: To determine if therapeutic hypothermia to 33°C for 48 hours reduces the incidence of cortical spreading depolarization in patients with acute traumatic SDH.

Design and Outcomes

This is a prospective, pragmatic, randomized, controlled, multi-center trial of the safety and efficacy of intravascular cooling to induce hypothermia in TBI patients prior to and after surgical evacuation of traumatic SDH. **The hypothesis** of the study is that early induction and maintenance of therapeutic hypothermia in patients with TBI undergoing hematoma evacuation will improve global neurologic outcome as measured by GOSE at 6 months. Patients with moderate to severe acute TBI with SDH who require emergent craniotomy will be enrolled into this study. Patients will be randomized into two groups: 1) intervention - rapid induction of hypothermia to 35°C followed by maintenance at 33°C or 2) standard care - normothermia (37°C). All patients will have an intravascular temperature management catheter inserted into the femoral vein.

The trial is aimed for N=120 subjects, but allows an extension up to a maximum of up to 350 patients. The design includes multiple interim looks at the data, after 60, 120, 180, 240, and 300 patients randomized. At each interim, Bayesian predictive probabilities will be used to determine if enrollment should stop before the maximum, either due to futility or expected success.

Patients may have a 6-lead platinum strip electrode placed on the surface of the brain at the time of craniotomy and hematoma evacuation with subsequent monitoring for cortical spreading depression for up to 7 days following injury. The relative incidence of cortical spreading depression in patients treated with hypothermia will be compared against patients treated with normothermia.

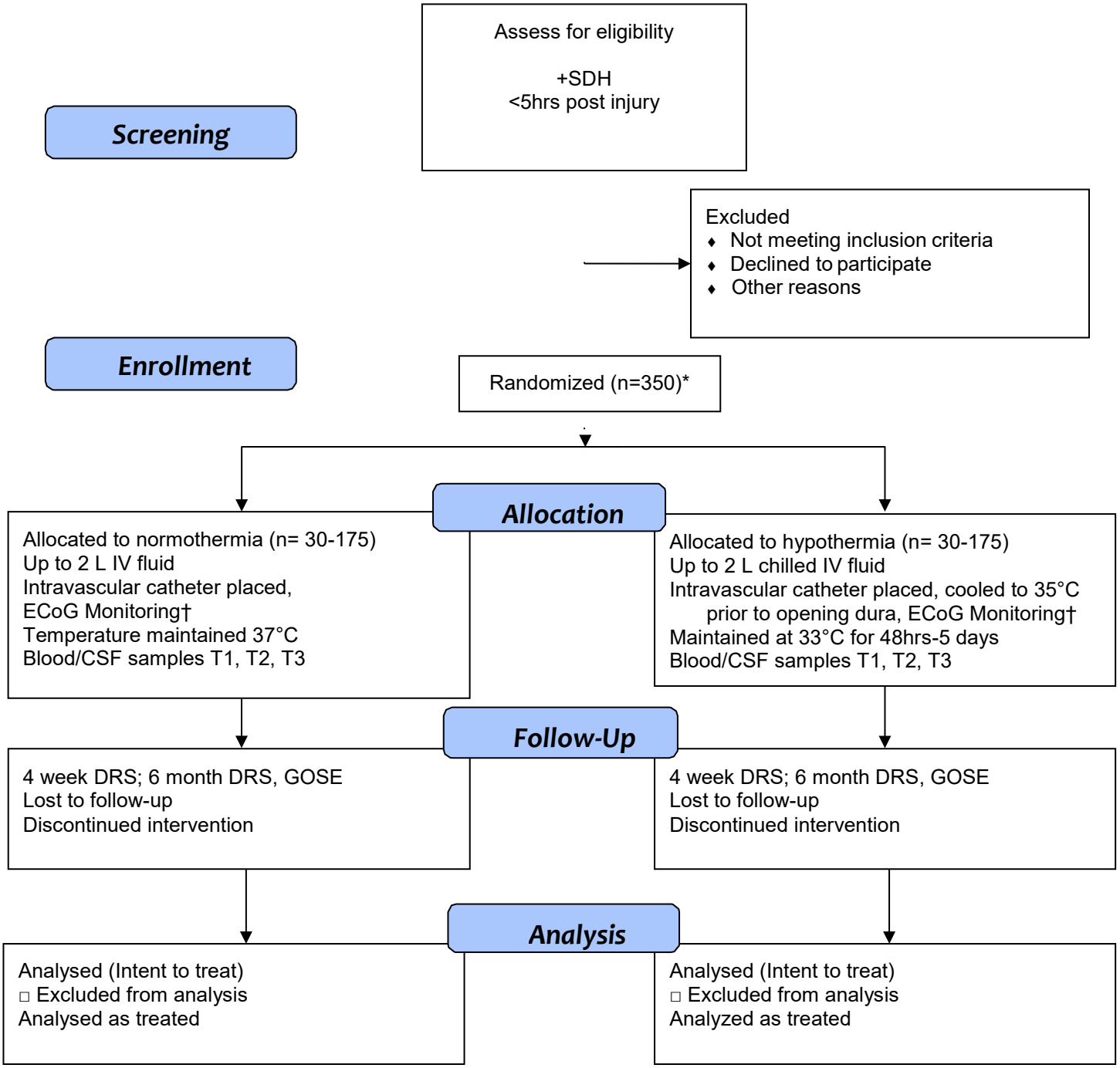
Patients will undergo neuropsychological assessment of their level of recovery at 4 weeks and 6 months post-injury. These outcomes assessments will be performed by investigators who are unaware of the treatment group assignment. GOSE (dichotomous: Good recovery and moderate disability will be designated as favorable outcomes; severe disability, vegetative state,

and death as poor outcomes) at 6 months post-injury will be the primary outcome. Disability Rating Scale (DRS) at 4 weeks will be used to impute missing GOS/GOSE scores and will be incorporated into the Bayesian monitoring model.

Patients will have blood and CSF (when available) samples taken at 3 time points [T1, within 6 hrs and as close to time of injury as possible (pre-hypothermia for the treatment arm); T2, post-surgical evacuation of hematoma (7-48 hrs); and T3, 5-14 days post-injury or discharge (DC)], whichever comes first.

Study Schematic

Study Schematic



*Enrollment is intended for N=120 subjects but allows for an extension to a maximum sample size of 350;enrollment may stop after 60, 120, 180, 240, or 300 subjects enrolled, as determined by the results of the interim analyses.
†ECoG Monitoring will be performed at approved centers only.

Interventions and Duration

Patients will be evaluated for enrollment criteria and once confirmed, randomized to standard care (normothermia) or hypothermia. Hypothermia will be initiated immediately after enrollment criteria are confirmed with up to 2 liters of chilled IV fluids. Normothermia patients will receive up to 2 liters of room temperature IV fluids. Intravascular temperature control utilizing the ZOLL CoolGard 3000 or Thermogard XP and femoral catheter ICY or Quattro will be used to induce and maintain normothermia or hypothermia. Normothermia patients will be maintained at 37°C ±0.5°C. Hypothermia patients will be cooled to a temperature of 35°C prior to opening the dura and maintained at a temperature of 33°C±0.5°C. They will remain cooled for at least 48 hours. Cooling may last for up to 5 days in patients who are refractory to re-warming (e.g., intracranial pressure elevates). Re-warming will be controlled at 0.25°C per hour. The intravascular cooling catheter will remain in place for the planned 48 hour cooling and 16-24 hour re-warming periods. However, once the goal temperature (33°C) has been met if for any reason the femoral cooling catheter needs to be removed or if the subject requires extended cooling, a subclavian cooling catheter may be placed or external cooling pads (Arctic Sun) may be used.

Sample Size and Population

We plan to enroll patients among the clinical sites into two study groups:

1. Patients who undergo emergent craniotomy and evacuation of acute subdural hematoma within 6 hours of injury treated with **hypothermia** (intervention).
2. Patients who undergo emergent craniotomy and evacuation of acute subdural hematoma within 6 hours of injury treated at **normothermia** (standard care).

Only TBI patients who are not following commands and who require emergent surgical evacuation of an acute subdural hematoma will be enrolled in this study. To reduce the likelihood of imbalance of important prognostic factors between centers, a blocked randomization scheme will be used in this study. Randomization will be divided among the centers by the Biostatistics Center of Berry Consultants.

A randomized design will be used in this study. The trial is intended for N=120 subjects but may extend to a maximum of 350 patients will be randomized equally at a 1:1 ratio to each of two arms (hypothermia versus control). The final analysis will use a one-sided Fisher's exact test with a significance level of 0.02 to compare proportions of patients with good outcome as measured by GOSE at 6 months between two treatment arms. Interim analyses will be performed after 60, 120, 180 240, or 300 patients randomized. The significance level of 0.02 accounts for the multiple interim looks to maintain overall type I error below 0.025. At each interim analysis, we will evaluate the predictive probability of statistical significance with the current sample size and with the maximum sample size. If the predictive probability of statistical significance with the current sample size is sufficiently high, then enrollment will stop and follow up will continue for 6 months. If the predictive probability of statistical significance with 350 patients is sufficiently low, then the study will stop for futility. Otherwise, enrollment will continue to the next analysis. Complete details may be found in Section 9. Operating characteristics of the design, such as power, type I error rate, and average sample size, were assessed by simulation and are described in Section 9.

HypOthermia for Patients requiring Evacuation of Subdural Hematoma: a Multicenter, Randomized Clinical Trial

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1. STUDY OBJECTIVES

1.1 Primary Objective

The primary objective is to determine if rapid induction of hypothermia prior to emergent craniotomy for traumatic subdural hematomas (SDH) will improve outcomes as measured by Glasgow Outcome Scale-Extended (GOSE) at 6 months. Treatment with hypothermia will lead to at least a 15% improvement in good outcomes. The primary outcome measure will be a dichotomized GOSE at 6 months.

1.2 Secondary Objectives

There are four secondary objectives of the study:

Safety Objective: To demonstrate the safety of intravascular cooling in the management of acute traumatic SDH.

Exploratory Objective: To determine the effect of hypothermia on TBI biomarkers: glial fibrillary acid protein (GFAP) and ubiquitin C-terminal hydrolase (UCH-L1).

Mechanistic Objective: To determine if the incidence of cortical spreading depolarization is reduced in patients undergoing therapeutic hypothermia compared to patient undergoing normothermia.

Impact on Resource Utilization Objective: To determine the effect of moderate hypothermia on ICU length of stay (LOS) and hospital LOS.

2. BACKGROUND

2.1 Rationale

Nearly 2 million Americans sustain a TBI annually and of these over 50,000 die and 90,000 remain permanently disabled(1). Brain damage as a result of TBI is caused both by the primary injury, and by a number of secondary pathological processes that occur as a result of the initial trauma(2). While there is presently no cure for the primary injury, there is ongoing work to develop neuroprotective treatments to prevent secondary injury. Early hypothermia is one modality shown to be neuroprotective in ischemia-reperfusion injuries such as in animal TBI models(3;4) after cardiac arrest (5-7) and in infants with moderate or severe hypoxic-ischemic encephalopathy(8). However, while clinical trials show that hypothermia can lower intracranial pressure, results of the effect of hypothermia on outcome have been inconclusive, in part because of mixed injury types, inexperience of centers in the use of hypothermia, initiation and period of cooling, and duration of rewarming (9;10).

Retrospective subgroup analysis of NABIS:H I (11) and NABIS:H II (12) hypothermia trials revealed that TBI patients treated with hypothermia undergoing surgical evacuation of

intracranial hematomas had significantly improved neurologic outcomes compared to patients treated with normothermia(13). We propose to perform a randomized trial to prospectively study the effect of very early cooling in patients undergoing surgical evacuation of acute subdural hematomas (35°C prior to opening the dura followed by maintenance at 33°C for a minimum of 48h). In the previous trials, hypothermia was induced via surface cooling, a strategy that carries significant challenges when treating patients with emergent neurosurgical conditions requiring surgery. In the trial proposed herein, hypothermia will be induced with intravascular cooling catheters, which, if successful, would greatly increase the generalizability of the treatment. Additionally, intravascular catheters will be employed to maintain normothermia as it is established that fever is detrimental to TBI patients(14-16). Furthermore, intravascular temperature management combines effective temperature control with central venous access and has been shown to effectively reach the target temperature rapidly and safely(17-21). Moreover, intravascular cooling has been shown to be efficient at quickly lowering body temperature and maintaining it with a lower variation of target temperature than surface cooling(17) . The proposed trial will employ several novel features that represent a major leap forward in clinical trial design and execution in traumatic brain injury. These innovative features include:

1. The trial will involve patients with TBI who all have similar **injury morphology and pathophysiology**. Previous clinical trials in TBI have employed the Glasgow Coma Scale score as the principal inclusion criterion and ignored the fact that TBI is a spectrum of heterogeneous pathophysiologies that may not all respond to a single treatment. Only patients with subdural hematomas requiring surgical evacuation will be included in this proposed study.
2. The trial will be conducted in **centers** that have sufficient volume to ensure swift trial completion, a strong track record of collaboration in multi-center clinical trials in TBI, and all are experienced in utilizing hypothermia. This will reduce cost, accommodate uniformity of study interventions, and reduce the effect of inter-center variance on trial statistics.
3. The trial will employ both **exception from informed consent (EFIC)** from the start of the trial and written informed consent per institutional and state requirements. EFIC will significantly reduce barriers to patient recruitment and help ensure timely completion of the trial. Houston and Pittsburgh have a documented track record in obtaining community and ethical approval for EFIC and both centers successfully employed EFIC in the most recent hypothermia trial. A plan to address EFIC requirements is attached.
4. The trial will assess whether **cortical spreading depression** is a mechanistic target in this TBI patient population. Previous studies, relying heavily on data from Pittsburgh and Miami, have documented that 55% of patients undergoing emergent craniotomy for traumatic intracranial hematomas develop cortical spreading depression. Further work has demonstrated that the occurrence of cortical spreading depression increases as body temperature increases (22). This trial will represent the first attempt to assess the impact of a therapeutic intervention (hypothermia) on cortical spreading depression. Cortical spreading depression will be monitored in IRB approved centers only.
5. The trial will assess if hypothermia will decrease the levels of **markers** for brain injury. We will also determine whether 4-6week DRS is an accurate predictor of 6-month GOSE outcomes, and thus a substitute endpoint.

2.2 Supporting Data

Because of differences of trial design and broad entry criteria, the results of 23 clinical trials of hypothermia treatment involving 1614 patients with severe traumatic brain injury (TBI) have been inconsistent(23). While the two U.S. prospective randomized clinical trials of hypothermia in TBI [The National Acute Brain Injury Study: Hypothermia, NABIS:H I (11) and, NABIS:H II(12)] failed to confirm the utility of hypothermia as a primary neuroprotectant for all TBI patients, retrospective subgroup analyses of both of these trials revealed that in the subgroup of patients who underwent surgical evacuation of intracranial hematomas, patients treated with hypothermia had better neurological outcomes than patients treated with normothermia. It makes far more intuitive sense that hypothermia would be beneficial to the specific subset of TBI patients with ischemia-reperfusion injury than to the global, extremely heterogeneous population of severe TBI patients as a whole. Reperfusion after evacuation of intracranial hematomas likely leads to excessive free radical production, release of inflammatory molecules and excitotoxicity leading to cell death. To date, no trial to investigate specifically the effect of hypothermia on patients undergoing surgical evacuation of intracranial hematomas has been performed.

In October 2007, a workshop convened by the NINDS and co-sponsored by several other national brain injury organizations concluded that future TBI trials should use targeted pathoanatomic injury type as an initial diagnostic entry criteria(24). Furthermore, the workshop stressed the need for establishing pathophysiologic mechanisms relevant to specific pathoanatomic types of TBI and verifying that a given therapeutic approach improves outcome in these targeted TBI types(24).

In 2009, the COSBID group demonstrated that patients who underwent craniotomy for TBI were at a 3-fold higher risk for cortical depolarization phenomena when they were hyperthermic (>38.4°C) as opposed to normothermic (≤38.4°C)(25). Recently, the same group has collected data that suggest that depolarizations are a causal pathomechanism with adverse effects on the traumatically injured brain(26). Taken together, these data suggest that therapeutic hypothermia may decrease the frequency of cortical depolarizations and thus improve outcomes.

As recommended by the 2007 NINDS TBI workshop, our proposed study would be the first TBI trial to use a specific pathoanatomic injury as opposed to the Glasgow Coma Scale (GCS) as the principal inclusion criterion. Additionally, it would be the first trial to study the efficacy and safety of hypothermia induction using intravascular cooling catheters. In previous trials, hypothermia was induced via surface cooling, a technique that is associated with both significant temperature variability as well as challenges for temperature control in TBI patients requiring emergent neurosurgical operations. Demonstration of safety and efficacy of hypothermia induction with intravascular cooling catheters would increase the generalizability of hypothermia as an intervention. Finally, our study could both confirm the NABIS:H I and NABIS:H II data regarding the benefit of hypothermia for TBI patients who undergo surgical evacuation of intracranial hematomas and potentially provide a mechanism to explain this phenomenon.

Significant morbidity and mortality occurs in traumatic SDH. Mortality rate estimates range from 40-70% of surgical SDH patients(27;28). SDH patients may experience elevated intracranial pressure (ICP), seizures, coagulopathy and hypotension(29-33). SDH patients enrolled in this study are expected to require mechanical ventilation and monitoring of intracranial pressure as part of their routine care(28). Risks associated with hypothermia may include shivering, hypovolemia, electrolyte disorders, hyperglycemia, pneumonia, (small risk of skin lesions if water-circulating surface cooling pads are used), and some risk of catheter-related thrombosis

or possible catheter-related infection with intravascular cooling devices. Risks are minimized by reaching the goal temperature as quickly as possible, rewarming slowly and removing the intravascular catheter within 5 days of placement(33).

Exploratory analysis is to assess if therapeutic hypothermia will decrease blood/CSF levels of two TBI biomarkers. Two markers (GFAP and UCH-L1) will be interrogated. GFAP is a monomeric intermediate filament protein expressed by astrocytes that is released after TBI(34;35). Elevated serum GFAP level following severe TBI is predictive of poorer outcome and has shown to be correlated with intracranial pressure (ICP), mean arterial pressure (MAP), cerebral perfusion pressure (CPP), Glasgow Outcome Score (GOS) and mortality. GFAP serum concentrations above a cut-off level of 1.5 µg/L were predictive of death or poor outcome (GOS at 6 months) with 85% sensitivity and 52% specificity, and 80% sensitivity and 59% specificity, respectively(35). UCH-L1 is a 24kDa protein thought to be involved with the removal of oxidized or misfolded proteins(36). It has been associated with neurodegenerative diseases and brain ischemia(37). UCH-L1 has been detected in both CSF and serum within 6 hours of injury, it has distinguished injury severity and predicted death(37;38).

3. STUDY DESIGN

This is a randomized clinical trial of patients with acute traumatic subdural hematomas who are not following commands and who require emergent craniotomy within 6 hours of injury. Patients meeting enrollment criteria will be randomized to hypothermia or normothermia as soon as the decision to perform emergent craniotomy is made by the attending neurosurgeon. Patients will undergo insertion of a femoral intravascular temperature management catheter. Patients randomized to hypothermia will be rapidly cooled to 35°C before removal of the subdural hematoma and then maintained at 33°C±0.5°C for a minimum of 48 hours. Patients randomized to normothermia will be maintained at 37°C±0.5°C. Neurologic outcome will be assessed in all subjects at 4-6 weeks and 6 months+/-3 weeks post-injury using the GOSE and DRS.

Multiple interim analyses will be performed to determine whether enrollment may stop for futility or expected success before the maximum sample size is reached. In the interim analysis, we will model the relationship between the short-term response (4-week DRS) and the long-term response (6-month GOSE) in order to impute final outcomes for those patients with only short-term data. Decisions to stop or continue enrollment will be based on Bayesian predictive probabilities of study success.

4. SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

1. Non-penetrating traumatic brain injury
2. GCS motor score ≤5 (not following commands)
3. Estimated or known age 22-65 years
4. Acute subdural hematoma requiring emergent craniotomy within 6 hours of initial injury
5. Estimated time of injury to time to reach temp of 35°C<6 hrs

4.2 Exclusion Criteria

1. Total GCS = 3 and bilateral fixed and dilated pupils
2. Following commands after an initial period of coma (GSC motor score of 6)
3. Known pre-existing neurological deficit (e.g., previous TBI, stroke)
4. Concomitant signs/symptoms of spinal cord injury (i.e., priapism, no spontaneous movement off of paralytics/sedation, no rectal tone, incontinent of stool, obvious presence of injury on imaging.)
5. Arrival temperature is <35°C
6. Hemodynamic instability (i.e., MAP<60mmHg for 30 minutes)
7. Active cardiac dysrhythmia resulting in hemodynamic instability
8. Pregnancy
9. Duret hemorrhage
10. Prisoner or Ward of the State
11. Known history of clotting disorder (e.g., heparin induced thrombocytopenia, PE/DVT)
12. Injury to other body organ where hypothermia would be precluded because of bleeding risk (e.g., grade 3 liver laceration; bowel laceration; flail lung or INR>1.4)
13. Inability to obtain informed consent or utilize exception to informed consent for emergency research.

4.3 Study Enrollment Procedures

***4.3.1 Identifying and Recruiting Candidates*.** Potential subjects for this trial will be recruited from all patients with a TBI presenting within 5 hours of injury to one of the participating trial centers. The therapeutic window of reaching 35°C within 6 hours of injury and before the dura is cut was selected based on evidence from previous studies in which patients with intracranial hematoma requiring evacuation reaching 35°C early post-injury had fewer experiencing poor outcomes compared to those who were treated with normothermia or late hypothermia (41% vs. 62% poor outcome, p<0.009)(13). In these multicenter, randomized controlled NABIS:H I and NABIS:H II trials surgery commenced within 3.1+/-3.6hrs and 3.9+/-4.3hrs of admission respectively. Analysis showed the goal of reaching 35°C prior to hematoma evacuation appears to be neuroprotective, reducing the biochemical cascade associated with reperfusion. Therefore the HOPES trial aims to achieve early cooling prior to surgery, without causing a delay in care. Each clinical site is staffed by trained research personnel capable of performing screening procedures for each potential subject according to the inclusion/exclusion criteria described above as well as clinicians skilled in the placement and management of intravascular cooling catheters. Acute subdural hematoma will be diagnosed by standard imaging used at enrolling centers. Decision regarding the need for emergent craniotomy is left to the opinion of the treating neurosurgeon.

4.3.2 Screen Failure Logs. A log of all screen failures will be maintained at each site. The information collected on the screen failure log will include basic demographic information as well as the reason for excluding the patient from randomization. The Screen Failure Log allows for the assessment of any selection bias in the enrollment of patients(39).

4.3.3 Informed Consent Procedures. Upon confirmation of a patient's eligibility for the trial, consent is obtained by either the clinical site PI or by the designated, trained research team

member whom the clinical site PI has delegated authority to obtain informed consent. The delegation of authority must be documented and a current copy of this document must be maintained at the clinical site. As with all delegated clinical trial responsibilities, it is the responsibility of each site PI to ensure that the delegation is made only to those individuals who are qualified and that there is adherence to all applicable regulatory requirements and Good Clinical Practices (GCP) Guidelines. Additionally, it is the investigator's responsibility to ensure that the patient's legally authorized representative (LAR) has been given an adequate explanation of the purpose, methods, risks, potential benefits and patient responsibilities of the study. In Houston, Cincinnati, Emory and Pittsburgh, if no legally authorized representative is available, Exception from Informed Consent for Emergency Research (EFIC) will be employed. EFIC is not permitted under Florida State law and will not be employed in Miami. EFIC is not permitted at the Japanese sites at this time. The consent form must be an up-to-date document that has been approved by the clinical site's IRB. A sample informed consent form is provided as **Appendix I**.

In this trial, all subjects will have an altered mental status and, therefore, either exception from informed consent will be employed or, when available, informed consent will be obtained from a LAR or person with power of attorney for the patient. Every attempt will be made to contact the patient's LAR/family as soon as possible after the patient's admission, and in accordance with the individual hospital's protocol. To the extent possible, these discussions should be carried out in a private setting without distraction. No coercion will be applied, and the LAR and other family members will be given an opportunity to read the informed consent document, ask and have answered any questions they may have about the study.

4.3.4 Randomization Procedure. Once all eligibility criteria have been confirmed the randomization process will begin. Block randomization within each site will produce a 1:1 ratio between subjects treated with hypothermia and subjects treated with normothermia. Block randomization within each site will be employed for the randomization to enroll comparable numbers of patients among the treatment groups at each trial center. Each study site will have sealed sequentially numbered opaque envelopes with the patient assignment at the respective site. The statistician will generate the study randomization codes using a computer program. The randomization series will yield codes for assignment of subjects to each of the study arms. The codes will be placed in sealed, sequentially numbered opaque envelopes. Envelopes will be opened in sequential order to determine study subject assignment.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

This is a pragmatic study; patients will be treated with standard care as established at each enrolling center. All of the enrolling sites utilize Brain Trauma Foundation Guidelines as foundation for delivery of care(40). Intravascular cooling catheters may be placed in the emergency room, the operating room or neurotrauma intensive care unit (NTICU). Patients randomized to hypothermia will be rapidly cooled to 35°C before opening the dura and then maintained at 33°C±0.5°C for a minimum of 48 hours and a maximum of 5 days. After evacuation of SDH all patients will be cared for in the ICU by teams experienced in hypothermia and the management of TBI.

Intravascular cooling will be provided by CoolGard 3000 or Thermogard XP which use an intravenous central catheter circulating cooled saline in a closed loop system. These devices

are currently in clinical use at the enrolling centers. The cooling system is cleared by the FDA as 510K devices (Thermogard System – K072234 and Quattro – K101987). Indications for use includes *in cardiac surgery patients to achieve and or maintain normothermia during surgery and recovery/intensive care, and to induce maintain and reverse mild hypothermia in neurosurgery patients in surgery and recovery/intensive care.* The intravascular cooling system is a portable temperature regulation system that contains a computerized user interface and a cooling and warming unit that circulates sterile saline through polymeric balloons that surround catheters. (This is a closed system; additional fluid is not introduced into the circulatory system for temperature management purposes.) The system continuously compares a patient's core body temperature to the programmed target body temperature and automatically adjusts the temperature of the saline flowing through the catheter to maintain the programmed temperature.

Arctic Sun temperature transfer pad device by Medivance (cleared by the FDA, K010338) may be utilized after reaching core temperature if the intravascular cooling device must be removed. Each of these devices utilizes a temperature feedback loop provided by a urinary/rectal catheter.

Spreading depolarizations will be monitored using electrocorticography (ECoG) electrode strips (Wyler, platinum, 4 mm diameter, 10 mm interval between electrode centers; Ad-Tech Medical Instruments Corp., Racine, WI, USA) placed in the subdural space. The electrodes that are used are not being evaluated in the proposed research. The strip has received FDA approval under section 510(k) for the temporary placement on the surface of the brain for recording or stimulating electrical activity of the brain.

5.2 HANDLING OF STUDY INTERVENTIONS

All sites currently have intravascular cooling systems and use them as part of standard care. ZOLL Circulation has agreed to provide the study with the catheters required for cooling with the Thermogard System (Quattro – K101987) for use in study patients. Catheters provided for study use will be maintained in a separate secure area so that they are accessible at the location of use (ED, OR or NTICU) but are not intermingled with standard care catheters. Study personnel will be responsible for accountability of catheters, maintaining a log of catheters used per study subject (e.g., successful placement, wasted due to contamination, etc.).

5.3 Concomitant Interventions

5.3.1 Required Interventions. Enrolled subjects will be randomized to standard care/normothermia or standard care with the intervention of hypothermia. Required interventions include the administration of up to 2 liters of IV fluid per standard head trauma resuscitation (chilled for hypothermia arm) prior to evacuation of SDH, and the placement of the intravascular temperature management catheter. Core body temperature will be measured by urinary bladder Foley catheter, rectal probe or esophageal probe whichever is standard care at each institution.

Patients in the control arm will be maintained at normothermia 37°C. Patients in the treatment arm will be cooled to 35°C prior to opening the dura and maintained at 33°C for a minimum of 48 hours up to a maximum of 5 days. Cooling will be initiated with the up to 2 liters of chilled IV fluids, and intravascular cooling with the Thermogard System and catheter which is to be placed in the femoral vein

The surgical procedure will be tailored according to the pathology of the patient. Frontal, parietal, temporal or occipital craniotomies or any combination of those will be performed as per standard-of-care for the injury each patient has sustained. Following hematoma evacuation and hemostasis, a subdural strip electrode will be placed on the brain surface near the lesion. Considering the lesion distribution on pre-operative scans and the craniotomy location/size, the ECoG electrode strip is placed radiating outward from, or lying parallel to, an accessible injured region such that the closest electrode contacts are placed on viable, but often edematous or contused cortex with a low degree of sub-arachnoid blood. The intention is to monitor peri- lesion ("penumbral") cortex that is at greatest risk for further deterioration. The strip is placed, so far as possible, along a single gyrus. The strip may be tunneled under intact skull, so that distal electrodes lie outside the visible craniotomy field, or may be placed entirely within the field.

Following placement of the electrode, the lead will be externalized through the dura and craniotomy. If the bone flap is replaced, the lead will be exteriorized through a burr hole to facilitate subsequent removal. Furthermore, the lead wire will be exteriorized in a straight line with the electrode strip, also to facilitate removal. Finally, the lead is tunneled under the scalp and out through a stab wound distant from the craniotomy incision line in order to reduce the risk of infection. When ECoG recordings are complete, the strip is removed by gently pulling it through the stab wound followed by watertight closure of the skin incision.

The technique of ECoG strip placement is a standard surgical procedure in epilepsy neurosurgery, and has been used as described to monitor surgical patients with severe stroke or traumatic brain injury at more than a dozen neurosurgical centers.(41-45)

Upon admission to the neuro-intensive care unit (NICU), following surgery, the leads from the ECoG electrode strip will be connected to an EEG amplifier. External ground and reference electrodes will be placed and continuous ECoG recordings will then commence. The reference electrode is a platinum needle placed under the scalp.

Continuous ECoG monitoring will be performed for at least the same duration as ICP monitoring. In patients randomized to hypothermia, this is until at least 24 hours after re- warming is complete. In normothermia patients, patients will be monitored a minimum of 96 hours, and longer if continued ICP monitoring is clinically indicated. When monitoring is complete, the electrode strip will be removed at the bedside under sterile conditions, as is performed for standard-of-care intracranial devices.

Blood samples for biomarker analysis will be taken at 3 time points (T1, within 6 hrs and as close to time of injury as possible (pre-hypothermia for the treatment arm); T2, post-surgical evacuation of hematoma (7-48 hrs); T3, 5-14 days post-injury or DC whichever comes first. If the patient has a ventricular drain in place, CSF samples will also be collected.

As part of standard care all patients are expected to have an intracranial pressure monitor (either extraventricular drain or intraparenchymal monitor).

5.3.2 Prohibited Interventions. Please see re-warming protocol regarding fluids and electrolytes.

5.3.3 Precautionary Interventions

5.3.3.1 Induction of Hypothermia. Cold fluid infusion with up to 2 liters of chilled (4°C) IV fluids over approximately 30 minutes should be initiated after randomization. Once the intravascular cooling catheter is in place, goal temperature should be 35°C prior to dura opening, with maintenance at 33°C (32.5-33.5°C).

5.3.3.2 Procedure for Re-warming. **At or shortly after the 48-hours of cooling**, re-warming will be done very gradually. This will allow body temperature to increase no faster than 0.25ºC every hour. This will be accomplished by setting the following method:

1. Set the intravascular cooling catheter controls to automatic with the target temperature to be 37.0°C. (The machine itself should be set to 36.5°C to avoid overshooting the target temperature.)

2. Set machine to rewarm at a rate of 0.25°C/hour. (The machine itself may need to be set to 0.1°C/hour to achieve this goal.)

3. It takes 16-20 hours to rewarm a patient successfully and the unit must be on automatic at all times.

4. Continue use of room temperature ventilated air until 37.0ºC is reached.
   a. If the ICP is elevated (≥20mmHg) do not rewarm at 48 hours, may keep the subject cool up to 5 days.
   b. If the ICP elevates as rewarming hold the temperature where it is and add additional standard measures for treating elevated ICP. If no response to treatments in 6 hours and ICP is ≥25mmHg, re-cool to 33°C.
   c. Goal is to have the subject re-warmed within 5 days.

8 Hours Prior to Re-warming:

1. Stop all potassium and magnesium administration 8 hours before the start of re-warming to reduce the likelihood of hyperkalemia and hyper-magnesium during re-warming.

2. Determine fluid balance 8 hours prior to the start of re-warming:
   a. If <0 cc, administer additional intravenous fluid (colloid, crystalloid, or a combination) to achieve a positive balance.
   b. Administer 1000cc volume load to all subjects who have a cumulative fluid balance of 0 – 999cc.
   c. It is important to ensure that there is adequate circulating blood volume (Hgb>8 grams and Hct > 30%) when the patient begins to vasodilate with re-warming.

During re-warming:

1. Monitor bladder temperature, ICP, MAP, and CPP hourly.

2. If ICP increases above 20mmHg, rewarming will be suspended per protocol.

3. Maintain CPP between 50 and 70 mmHg using volume expansion and vasopressors, as needed. If MAP <90 mm Hg, start a vasopressor agent and evaluate response, additional agents may be used if necessary.

4. The ICP monitor must remain in place for at least 24 hours after re-warming is complete, (even if the ICP's are within normal limits) in order to detect rebound increase in ICP after re- warming.

5.4 Adherence Assessment

Compliance with the study intervention will be assessed by monitoring temperature data. Analysis will be performed on time to reach goal temperature, duration of cooling, and temperature ranges for each group during the intervention period.

6. CLINICAL AND LABORATORY EVALUATIONS

Management is per standard care at each institution. All centers practice in accordance with Brain Trauma Foundation Guidelines.

6.1 Schedule of Evaluations (Table 1.)

Evaluation	Screening (<5hrs of injury)	Entry T1 <6hrs of injury	7 to 48hrs T2	>48 hrs-5d	5-14d T3	4-6 wk	6mons+/-3 weeks
Documentation of Injury (Head CT/MRI)	SOC		SOC				
Medical/Treatment History	SOC						
Clinical Assessment	SOC		X	X	X		
Physical Exam	SOC						
Informed Consent	Per center approved process						
Hypothermia (Control)			X	X			
Dura Opening/SDH Evacuation		SOC					
Brain Activity Monitoring			X	X	X		
Rewarming				X			
Hematology	SOC		SOC		SOC		
Chemistry	SOC		SOC		SOC		
Pregnancy Testing	SOC						
Stored Plasma/CSF		X	X		X		
Adherence Assessments			X	X			
Adverse Event Assessments		X	X	X	X	X	X
Outcome (DRS; GOSE)						X	X

SOC=per standard care

6.2 Timing of Evaluations

6.2.1 Pre-Randomization Evaluations

These evaluations occur prior to the subject receiving any study interventions.

Screening
Subjects enrolled in this study will have a goal of SDH evacuation within 6 hours of injury. Screening must be completed to allow time for catheter placement and cooling down to 35°C prior to opening of the dura. All screening evaluations are part of routine patient management for TBI patients.

Pre-Entry
T1 blood draw may be taken with routine blood draw, processed and held (discarded if subject is not enrolled).

Entry
Randomization should occur immediately upon confirmation of enrollment criteria. Initiation of study intervention should commence immediately after randomization.

6.2.2 On-Study/On-Intervention Evaluations

- Within 6 hours of injury (T1)
  - Blood (and CSF if available) should be collected
  - Up to 2 liters IV fluid administered
  - Placement of intravascular catheter
  - Cooling to 35°C for hypothermia arm; 37°C for normothermia
  - Opening of dura (followed by evacuation of SDH)
  - Adverse events monitored
- >6 to 48 hours post-injury (T2)
  - Following hematoma evacuation and hemostasis ECoG Electrode strips should be placed
  - Upon admission to the ICU, following surgery, the leads from the ECoG electrode strip will be connected to an EEG amplifier. External ground and reference electrodes will be placed and continuous ECoG recordings will then commence.
  - Repeat head CT as indicated for clinical care
  - Temperature maintenance of 33°C for hypothermia arm; 37°C for normothermia arm
  - Blood (and CSF if available) should be collected
  - Adverse events monitored
- >48 hours to 5 days
  - Rewarming initiated according to rewarming protocol (37°C for normothermia arm)
  - Continuous ECoG monitoring will be performed for at least the same duration as ICP monitoring. In patients randomized to hypothermia, this is

until at least 24 hours after re-warming is complete. In normothermia patients, patients will be monitored a minimum of 96 hours, and longer if continued ICP monitoring is clinically indicated. When monitoring is complete, the electrode strip will be removed at the bedside under sterile conditions, as is performed for standard-of-care intracranial devices.
Adverse events monitored

(±0.5°C for all temperatures)

6.2.3 Intervention Discontinuation Evaluations

Subjects who prematurely discontinue study intervention will complete controlled rewarming per protocol for patient safety. This trial follows an intention-to-treat design, subjects who discontinue intervention will continue to be followed and evaluated on study. Efforts will be made to retain such subjects on study for the 4-6 week and 6 month outcome assessments. Once a subject discontinues from the study intervention they will not receive continued intravascular hypothermia.

6.2.4 On Study/Off-Intervention Evaluations

- 5-14 days (T3)
  Blood (and CSF if available) should be collected
  Adverse events monitored
- 4-6 weeks
  DRS
  GOSE
  Adverse events monitoring
- 4 weeks – 6 months
  Follow-up on adverse events as necessary
  Maintain subject contact (Phone calls/emails as necessary)

  i. Final On-Study Evaluations

- 6 months±3 weeks
  DRS
  GOSE
  Adverse events monitoring

6.3 Special Instructions and Definitions of Evaluations

6.3.1 Informed Consent. Patients will be randomized within 5 hours of arrival to the ED. If a patient arrives in the ED with family members present or before craniotomy is performed, then a prospective informed consent will be obtained. In Houston, Cincinnati, Atlanta and Pittsburgh, every attempt will be made to identify family as soon as possible but randomization will not be delayed for this purpose. If no family is identified the study team will continue to make every attempt to locate the family throughout the patient's hospital stay. In Miami, exception from informed consent is not permitted according to state law; consent will be obtained per state regulations. The Japanese sites will obtain consent per their local regulations.

Centers must comply with Federal standards for community consultation and notification. In particular, community consultation as directed by each site's institutional review board. (Please see attached plan.) For those patients enrolled and randomized under waiver, a study team member must meet with the family as soon as possible and explain the study in detail to them. The Legally Authorized Representative must be identified and permission to continue the study must be requested. Should permission be denied then those patients assigned to hypothermia will be gradually re-warmed. If the patient has been cooled to 33°C then the re-warming should be performed per protocol.

In Randomized patients, permission must be obtained from the Legally Authorized Representative or the patient to use the data collected for that patient. This will be documented on the appropriate HIPPA forms.

6.3.2 Documentation of Traumatic Brain Injury requiring Emergent Craniotomy. Subdural hematoma will be documented by standard of care brain imaging (head CT or MRI)

6.3.3 Medical History. Medical history will be obtained from family member if available.

6.3.4 Concomitant Treatments. Documentation of therapeutic intensity level (TIL) and concomitant treatments per the Common Data Elements (CDE) forms will be collected.

6.3.5 Study Intervention Modifications. Any modification to hypothermia/normothermia will be documented with rationale.

6.3.6 Clinical Assessments. A targeted physical exam is completed on presentation to the emergency department. Clinical events should be recorded on the case report forms (CRFs) and will include adverse events, temperature, ICP, MAP, pupil size and reactivity, hematoma size, midline shift, GCS, GOSE, and DRS. GOSE and DRS will be assessed by evaluator who is unaware of (blind) the study group assignment.

6.3.7 Laboratory Evaluations. Baseline standard care laboratory studies will be recorded utilizing the CDE data elements, thereafter relevant abnormal laboratory studies during the treatment period will be evaluated against the USDHHS Common Terminology Criteria for Adverse Events V4.0 USDHHS criteria for adverse events(46). Those with a grade >3 will be documented.

6.3.8 Other Laboratory Studies. Plasma for biomarker analysis: Blood will be withdrawn from existing lines or by venipuncture and collected into two pink top K_2EDTA 6ml (plasma) Vacutainers per time point (36 ml). The samples will be placed on ice and will be centrifuged at 1,459 X g for 10min at 4°C. The supernatant solution will be removed and centrifuged at 1,459 X g for 10min at 4°C to generate platelet-poor plasma. Plasma will be divided into aliquots and frozen at -80°C until needed. For those subjects providing consent, any residual sample and buffy coat will be frozen at -80°C for future study.

CSF for biomarker analysis: Patients with a ventriculostomy drain will have 1-5 ml of CSF sampled from the receptacle at each of 3 time points. The receptacle will be emptied into the collection bag (the volume will be noted in the nursing notes) to start with an empty receptacle, several drops of CSF will then be allowed to drip into the chamber. The drain will be re- clamped; the chamber port will be cleaned with chlorhexidine as per hospital specifications and

the CSF sample drawn from the port with a sterile syringe. CSF will be centrifuged (4°C, 1,459 X g for 10 minutes) and portioned into aliquots and frozen at -80°C; any residual sample will be frozen at -80°C for future study. The CSF pellet should be covered in a 10% DMSO solution (e.g., 100µl CSF plus 11µl DSMO) and frozen at -80°C and transferred to -145°C after 24hrs when possible.

Samples will be labeled with bar-coded subject study identification numbers, sample type and time point. They will be stored indefinitely at the University of Texas Health Science Center at Houston, Neuroscience Research Repository, Hergenroeder Laboratory, The Vivian L. Smith Department of Neurosurgery, [redacted]

6.3.9 Adherence Assessments. Temperature will be monitored for adherence to study assignment.

7. MANAGEMENT OF ADVERSE EXPERIENCES

Adverse events will be graded according to the USDHHS Common Terminology Criteria for Adverse Events V4.0 (USDHHS, Table 2) and summarized according to body system. Primary focus for analysis will be on 6-month mortality rate, incidence of pneumonia, incidence of DVT/PE, incidence of bleeding and incidence of arrhythmia. For the purpose of safety monitoring, adverse events in the table below of Grade 3 or higher will be classified as “Important AEs” or selected AEs of interest.

Table 2. Selected AEs from USDHHS Common Terminology Criteria for Adverse Events V4.0 USDHHS

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Sinus Bradycardia	Asymptomatic, intervention not indicated	Symptomatic, medical intervention indicated	Severe, medically significant, medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Ventricular arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Thromboembolic event	Venous thrombosis (e.g., superficial thrombosis)	Venous thrombosis (e.g., uncomplicated deep vein thrombosis),	Thrombosis (e.g., uncomplicated pulmonary embolism [venous],	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial	Death

		medical intervention indicated	nonembolic cardiac mural [arterial] thrombus), medical intervention indicated	insufficiency); hemodynamic or neurologic instability; urgent intervention indicated	
Pneumonia			Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Pulmonary edema	Radiologic findings only; minimal dyspnea on exertion	Moderate dyspnea on exertion; medical intervention indicated; limiting instrumental ADL	Severe dyspnea or dyspnea at rest; oxygen indicated; limiting self care ADL	Life-threatening respiratory compromise; urgent intervention or intubation with ventilatory support indicated	Death
Bleeding/hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Intraoperative hemorrhage			Postoperative radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Infection (culture positive) (e.g., blood stream infection, urinary tract infection, ventriculitis)		Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Device-related infection			IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative	Life-threatening consequences; urgent intervention indicated	Death

			intervention indicated		
Death					Death

8. CRITERIA FOR INTERVENTION DISCONTINUATION

Subjects may be discontinued from hypothermia at any time for patient safety per the decision of the site PI.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a randomized study of hypothermia for patients with traumatic brain injury. The primary hypothesis of the study is that early induction and maintenance of hypothermia in patients with traumatic brain injury undergoing hematoma evacuation will improve global neurologic outcome. Global neurologic outcome will be assessed using the Glasgow Outcome Scale (GOSE). The primary outcome measure is the GOSE at 6 months.

9.2 Outcomes

9.2.1 Primary outcome. Primary outcome is GOSE at 6 months±3weeks post injury. GOSE (dichotomous: Good recovery and moderate disability will be designated as favorable outcomes; severe disability, vegetative state, and death as poor outcomes) at 6 months post-injury will be the primary outcome. Disability Rating Scale (DRS) at 4-6 weeks will be used to impute missing GOS/GOSE scores for futility analysis. Outcome scales will be assessed by an evaluator who is blind to study group assignment.

Glasgow Outcome Scale-Extended (GOSE) is a widely used global outcome score including 8 categories: dead, vegetative state, lower/upper severe disability, lower/upper moderated disability , lower/upper good recovery(47). GOSE assesses consciousness, independence, work status, return of lifestyle via a structured interview. It is relatively easy to administer and has good inter-rater reliability and content validity. (Appendix II)

Disability Rating Scale (DRS) is a global outcome scale that measures the level of arousal, cognitive ability related to activities of daily living and level of functioning. It includes eye opening, communication ability, motor response, feeding, toileting, grooming and employability(48). Scores range from 0 (no disability) to 29 (profound vegetative state) and death is scored at 30. It has been shown to be a good predictor of later outcome with the one month exam having an 87% correlation with the 6 month GOSE(12). (Appendix III)

9.2.2 Secondary outcomes. Secondary outcomes will include:

- adverse event rates (e.g., infection, pneumonia, hemorrhage, thrombosis)
- ICU LOS, hospital LOS
- incidence of cortical spreading depolarization

- levels of biomarkers (e.g., GFAP, UCH-L1)

9.3 Sample Size and Accrual

A randomized design will be used in this study. Enrollment is intended to be N=120 but the trial allows an extension to a maximum of 350 patients randomized equally at a 1:1 ratio to each of two arms (hypothermia versus control). The final analysis will use a one-sided Fisher's exact test with significance level of 0.02 to compare proportions of patients with good outcome of GOSE at 6 months between two treatment arms. Interim analyses will be performed after 31, 60, 120, 180, 240, and 300 patients randomized. The 0.02 significance level has been calibrated to adjust for the multiple interim analyses and maintain an overall study type I error rate below 0.025. At each interim analysis, we will evaluate the predictive probability of statistical significance with the current sample size and with the maximum sample size. If the predictive probability of statistical significance with the current sample size is sufficiently high, then enrollment will stop and follow up will continue for 6 months. If the predictive probability of statistical significance with 350 patients is sufficiently low, then the study will stop for futility. Otherwise, enrollment will continue to the next analysis.

9.4 Data Monitoring

A Data and Safety Monitoring Board (DSMB) will be established. The DSMB will include a biostatistician with expertise in research design and an expert in management of brain injured patients. Site PIs will monitor safety of each enrolled subject. In addition, safety analysis will be ongoing with interim monitoring for safety and study performance for every 20 patients or at least annually following the randomization of the first subject. Interim analysis for consideration of discontinuing the study for futility or discontinuing enrollment for predicted success will be performed after 31, 60, 120, 180, 240, and 300 patients have been randomized. Enrollment will be ongoing during this assessment.

Authorized representatives of the US Army Medical Research and Materiel Command (USAMRMC), who is one of the funding agency for this study, may review or obtain identifiable information (including the case ID number) related to participation in this research study for the purpose of monitoring the accuracy and completeness of the research data, for performing required scientific analyses of the research data, and as part of their responsibility to protect human research volunteers.

9.5 Data Analyses

The primary analysis population will be an Intention-to-Treat population, all randomized subjects, followed by an As-Treated analysis for sensitivity. As described below, for the primary outcome, 4-week DRS will be used to impute missing 6-month GOSE for the interim analyses. Demographic and baseline laboratory results will be summarized using descriptive statistics, including means, standard deviations, medians, ranges, histograms and box-plots. Fisher's exact test and Wilcoxon rank sum test will be used in the data analyses of categorical and continuous variables, respectively. Adverse events will be reported by type, frequency and severity.

9.5.1 Statistical Modeling. The National Acute Brain Injury Study: Hypothermia II (NABIS:H II) shows that there was a strong correlation between 4-week Disability Rating Scale (DRS) and 6-month GOSE (Table 1). In particular, there were 2 false negatives out of 45 patients (4%) and 6 false positives out of 30 patients (20%). It shows that the short-term response is a good predictor for 6-month GOSE.

Table 3 summarizes the historical data (NABIS:H II study) comparing the 4-week DRS score and 6-month outcome; 80% (24/30) of good short-term DRS had a good long-term GOSE, while 4% (2/45) poor DRS had a good GOSE:

Table 3

	6-month GOSE		
4-week DRS Score	Poor	Good	Total
Poor (19 or larger)	43 (96%)	2 (4%)	45
Good (18 or less)	6 (20%)	24 (80%)	30

The statistical model used in this study explicitly models the relationship between 4-week DRS and 6-month GOSE score. Let p_{Dc} and p_{Dt} be the probabilities of good 4-week DRS scores in the control and treatment groups. Furthermore, define

p_{Gc0} = Pr(GOSE good | control, DRS poor)
p_{Gc1} = Pr(GOSE good | control, DRS good)
p_{Gt0} = Pr(GOSE good | treatment, DRS poor)
p_{Gt1} = Pr(GOSE good | treatment, DRS good)

These probabilities define the conditional probabilities of achieving a good GOSE score given the DRS score and treatment group.

Together, p_{Dc}, p_{Dt}, p_{Gc0}, p_{Gc1}, p_{Gt0}, and p_{Gt1} define a joint distribution over DRS and GOSE scores. The key parameter of interest is the probability of a good GOSE score within each group, which can be derived from these parameters.

We estimate these parameters in a Bayesian fashion, placing Beta(2,3) priors on p_{Dc} and p_{Dt}, Beta(1,4) priors on p_{Gc0} and p_{Gt0}, and Beta(4,1) priors on p_{Gc1} and p_{Gt1}. These priors reflect the historical data but are weak in that each prior has 5 observations worth of weight, meaning that accumulating data in contrast to the historical data above will result in inferences based on the current data, not the historical data. Thus this model is sufficiently flexible that it may be used when DRS is highly predictive of GOSE and also may be used if DRS is not predictive of GOSE.

The final analysis is a one-sided Fisher exact test with significance level 0.02 conducted only on the GOSE scores. Thus, the DRS values are only used in the analysis to predict GOSE scores for subjects who have a DRS score but not a GOSE score. For the final analysis, 6-month GOSE scores will be used. If the 6-month GOSE score is missing the 4-week DRS score will be used to impute the 6-month GOSE score.

At each interim analysis we compute two predictive probabilities. The first is the predictive probability of trial success if enrollment stops, the current subjects are followed to completion, and the Fisher's exact test is conducted on the final data. For this predictive probability many of the subjects will have 6-month GOSE scores reported. The uncertainty in the predictive

probability involves the potential GOSE scores for subjects with 4-week DRS observations, but have not reached their 6-month visit, and also potential GOSE scores for subjects with neither 4-week DRS nor 6-month GOSE scores (recent enrollees). The predictive probability accounts for the uncertainty in those two sets of incomplete subjects. If this probability is sufficiently high (indicating the current data, when complete, is very likely to produce a significant result) then the trial stops enrollment and follows the current subjects to completion.

The second predictive probability is the probability of trial success if the trial is continued to 350 subjects. In addition to the uncertainty for incomplete subjects, this predictive probability also incorporates uncertainty for subjects that have not yet enrolled, but will be enrolled in the future in order to reach a sample size of 350. If this probability is sufficient low (indicating that extending the trial to its maximum is unlikely to result in statistical significance) then the trial is discontinued for futility.

9.5.2 Interim Analyses for Futility or Expected Success. Interim analyses will occur at 31, 60,120,180, 240, and 300 subjects enrolled.

The analysis plan is as follows for the N=31 subjects:

When N=31 subjects are complete, we will observe the number of subjects on each arm (n_ctrl and n_trmt), and the number of observed successes on each arm Y_ctrl and Y_trmt. The predictive probability of success at N=60 subjects will be computed. This predictive probability incorporates uncertainty both in the true underlying treatment effect, for which we only have the random data on N=31 subjects, and the random variation in the N=29 potential future subjects in the trial. To compute this probability, we place noninformative Beta(0.5,0.5) priors on the true underlying success rates in both the control and treatment arms p_ctrl and p_trmt. The resulting posterior distributions based on the N=31 observations result in p_ctrl | data ~ Beta(0.5+Y_ctrl, 0.5+n_ctrl-Y_ctrl) and p_trmt | data ~ Beta(0.5 + Y_trmt, 0.5+n_trmt-Y_trmt) capturing the uncertainty in the true rates. Conditional on those rates, the future successes among the 29 remaining subjects will follow a Binomial distribution with a known number of future patients on each arm and the unknown true rate. Averaging across the uncertainty in the unknown true rate, we observe that the unknown number of future successes in each arm follows a Beta Binomial distribution.

These Beta Binomial predictive distributions provide the likely range of values for future observations. For example, if at the interim we observe 9 successes in 16 control patients, with 14 control patients remaining, we would observe that the true rate currently has a Beta(9.5,7.5) distribution and the number of future control successes is distributed BetaBinom(14,9.5,7.5), a distribution whose most likely value is 8/14 future successes, in line with our current observed rate and with approximately a 96-97% predictive probability the number of future successes will be between 3 and 12 inclusive, reflecting the high uncertainty in the true underlying rates and the sampling variability in the future subjects. The predictive distribution will likely have a high variance reflecting the small sample size at the interim. Performing this prediction for both the control and treatment arms, we may compute the predictive probability the future data will lie in a region where the final analysis will result in $p<0.025$ and trial success, known as the predictive probability of success.

<u>This predictive probability will be provided to the DSMB. The trial should continue for predictive probabilities greater than 60% and stop for futility for predictive probabilities below 40%. If the</u>

predictive probability is between 40-60% the DSMB will provide a recommendation for whether the trial should continue based on the totality of the evidence. The DSMB will only report "continue" or "stop for futility" to the sponsor to maintain blinding of the exact predictive probability.

The next interim analyses if applicable will be performed at 60,120,180, 240, and 300 subjects enrolled. At each interim analysis (60,120,180, 240, and 300 subjects enrolled), we will evaluate two predictive posterior probabilities:

Let ppnow be the predictive probability that the final efficacy analysis (Fisher's exact test) will be statistically significant if enrollment stops at the current sample size and all subjects are followed to the 6-month GOSE outcome. If this probability is sufficiently high, then enrollment will stop for expected success.

Let ppmax be the predictive probability that the final efficacy analysis (Fisher's exact test) will be statistically significant if enrollment continues to 350 patients and all subjects are followed to the 6-month GOSE outcome. If this probability is sufficiently low, then the trial will stop for futility.

Table 4 presents the stopping boundaries for the interim analyses. The trial will stop for success if ppnow exceeds the given success threshold, while the trial will stop for futility if ppmax is below the futility threshold. Note the values are calibrated to increase the likelihood of stopping at N=120 subjects. The trial has been powered to detect a moderately large effect at N=120 while maintaining the option of extending the trial should the results appear promising with a more moderate effect.

Table 4. Summary of Stopping Boundaries for Interim Analyses

	N=60	N=120	N=180	N=240	N=300
success threshold for ppnow	0.95	0.85	0.95	0.95	0.95
futility threshold for ppmax	0.10	0.40	0.10	0.10	0.10

The operating characteristics of this design (type I error, power, and expected sample size) were computed by simulation in a variety of possible scenarios. These scenarios were constructed by crossing four possible treatment effects with two possible relationships between 4-week DRS and 6-month GOSE scores (predictive and nonpredictive). Table 5 shows the values of the parameters for each of the simulated scenarios. In all scenarios the probability 6- month GOSE is good in the control arm is 0.347. In the *null* scenarios, scenarios where there is no difference between the scores, the probability 6-month GOSE is good in the treatment arm is also 0.347 (no treatment effect). We also consider low scenarios where the probability 6-month GOSE is good in the treatment arm is 0.498, medium scenarios where the probability 6-month GOSE is good in the treatment arm is 0.536, and alternative scenarios where the probability 6- month GOSE is good in the treatment arm is 0.604. The trial is powered for values closer to the 0.604 6-month scenario.

In the non-predictive scenarios, 6-month GOSE and 4-week DRS scores are independent, while in the predictive scenarios the relationship between 6-month GOSE and 4-week DRS is equal to the observed relationship in the historical data above.

Table 5. The values of the parameters in each of the eight simulated scenarios

	pDc	pDt	pGc0	pGc1	pGt0	pGt1	Pr(GOSE good in ctrl)	Pr(GOSE good in trmt)
Null Pred.	0.40	0.40	0.045	0.800	0.045	0.800	0.347	0.347
Null Non.	0.50	0.50	0.347	0.347	0.347	0.347	0.347	0.347
Low Pred.	0.40	0.60	0.045	0.800	0.045	0.800	0.347	0.498
Low Non.	0.50	0.50	0.347	0.347	0.498	0.498	0.347	0.498
Med Pred.	0.40	0.65	0.045	0.800	0.045	0.800	0.347	0.536
Med Non.	0.50	0.50	0.347	0.347	0.536	0.536	0.347	0.536
Alt Pred.	0.40	0.74	0.045	0.800	0.045	0.800	0.347	0.604
Alt None.	0.50	0.50	0.347	0.347	0.604	0.604	0.347	0.604

The table below provides the operating characteristics (probabilities of success or futility at each possible sample size). As noted above, the trial is powered for effect sizes closer to the "alternative" scenarios, where the trial has over 90% power and a high likelihood of stopping (typically for success) at or before the N=120 interim analysis. Similarly, type I error is controlled at 0.025 for the null scenarios and they are quite likely to stop (typically for futility) at or before the N=120 interim analysis. Power is as expected reduced for effect sizes below where the trial is powered, although the medium scenarios still retain power in the 75-80% range.

Operating characteristics for each of the eight scenarios is summarized in Table 6. The first column provides the scenario name, while the next 6 columns (N=60 through N=350) provides the probability of futility (top number in each cell) and success (bottom number in each cell) at those sample sizes. Thus, for example, in the low predictive scenario the probability of stopping at N=120 and having a successful trial is 0.179. The expected sample size for each trial is given in the E[N] column while the probability of trial success (the sum of the bottom numbers in the N=60 through N=350 cells) is given in the Pr(success) column. The trial is powered for the alternative (bottom two) scenarios, where power is over 90%, although the trial retains modest (75-80%) power for more moderate effect sizes. In the null and alternative scenarios the trial is quite likely to stop at or before the N=120 interim analysis. Results in this table were computed by simulating 10,000 trials in each scenario.

Table 6. Operating Characteristics

	N=60	N=120	N=180	N=240	N=300	N=350	E[N]	Pr(success)
Null Pred	0.344 0.003	0.513 0.009	0.024 0.004	0.039 0.002	0.030 0.002	0.026 0.004	118.3	0.024
Null Non	0.322 0.002	0.527 0.006	0.026 0.003	0.042 0.003	0.033 0.001	0.030 0.005	121.9	0.021
Low Pred	0.061 0.057	0.227 0.179	0.006 0.136	0.012 0.114	0.016 0.075	0.040 0.078	180.0	0.637
Low Non	0.083 0.030	0.248 0.160	0.007 0.125	0.013 0.112	0.013 0.077	0.042 0.091	182.8	0.594
Med Pred	0.035 0.088	0.137 0.289	0.003 0.179	0.005 0.130	0.006 0.068	0.016 0.044	166.9	0.798
Med Non	0.053 0.050	0.165 0.254	0.004 0.178	0.005 0.138	0.005 0.078	0.014 0.059	173.3	0.756
Alt Pred	0.014 0.200	0.042 0.438	0.001 0.195	0.000 0.083	0.000 0.019	0.001 0.007	134.3	0.942
Alt Non	0.024 0.115	0.058 0.452	0.000 0.220	0.000 0.096	0.000 0.025	0.001 0.009	143.2	0.917

9.5.3 Interim Analysis on Safety.

The probability of selected adverse events of interest (defined in Section 7), and separately of deaths, will be monitored based on a beta-binomial model. Enrollment will be placed on hold pending DSMB review if the proportion of selected adverse events of interest in the treatment arm is too high in comparison to the control arm or if the proportion of deaths in the treatment arm is too high in comparison to the control arm. The selected adverse events of interest will also include patient deaths.

The DSMB will perform a more detailed review of the selected AEs of interest to determine if the study should continue. In particular, enrollment will be placed on hold if,
$Pr(p1 > p0 \mid data) > 0.98$ OR $Pr(pdeath1 > pdeath0 \mid data) > 0.98$,

where p1 and p0 are the proportion of patients with selected AEs of interest in the hypothermia and control arms, respectively, and pdeath1 and pdeath0 are the proportion of patients that died. The prior distributions for p1, p0, pdeath1, and pdeath0 are independent, non-informative Beta (1, 1). The 0.98 thresholds were selected to adjust partially account for the multiple interim analyses scheduled to occur. We will start to perform the interim analysis on safety for the first 10 patients in each arm randomized, and then other interim analyses will be carried out every 10 patients in both arms (20 patients). The operating characteristics for the stopping rules under various scenarios are summarized in Table 5, with results based on 10000 simulations.

Table 7**.** summarized the simulation results with interim analyses for safety every 20 patients randomized, assuming there will be 120 patients (60 per arm).

Table 7

Scenario	Selected AEs of Interest proportions (Control, Treatment)	Death proportions (Control, Treatment)	% trials with at least one hold for safety evaluation	Mean number of pts
1	(0.25, 0.10)	(0.125), 0)	0.08%	120
2	(0.25, 0.15)	(0.125, 0.025)	0.4%	120
3	(0.25, 0.25)	(0.125, 0.125)	7.5%	115
4	(0.20, 0.30)	(0.10, 0.20)	39.7%	96
5	(0.20, 0.40)	(0.10, 0.30)	81.1%	66
6	(0.20, 0.50)	(0.10, 0.40)	97.4%	45
7	(0.20, 0.60)	(0.10, 0.50)	99.8%	33

For a trial with 120 patients, there would be five interims (after 20, 40, 60, 80, and 100 patients). We summarized in Table 8 the number of times per simulated trial that enrollment was held. For example, in scenario 7, over half of the simulated trials met the “hold” criterion at every single interim assuming that at each hold the DSMB recommended the trial continue.

Table 8. Number of holds per trial in the safety simulation study.

Scenario	Important AE proportions	% of trials with 0, 1, 2, 3, 4, or 5 holds per trial					
	(Control, Hypothermia)	0	1	2	3	4	5
1	(0.25, 0.10)	99.9	0.1	0	0	0	0
2	(0.25, 0.15)	99.6	0.4	0.1	0	0	0
3	(0.25, 0.25)	92.5	3.9	2.0	1.1	0.4	0.2
4	(0.20, 0.30)	60.3	13.7	10.1	8.1	5.5	2.4
5	(0.20, 0.40)	18.9	13.3	16.4	18.9	19.8	12.6
6	(0.20, 0.50)	2.6	4.8	9.4	19.8	33.5	30.0
7	(0.20, 0.60)	0.2	0.7	2.7	11.0	33.0	52.4

10. DATA COLLECTION, SITE MONITORING, AND ADVERSE EVENT REPORTING

10.1 Records to Be Kept

Data collection will be based off Case Report Forms (CRFs) derived directly from the NIH TBI Common Data Elements project (www.commondataelements.ninds.nih.gov/TBI.aspx). This trial will leverage the CRFs and web-based database already developed by REDCap (Research Electronic Data Capture - Vanderbilt University) to utilize the TBI Common Data Elements project in which the University of Pittsburgh (David Okonkwo, site PI) participated. The CRFs have already been designed and implemented, which will contribute significantly to rapid, smooth rollout of the trial proposed herein.

Study personnel will collect information on subject characteristics such as demographics, medical history, and injury information. The initial assessment of the subject will be recorded including physical and neurological examination, vital signs, laboratory tests, and radiographic

imaging. In addition, as part of the baseline data collection, family members will be asked to complete a contact information form with the names, addresses and phone numbers of other people who could assist in locating him/her if the study coordination cannot locate him/her for the scheduled phone interviews. The study will consider the use of a locator service for patients potentially lost to follow-up.

Additional CRFs will be generated to record disease and injury-related events, treatments and interventions during the initial hospitalization, and safety data for adverse event reporting. The outcome end points will be based off the Core measures of the TBI Common Data Elements.

Federal law now holds the statute of limitations at six years to bring forward an allegation of research misconduct. In response to this extension, research records must be retained for a sufficient period to investigate an allegation of research misconduct - - a minimum period of six years. Additionally, existing Federal regulations [56 CFR 56.115(b)] require that IRB records be retained for at least 3 years after completion of the research. All records must be accessible for inspection and copying by authorized representatives of HHS and Food and Drug Administration at reasonable times and in a reasonable manner. At the end of the three year period, the IRB records may be boxed, labeled and sent to central storage for an additional 3-10 years. A log of stored records is maintained in the IRB office for retrieval if files are needed for audit or other purposes.

Records will be maintained in a de-identified manner in a secure, locked location to ensure confidentiality. Subjects will not be identified in any manner in any publications resulting from this project.

10.2 Role of Data Management

De-identified data will be collected from the pre-hospital period through 6 months post injury. A linking list will be maintained by the investigative team at each site to allow for patient follow-up. Protected health information (PHI) is confidential and not shared outside the study team. Written data will be stored in locked areas; electronic data will be password protected in secure zones. Patient name and contact information will be separated from subject data. The PI will monitor protocol compliance and data integrity. Routine data audits will be conducted internally to assure consistency and integrity of the data. Additionally, an independent data auditor will verify data quality.

10.2.1 Data Management Overview. The statistical center will manage the study specific database. Data will be linked by unique ID. The study statistician will independently review the forms and the entered data. The database will incorporate quality control checks at data entry, and quality assurance programs will be written for acquisition, management, tracking and retrieval and will be run regularly. The database will be backed up onto separate media. The database is maintained for statistical analysis purpose only; thus, all electronic files will be de- identified. The database will be password protected and maintained in secure research offices in a secure research building. Data validation checks identifying outliers will generate queries which will be evaluated and if necessary returned to the clinical study site for data validation. An audit trail will be maintained on changes to the database.

10.3 Quality Assurance

The Medical Monitor will oversee the Quality Assurance procedures related to the ICU management of episodes of intracranial hypertension. Dr. Elisabeth Wilde will ensure all outcomes personnel are properly trained and will review scoring of all outcome measures.

Database queries will be designed and implemented to oversee compliance with all study documentation and timely completion of CRFs. Protocol deviations, record completion, and regulatory compliance will be reviewed by PIs and Site Study Coordinators at each monthly conference call. All study documents and pertinent records will be available for inspection by the DSMB, the sponsor, or other designated monitoring authority.

10.4 ADVERSE EVENT REPORTING

Complications due to hypothermia include bradycardia or arrhythmias, a reduced immune system, blood clotting, increased insulin resistance, and electrolytes to shift, causing potassium levels to appear low because of increased absorption into cells(33;49). However, patients treated with intravascular cooling do not experience the complications of skin rashes, burns and skin death(33). Intravascular cooling catheters function as central venous catheters and contain working ports that facilitate routine critical care such as administering drugs and fluids and drawing blood.

Safety assessments will consist of monitoring and reporting adverse events (AEs), selected adverse events of interest, and serious adverse events (SAEs), both anticipated and unanticipated. An *Adverse Event* is any undesirable and unintended, although not necessarily unexpected, event occurring in human subjects as a result of (a) the interventions and interactions used in the research; or (b) the collection of identifiable private information under the research. *A Serious adverse event* is an adverse event that led to death, or to serious deterioration in the health of the subject, that resulted in death, was life-threatening, required hospitalization (initial or prolonged), resulted in disability or permanent damage, congenital anomaly/birth defect, required intervention to prevent permanent impairment or damage, or other serious events (Important Medical Events). NOTE: Planned hospitalization for a preexisting condition, or a procedure required, without serious deterioration in health, is not considered a serious adverse event. *An unanticipated adverse device effect* as defined by FDA regulations, 2CFR 812.3(s) is any serious adverse effect on health or safety or any life- threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Each clinical site is instructed to report all fatal events, SAEs, and other unanticipated problems in the central database within 24 hours of first knowledge of the event. Additionally, all current study data for that particular subject must be entered to allow for timely review by the internal and external medical monitors. Upon entry of a SAE, the central database triggers notification of the SAE to the medical monitor. Following formal review, the SAE is forwarded to the DSMB for review.

The independent Research Monitor for the HOPES Trial is Michael Diringer, MD, Chairman of the DSMB. Dr Diringer has applicable expertise in managing neuro-critical care patients, the use of temperature management and treatment with hypothermia; he is a former member of his local IRB and is an experienced, highly regarded researcher. He is an expert with the nature of risk(s) identified in the research protocol, and he is independent of the team conducting the research involving human subjects. He has no conflict of interest and is not be under the supervision of the PI, other investigators or research staff. Dr Diringer, as the independent research monitor, will identify to the research team any concerns regarding safety, ethical and scientific integrity. Serious, unexpected, related events are reported to the IRB by the site PI. Dr. Diringer's comments on these events will be included in the IRB reporting. Dr Diringer as the independent Research Monitor has the authority to stop the research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects. The research monitor will review adverse events reported to him by the study team and, report if he agrees with the site- PI's assessment of relationship to the study. The research monitor reviews the principal investigators reports on serious adverse eents and indicats whether he agrees with the assessment provided by PI. Reports for events determined by either the investigator or research monitor to be possibly or definitely related to participation and reports of events resulting in death will be promptly forwarded to the USAMRMC ORP HRPO by the study team.

If the investigator and/or the medical monitor believe the AE is serious, study related (possibly, probably or definitely), and unexpected, the SAE will be sent immediately to the DSMB. The determination of a probable or possible relationship to the hypothermia treatment will be discussed with the DSMB to determine what, if any, action should be taken with regard to continuation of the trial.

Following the determinations made by the DSMB, the PI will distribute all appropriate information to the clinical sites and their respective IRBs per local requirements. Finding of a significant number of study-related AEs and SAEs may lead to a change in consent forms or lead to decisions about modifying the protocol or discontinuing the trial.

11. HUMAN SUBJECTS

11.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB responsible for oversight of the trial at each of the participating centers. A signed consent form will be obtained for every subject when feasible. Since subjects in this trial cannot consent for themselves, a LAR, or person with power of attorney, must sign the consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the LAR, and this fact will be documented in the subject's record. A proposed Informed Consent template is attached as **Appendix I.** If a subject is enrolled in the study and subsequently dies prior to obtaining consent, when feasible, the investigator will inform the subject's LAR or family members about the subject's participation personally at the earliest feasible opportunity. The study team will work within existing hospital practices to locate patients' next of kin. The study will maintain copies of medical record documentation indicating efforts made to identify the subject and their next of kin. If the hospital team (e.g.,

social work) identifies next of kin, after the hospital team has contacted the next of kin and informed them of the subject's death we will attempt to talk with family about the subject's participation in the study for up to 5 days after death. In cases where it is not feasible to provide information to the subject (e.g.,death, mentally incompetent) or the LAR/family (e.g., identitiy never determined) each site is requested to obtain a HIPAA Privacy Rule waiver to allow study use and retention of the data.

11.2 Subject Confidentiality

All CT scans, evaluation forms, reports, and other records required by this trial that leave the site will be identified only by the Uniform Identification Number (UID) to maintain subject confidentiality. All on-site records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, or the Office of Human Research Protection (OHRP).

11.3 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the sponsor, the OHRP, or other government agencies as part of their duties to ensure that research subjects are protected. An individual IRB may discontinue the study at the clinical site it oversees, but the action is limited to that individual site.

11.4 Risk Analysis

Biocompatibility, bench, animal, other clinical studies (IDE 990263) and long-term use in humans have all shown that the ZOLL IVTM System appears to be safe for use. The system is made of materials that are commonly used in other medical devices with comparable applications and all materials have been tested in accordance with ISO 10993-1. All components of the ZOLL IVTM Catheters and ZOLL Thermogard XP System, and accessories have been cleared for commercial use by the FDA under 510(k) (K101987 and K072234).

11.4.1 Increased Risks and Benefits to Study Participants Elevated ICP secondary to TBI which is associated with increased morbidity and mortality is responsive to hypothermia. Increasingly, therapeutic hypothermia is used to treat refractory intracranial hypertension in TBI. Additionally, experimental evidence suggests induced hypothermia of 32-35°C early post injury may be neuroprotective. It is this early neuroprotective effect of hypothermia that is therapeutic aim of this study. TBI resulting in SDH occurs in over 40,000 Americans annually with up to 70% of these injuries resulting in death or severe disability(27). Risks associated with hypothermia may include shivering, hypovolemia, electrolyte disorders, hyperglycemia, pneumonia, and some risk of catheter-related thrombosis or possible catheter-related infection with intravascular cooling devices. Risks are minimized by reaching the goal temperature as quickly as possible, rewarming slowly and removing the intravascular catheter within 5 days of placement(33). Risk is relative in an entity with high mortality, and may be considered relative to a procedure that may increase the chances of good neurological outcome. The risk of ECoG brain activity monitoring includes the risk of infection or bleeding in approximately 1-5%, but no such complications have been observed previously in similar patients who have undergone this procedure. The electrode strip will be removed at the bedside by the neurosurgeon. There is approximately a 1-2% risk for difficulty in removing the strip.(43)

11.4.2 Potential Benefits Use of therapeutic hypothermia (cooling) following traumatic SDH may offer certain advantages to subjects prior to surgical evacuation of the SDH. Cerebral ischemia and hypoxia along with excitotoxicity, inflammation, disruption of blood brain barrier and edema are some of the pathological consequences of TBI. Therapeutic hypothermia may attenuate hypoxia, ischemia and energy dysfunction and it may reduce reperfusion injury. Hypothermia may decrease the frequency of cortical depolarizations which are a pathological mechanism associated with TBI.

Benefits known to be associated with therapeutic hypothermia as described in the scientific literature include:

- Improved neurologic outcome
- Improved management of elevated intracranial pressure.

Potential benefits that may be associated with use of the ZOLL IVTM System include:

- Improved neurologic outcome
- Improved management of elevated intracranial pressure.

Potential benefits to all subjects may be associated with participation in the study this may include:

- Serial assessments performed by the study team and others including monitoring for shivering, monitoring compliance with brain trauma guidelines and/or local guidelines; research team members monitoring of subjects for adverse events.
- Controlled temperature management (at least 48hrs) will minimize risk of fever in subjects during that period.
- Follow-up care including functional outcomes assessments performed at 4-6 weeks and 6months (±3 weeks).

There is no guarantee that participation in this study or use of hypothermia will benefit the study subject. However, collection of such study data may provide added benefit for future traumatic SDH subjects.

11.4.3 Methods to Minimize Risk Although no assurances or guarantees can be made, there is a reasonable expectation that the use of this device is safe within the context of the trial and may be beneficial. Cooling using the IVTM System, for instance, may result in improved temperature control relative to the standard techniques already in use (i.e., surface cooling).

Additionally, the following measures will be taken to minimize risk to subjects:

- The protocol will be evaluated by the investigators, institution review boards and DSMB to ensure subject safety and welfare throughout the study.

- Potential subjects will be carefully evaluated against the inclusion/exclusion criteria before entering the clinical study to ensure that their medical status is appropriate.

- Physicians and staff will receive adequate training 1) in the protocol before first enrollment, and 2) in the IVTM System prior to first use. Physicians will employ sterile technique during catheter insertion and extraction and will follow aseptic wound care procedures. The puncture site will be evaluated on a regular basis.

- Patients will be carefully monitored for potential side effects (shivering, electrolyte disorders, infections, arrhythmias) and rewarming will be slow and controlled to avoid rebound elevated ICP. Duration of cooling (48hr-5d) and timing of rewarming will be individualized (based on ICP, potassium levels, etc.).

- Conventional means of temperature control (cooling/warming blankets, etc.) may be kept on "standby" should use be deemed necessary by the Investigator. Subjects will receive standardized critical care with careful monitoring of: vital signs, cardiac rhythm, pulmonary status, renal function, fluid electrolytes and blood coagulation, etc.

- Study procedures will be performed in appropriate treatment rooms using trained emergency, neurosurgery or other personnel. Therefore, should a subject require additional interventions, these procedures may be initiated as soon as possible. Subjects will be carefully monitored throughout the treatment and follow-up period. Subjects will have frequent physical exams that include general physical assessment and evaluation for symptoms and assessment existing or developing adverse events. Subjects who require additional procedures will be carefully monitored in a method appropriate for that procedure.

- Data will be monitored as it is submitted to the coordinating center. The study monitor and statistical team will conduct monitoring throughout the course of the study to assess protocol compliance and identify any issues that could affect study subject safety or welfare.

- The DSMB and Sponsor will receive regular reports of subject outcomes and adverse events. Should any trend substantiate possible harm, the study will be terminated. Unanticipated adverse device effects/events will be reported to the IRB, DSMB, Sponsor and FDA.

11.4.4 Justification of the Study Based on the risks identified and the procedural and monitoring methods employed to minimize these risks, the investigators believe that the potential benefits of treatment with the ZOLL IVTM System outweigh the associated risks with the treatment procedure.

12. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the institutional agreements and Principal Investigators. Any presentation, abstract, or manuscript may be made available for review by the sponsor prior to submission.

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