Therapeutic Hypothermia After Pediatric Cardiac Arrest (The THAPCA Trials)

The THAPCA Trials Investigators
Funded by the National Heart, Lung, and Blood Institute (NHLBI)

Protocol Version 1.12
Version Date: October15, 2012
Printing Date: October 8, 2012

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The THAPCA Trials Protocol was developed with active support and participation of two Federally funded research networks, and grants R21-HD044955 and R34-HD050531 from the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development (NICHD). The THAPCA Trials are funded by the National Heart, Lung, and Blood Institute (NHLBI) through Cooperative Agreements with the University of Michigan (U01-HL094345, PI Frank Moler, M.D.) and the University of Utah (U01-HL094339, PI J. Michael Dean, M.D.).

The Pediatric Emergency Care Applied Research Network (PECARN) Research Node Centers are the University of California at Davis, Children's National Medical Center, University of Michigan at Ann Arbor, and Columbia University, and are supported by Cooperative Agreements U03-MC00001, U03-MC00003, U03-MC00006, and U03-MC00007, from the Emergency Medical Services for Children (EMSC) Program, Maternal and Child Health Bureau, Health Resources and Services Administration. The lead PECARN investigator for the development of this protocol was Frank Moler, M.D., University of Michigan.

The NICHD Collaborative Pediatric Critical Care Research Network (CPCCRN) Clinical Centers are the Arkansas Children's Hospital, Children's Hospital of Pittsburgh, Children's National Medical Center, Children's Hospital of Los Angeles, Seattle Children's Hospital, and Children's Hospital of Michigan, and are supported by Cooperative Agreements U10-HD500009, U10-HD049983, U10-HD049981, U10-HD050012, U10-HD049945, and U10-HD050096, respectively, from the National Institute for Child Health and Human Development (NICHD). The lead CPCCRN investigator for the development of this protocol was Kathleen Meert, M.D., Wayne State University.

This document was prepared by the THAPCA Data Coordinating Center located at the University of Utah School of Medicine, Salt Lake City, Utah. The THAPCA Data Coordinating Center is supported by Cooperative Agreement U01-HL094339 from the National Heart, Lung, and Blood Institute (NHLBI). The University of Utah is also the PECARN Central Data Management and Coordinating Center and the CPCCRN Data Coordinating Center. The CDMCC at the University of Utah is supported by Cooperative Agreement U03-MC00008 from the Emergency Medical Services for Children (EMSC) Program, Maternal and Child Health Bureau, Health Resources and Services Administration. The CPCCRN Data Coordinating Center at the University of Utah is supported by Cooperative Agreement U01-HD049934 from the National Institute for Child Health and Human Development (NICHD).

This document was written and typeset using LaTeX 2ε.

PROTOCOL TITLE:

Therapeutic Hypothermia After Pediatric Cardiac Arrest

Short Title: The THAPCA Trials

Lead Investigator and Author:
Frank Moler, M.D.
University of Michigan

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I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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1 Study Overview

Cardiac arrest (CA) in childhood is a tragic event that often results in either death or poor quality neurological survival. This observation is especially true of CA in the out-of-hospital setting where asphyxial arrests are common. In this setting, mortality is very high and neurological sequelae are common in survivors. In contrast, outcomes after cardiac arrest in the in-hospital setting are better. Approximately a quarter of cases survive with the majority reported to have good neurological outcomes. This protocol describes the Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) Trials. THAPCA will consist of two simultaneous trials for children suffering cardiac arrest in the out-of-hospital setting (THAPCA-OH Trial) or in the in-hospital setting (THAPCA-IH). Findings of a well-executed randomized controlled trial (RCT) in the pediatric population are urgently needed based on prior animal studies and recent clinical trials information in adults with out-of-hospital cardiac arrest and newborns with hypoxic ischemic encephalopathy that demonstrated efficacy of therapeutic hypothermia to improve neurological outcome.

1.1 Study Design

The THAPCA Trials are two prospective randomized controlled trials of therapeutic hypothermia after cardiac arrest in children. Each THAPCA Trial will be analyzed as an intention to treat study. The THAPCA Trials include one for out-of-hospital cardiac arrests (THAPCA-OH Trial), and one for in-hospital cardiac arrests (THAPCA-IH Trial). These trials will be analyzed separately, because etiologies and patient outcomes of these groups are substantially different.

1.2 Study Hypotheses and Endpoints

1.2.1 Study Hypotheses

The hypotheses of the THAPCA Trials are that (1) therapeutic hypothermia will improve survival and neurobehavioral outcome following out-of-hospital cardiac arrest in children (THAPCA-OH Trial); and (2) therapeutic hypothermia will improve survival and neurobehavioral outcome following in-hospital cardiac arrest in children (THAPCA-IH Trial). These hypotheses will be tested independently.

1.2.2 Primary Endpoint

The primary endpoint of each THAPCA trial is survival with good neurobehavioral outcome at 12 months post arrest. The Vineland Adaptive Behavior Scales (VABS-II) will be used to provide a standardized, quantifiable measure of neurobehavioral function in survivors. Poor neurobehavioral functioning is defined as a standardized VABS-II score less than 70 at 12 months. Children with a pre-cardiac arrest baseline VABS-II standardized score less than 70 will be included in the trials but will be excluded from analysis of the primary outcome. Pre-cardiac arrest baseline VABS-II information will be completed retrospectively by the caregiver (as soon as possible after enrollment to decrease retrospective bias), and the 12 month VABS-II assessment will be conducted centrally by telephone interview by the Kennedy Krieger Institute (Johns Hopkins School of Medicine, Baltimore, MD).

1.2.3 Secondary Endpoints

Secondary endpoints of each THAPCA trial are:

1. Survival at 12 months post cardiac arrest;
2. Change in neurobehavioral function from pre-cardiac arrest baseline to 12 month measurement (VABS II);

For survivors only,

3. Neuropsychological scores at 12 month evaluation;
4. Neurological abnormality scores at 12 month evaluation.

1.2.4 Safety Endpoints

Safety endpoints of this study are:

1. All-cause 28 day mortality;
2. Incidence of culture proven infection (blood, urine, respiratory, or other) within 7 days of cardiac arrest;
3. Incidence of arrhythmias within 7 days of cardiac arrest;
4. Blood products required within 7 days of cardiac arrest. Blood products are defined specifically here to include red blood cells, platelets, fresh frozen plasma, and cryoprecipitate.

1.3 Patient Eligibility

The study population is the pediatric population greater than 48 hours and less than 18 years of age who experience cardiac arrest for two minutes or longer with return of spontaneous circulation (ROSC). Recently the nomenclature for ROSC has been changed to return of circulation (ROC) by the AHA 2005 guidelines to account for cases with mechanical life support rescue. The term ROSC/ROC will be used in this protocol to reflect the recent change in terminology.

1.3.1 Inclusion Criteria

Patients will be eligible for enrollment if they meet *all* of the following inclusion criteria:

- patient suffered cardiac arrest requiring chest compressions for at least 2 minutes (120 seconds) with ROSC/ROC for at least 20 minutes; AND
- age greater than 48 hours (with a corrected gestational age of at least 38 weeks) and less than 18 years; AND
- patient requires continuous mechanical ventilation; AND
- the cardiac arrest was unplanned (i.e., not part of cardiac surgical procedure)

1.3.2 Exclusion Criteria

Patients will be ineligible for enrollment if *any* of the following exclusion criteria are met:

- the parent or legal guardian does not speak English or Spanish (the only two languages in which VABS II is standardized)
- randomization is impossible within six hours of ROSC; OR
- patient is on extracorporeal membrane oxygenation (ECMO) when arrest occurs; OR
- continuous infusion of epinephrine or norepinephrine at very high doses (≥ 2 μg/kg/minute) received immediately prior to randomization; OR

- Glasgow Coma Scale motor response of five (localizing pain or for infants less than two years, withdraws to touch) or six (obeys commands, or for infants, normal spontaneous movement) prior to randomization; OR
- history of a prior cardiac arrest with chest compressions for at least two minutes during the current hospitalization but outside the 6 hour window for randomization; OR
- pre-existing terminal illness with life expectancy < 12 months; OR
- lack of commitment to aggressive intensive care therapies including do not resuscitate orders and other limitations to care; OR
- cardiac arrest was associated with severe brain, thoracic, or abdominal trauma; OR
- active and refractory severe bleeding prior to randomization; OR
- near drowning in ice water with patient core temperature ≤ 32 °C on presentation; OR
- patient is pregnant; OR
- patient participation in a concurrent interventional trial whose protocol, in the judgment of the THAPCA investigators, prevents effective application of one or both THAPCA therapeutic treatment arms, or otherwise significantly interferes with carrying out the THAPCA protocol; OR
- patient is newborn with acute birth asphyxia; OR
- patient cared for in a neonatal intensive care unit (NICU) after arrest (ie, would not be admitted to PICU); OR
- patient has sickle cell anemia; OR
- patient known to have pre-existing cryoglobulinemia; OR
- central nervous system tumor with ongoing chemotherapy or radiation therapy; OR
- chronic hypothermia secondary to hypovolemic, pituitary, or related condition for which body temperature is consistently below 37 °C ; OR

- progressive degenerative encephalopathy; OR
- any condition in which direct skin surface cooling would be contraindicated, such as large burns, decubitus ulcers, cellulitis, or other conditions with disrupted skin integrity (NOTE: patients with open chest CPR should be included but placement of cooling mattresses will be modified as needed); OR
- previous enrollment in the THAPCA Trials.

1.3.3 Decision to Enroll Subject

Participation in THAPCA should be offered to all patients who meet inclusion and exclusion criteria, unless:

- the attending physician does not wish the patient to be offered the opportunity to participate in the study; OR
- the site investigator and/or study coordinator are unable to recruit an additional patient into the study at the time that a new eligible patient is identified.

Parents or legal guardians who are not approached because the attending physician does not wish the patient to be offered participation in the study will be tracked by the DCC in order to assure that enrollment bias does not occur. The attending physician will be asked for the specific reasons for not offering participation for the patient.

1.4 Interventions

Patients will be randomly assigned, in a 1:1 ratio, to receive either therapeutic hypothermia or normothermia (control) therapy within six hours of ROSC/ROC. Therapeutic hypothermia is defined as surface cooling to 32-34 degrees Celsius (°C), for a total duration of 48 hours. This will be followed by slow rewarming to a normal temperature (36.0-37.5 °C range) over approximately 16 hours. The control group will have patient temperature maintained within the defined normothermic range (36-37.5 °C). Normothermia will be maintained in the control arm during the periods corresponding to cooling, hypothermia, and rewarming of the hypothermia arm. Both study groups will then have temperature maintained in the normal range (36-37.5 °C) until 120 hours post ROSC/ROC. Thereafter, temperature will be maintained as is practiced routinely in the clinical center's PICU.

1.5 Anticipated Recruitment and Study Duration

The planned duration of the study is six years; five years will be used for patient recruitment and one additional year for patient follow up. It is anticipated that participating sites will recruit between 5 and 20 patients annually. Based on HD044955 cohort pilot data and the size and number of sites participating in the current study, we anticipate enrolling between 150 to 250 patients per year for a total enrollment of 750 to 950 patients (300 to 350 out-of-hospital arrests and 450 to 600 in-hospital arrests).

2 Background and Significance

2.1 Epidemiology and Outcomes of Cardiac Arrest

Cardiac arrest (CA) in childhood is a tragic event that often results in either death or poor quality neurological survival. This is especially true of CA that occurs in the out-of-hospital (OH) setting where the majority of reports describe very poor quality neurological outcomes or death in the large proportion of cases even with return of spontaneous circulation.[1–15] For CA occurring in the in-hospital (IH) setting outcomes are also poor, but significantly better than in the OH setting. Survival is much higher and neurological status usually returns to baseline.[16–19] Young and Seidel reviewed the literature of pediatric CPR and summarized 44 studies conducted since 1970.[20] A total of 3,094 patients were analyzed with an overall survival from OH CA of 8.4% and overall survival for IH CA of 24%. Similarly, Nadkarni reported 236 survivors of 880 cases (27%) from a national database of IH CA.[19] Neurological outcome in survivors was reported as good in 58%, poor in 17%, and unknown in 25% (good in 77% of subset known). Johns Hopkins investigators summarized a 20-year experience of 89 hospital survivors to hospital discharge of IH and OH CA.[21] At one year follow up, 86/89 (96%) were alive, and in the subgroup available, 71/73 (97%) had no change from discharge to one year follow up in their general classification of disability.[21]

2.2 Hypothermic Neuroprotection

2.2.1 Animal Studies

In experimental animal models there is strong evidence that post-ischemia therapeutic hypothermia (TH) can protect the brain from injury.[22–25] Major

variables that influence the efficacy of post-ischemic cooling include: the experimental model (animal species and age, focal or global cerebral ischemia); the time interval between the ischemic event and the initiation of cooling (efficacy generally declines with increased delay); the depth of cooling (mild TH typically defined as core and/or brain temperature reduction to 32 to 34 °C can be effective); duration of cooling (longer cooling periods (>24 hours) more effective); and whether specific drugs (e.g., anesthetic agents[26]) are administered in conjunction with cooling. In adult rodent global and focal cerebral ischemia models, TH protocols that incorporate prolonged (e.g. 24-36 hours) periods of post-ischemic mild cooling result in sustained decreases in neuronal damage and improved functional performance.[23, 24]

2.2.2 Adult Studies

Until recently, interventions to improve neurological outcome and survival following CA had not been observed in human RCTs. In 2002, two RCTs conducted in Europe and Australia reported higher survival and improved neurological outcome in adults who were treated with mild TH (32-34 °C) following OH CA secondary to ventricular fibrillation.[27, 28] In the European trial, 55% receiving TH had a favorable neurological outcome compared to 39% in the control normothermic group.[27] In the Australian RCT, 49% of patients receiving TH had a good neurological outcome compared to only 26% in the control group.[28] Duration of cooling was short and varied in the studies from 12 to 24 hours. Most patients received surface cooling by application of ice packs around the head and torso in order to achieve mild TH (32-34 °C). After the hypothermia period of 12 to 24 hours, rewarming was initiated and achieved over approximately 6 to 12 hours. Number-needed-to-treat estimates to prevent one death or for one additional good neurological outcome were in the 4 to 7 range.[27, 28] Increased rates of serious adverse patient events attributed to TH were not observed in either adult study, although the European study reported a trend for increase in infection risk.[27]

2.2.3 Neonatal Studies in Hypoxic Ischemic Encephalopathy

Results from two RCTs of TH for treatment of neonatal hypoxic ischemic encephalopathy (HIE) have recently been reported. In the CoolCap Study, selective head cooling resulting in mild systemic TH (34-35 °C) for 72 hours, improved neurodevelopmental outcome at 18 month follow-up in infants with moderate but not severe HIE.[29] The NICHD Neonatal Research Network re-

cently reported the efficacy of whole body TH in term infants with moderate and severe HIE.[30] Cooling to 33.5°C was initiated within six hours after birth, achieved within 90 minutes, and maintained for 72 hours. Primary outcome of death or moderate/severe disability at 18 months occurred in 44% of infants treated with TH and in 62% of controls, risk ratio 0.72(95%CI: 0.54-0.95), with a number-needed-to-treat (NNT) of 5.5. The authors concluded that TH was effective and safe in newborns with HIE.[30] At least three additional studies of TH in neonatal HIE are in progress. Table 1 on the facing page summarizes these adult and neonatal studies.

Table 1: Adult Cardiac Arrest and Neonatal HIE Studies of Hypothermia

Study	Population and Setting	Cooling Goal	Time to Cooling	Cooling Duration	Effect Size	Study Size
Australia[28] (2002)	Adult (Out of Hospital)	32 to 34°C	≈ 0 hours	12 hours	23 %	74
Europe[27] (2002)	Adult (Out of Hospital)	32 to 34°C	1.8 hours	24 hours	16 %	275
Cool Cap[29] (2005)	Neonatal (HIE)	34 to 35°C	≤ 6 hours	72 hours	18 %	234
NICHD[30] (2005)	Neonatal (HIE)	33.5°C	≤ 6 hours	72 hours	18 %	208
Eicher[31, 32] (2005)	Neonatal (HIE)	33.5°C	≤ 6 hours	48 hours	32 %	65
TOBY (in progress)	Neonatal (HIE)	33 to 34°C	≤ 6 hours	72 hours	Not Finished	236
ICE (in progress)	Neonatal (HIE)	33 to 34°C	≤ 6 hours	72 hours	Not Finished	276
Simbruner (in progress)	Neonatal (HIE)	33 to 34°C	≤ 6 hours	72 hours	Not Finished	150

2.2.4 Pediatric Studies

No RCTs have been conducted to examine TH use following CA in infants or children. Early phase II studies of TH for pediatric traumatic brain injury reported promising trends for improved outcomes.[33, 34] Adverse events were similar in controls and TH treated patients with the exception of tachycardia that was easily managed with fluid administration.[33, 34] However, a trend for higher mortality ($p = 0.06$) was observed in a recent RCT of therapeutic hypothermia for pediatric traumatic brain injury,[35] supporting the imperative of pediatric trials specific to cardiac arrest.

2.3 Rationale for Current Study

2.3.1 Different Etiology of Cardiac Arrest in Children and Adults

A recent survey ranked the efficacy of TH therapy as one of the most important unanswered questions related to pediatric resuscitation.[36] Since no effective interventions for neuroprotection following pediatric CA exist currently, some initially recommended extrapolation of adult study findings to pediatric practice.[27, 28, 37] However, an expert committee concluded that it was important to validate the adult TH for CA findings in infants and children,[38, 39] because of differences in the pathophysiology of CA between populations. For example, mechanisms of CA in pediatrics vs. adults differ, especially in the OH setting. Asphyxia with a period of hypoxia followed by later ischemia is the common sequence leading to CA in pediatrics; whereas, sudden cardiac arrhythmias cause CA more commonly in adults. In children, CA occurs with asystole and/or pulseless electrical activity (PEA) being the most common presenting cardiac rhythms, while in adults a primary cardiac arrhythmia, usually ventricular fibrillation (VF) or pulseless ventricular tachycardia, leads to CA. Survival from pediatric VF is reported to be much greater than survival from pediatric asystole.[20]

2.3.2 Differences Between Out of Hospital and In Hospital Arrests

In-hospital (IH) and out-of-hospital (OH) pediatric cardiac arrests differ significantly and separately powered trials are required to determine the efficacy of TH in each setting. First, patients with IH cardiac arrest commonly have a major preexisting or acute illness that resulted in hospitalization. Cardiac arrest occurs as a secondary event to a serious illness in most of these cases. OH cardiac arrests occur commonly in children with no preexisting

illness (e.g. near drowning event). Second, the pathogenesis of arrests are different in the two settings. OH arrests commonly are due to asphyxial type events with a prior hypoxic period leading to arrest.[40] For IH cardiac arrest events, hypotension most commonly preceded cardiac arrest.[19] A third major difference is the resuscitation response in the two settings. In the OH setting, initial responders are often not extensively trained in pediatric resuscitation and do not have advance life support personnel and equipment available. The initial EMS response is often by groups that most commonly treat adult cases and infrequently treat children. IH cardiac arrests in children's hospitals are performed by a group of trained pediatric experts specially configured into formalized code teams. A recent NRCPR report described most pediatric IH arrests as occurring in locations with skilled caregivers readily available (PICU 65% or ED 13% settings). Nearly 95% of IH arrests were witnessed or monitored, whereas only 31% of out of hospital arrests are witnessed.[19, 40] Another major difference is hospital survival. A recent review of OH arrests summarized the existing literature. Excluding trauma associated arrests, survival to hospital admission occurred in approximately 24% of cases. Survival to hospital discharge occurred in 7% (28% of live admissions) and survival with "intact neurological survival" occurred in 2% (9% of live admissions).[40] For in hospital cardiac arrests, a recent report described 459 of 880 (52%) arrests to have ROSC/ROC. Of those with ROSC/ROC, 236 of the 459 (51%) survived to discharge. Of these survivors, the outcome was known for 177 children of which 136 (77%) had neurological outcomes that were classified as "good".[19]

2.3.3 Selection of Outcomes and Evaluating Efficacy

The goal of a post-CA intervention such as TH will be to not only increase the number of long-term survivors, but to increase the number of survivors with good neurological outcomes. The use of TH following pediatric CA could potentially result in increased numbers of survivors, but also result in more survivors with poor neurological outcomes. Alternatively, TH could be efficacious in children and result in both greater numbers of survivors and more survivors with good neurological outcome. Unfortunately, TH is potentially associated with adverse effects (e.g. arrhythmias, infection risk, neutropenia, bleeding), requiring it to be validated for pediatric efficacy in order to avoid a potentially harmful and somewhat resource intensive intervention in the event it is determined to represent an ineffective therapy.[41] If the efficacy of TH for pediatric CA can be established with an appropriately powered and executed RCT, then major changes in emergency medicine and

critical care therapeutic management of children would be warranted in the US and elsewhere.

2.4 Hypothermia Cohort and Pilot Study

The principal investigator (Dr. Moler) was awarded funding for a Hypothermia for Pediatric Cardiac Arrest Planning Grant (HD044955) in July 2003. This cohort study of pediatric CA was conducted in conjunction with 15 participating sites from the Pediatric Emergency Care Applied Research Network (PECARN).[42, 43] Collectively the 15 sites have more than 340 PICU beds and over 21,000 annual PICU admissions. Each of the 15 clinical centers had a designated physician investigator and research assistant for data abstraction and data entry. Data were abstracted from medical records at each Center for the 18-month period from July 1, 2003 to December 31, 2004. The study population for this pilot study included all children hospitalized at one of the 15 clinical sites who sustained a CA requiring chest compressions for at least one minute and who had ROSC/ROC for at least 20 minutes in either the IH or OH setting during the 18 month period from July 1, 2003 to December 31, 2004.

From the HD044955 cohort study, we had access to an extensive database available to help plan the current protocol. The following types of information were available: number of arrests, demographic information (age, gender, ethnicity, race), proportion of cases of in-hospital and out-of-hospital arrests, arrest specific information (such as initial and other cardiac rhythms, duration of CPR until ROSC/ROC, medications administered, cause of arrest, etc), time from arrest to PICU admission, minimum and maximum temperature during first 6 hour and other intervals following arrest, PCPC and POPC (pre-arrest, PICU discharge, and hospital discharge), length of PICU and hospital stay, complications (seizures, blood stream and other infections), placement of tracheostomy, placement of feeding tube, survival to hospital discharge, major cause of death, and hospital discharge location. Etiology of arrest, pre-existing conditions, drug therapies administered through 7 days, monitoring utilized post arrest through 7 days, therapies administered post arrest through 7 days (ECMO, dialysis, mechanical ventilation, etc), minimum and maximum values of chemistries, coagulation measures, and blood counts through 7 days were also available. Additionally, Glasgow coma scale, pupillary size, and mental status through 7 days were collected.

We also performed a 10 to 16 week pilot study at clinical sites that investigated likely study yield based on the inclusion and exclusion criteria

for the THAPCA Trials. This was used in conjunction with the cohort data to estimate available sample size for the trials.

3 Study Organization

3.1 Participating Institutions

The PECARN[42, 43] and the NICHD Collaborative Pediatric Critical Care Research Network (CPCCRN)[44] will participate in the THAPCA Trials. Additional large children's hospitals from the United States and Canada have been recruited to assure adequate patient recruitment.

PECARN was established in 2001 as the first federally funded national network for research in emergency medical services for children. PECARN is funded by cooperative agreements with the Maternal and Child Health Bureau (MCHB) at the Health Resources Services Administration as part of the Emergency Medical Services for Children (EMSC) program. The goal of the network is to conduct meaningful and rigorous multi-institutional research in the prevention and management of acute illnesses and injuries in children. PECARN consists of four Research Nodal Centers and the Central Data Management and Coordinating Center. The network includes 21 affiliated hospitals with emergency departments, of which 17 have pediatric intensive care units.

The Collaborative Pediatric Critical Care Research Network (CPCCRN) is funded by cooperative agreements with the National Institute of Child Health and Human Development (NICHD). The network was formed in 2005 and consists of six clinical centers (seven hospitals) and the Data Coordinating Center. The network conducts collaborative clinical trials and meaningful descriptive studies in pediatric critical care medicine, with the goal of improving the long-term outcomes of children who require critical care.

The PECARN and CPCCRN have conducted pediatric clinical trials and research studies over the past several years and will work together to conduct the THAPCA Trials. The protocol requires involvement from both the emergency department and the intensive care unit at each site and participation from all investigators will be facilitated by the involvement of both networks. The networks share the same data coordinating center (DCC) and have similar structures and operations. Three sites from the CPCCRN have already been involved in the PECARN hypothermia planning grant, and all of the PECARN sites that will participate have previously been involved in the planning grant with the exception of two sites that are new to

the network. Investigators from both networks have been actively involved in the planning of this trial. The steering committees of both networks have endorsed the study concept, and working groups from both networks have contributed to writing this protocol.

The University of Utah School of Medicine is the data coordinating center for both of these networks, and the same information systems are used to support all current studies in these networks. This includes Web-based communication, study database software, statistical analysis software, document tracking systems used for monitoring IRB approvals, protocol development systems, randomization services, training, and remote site monitoring.

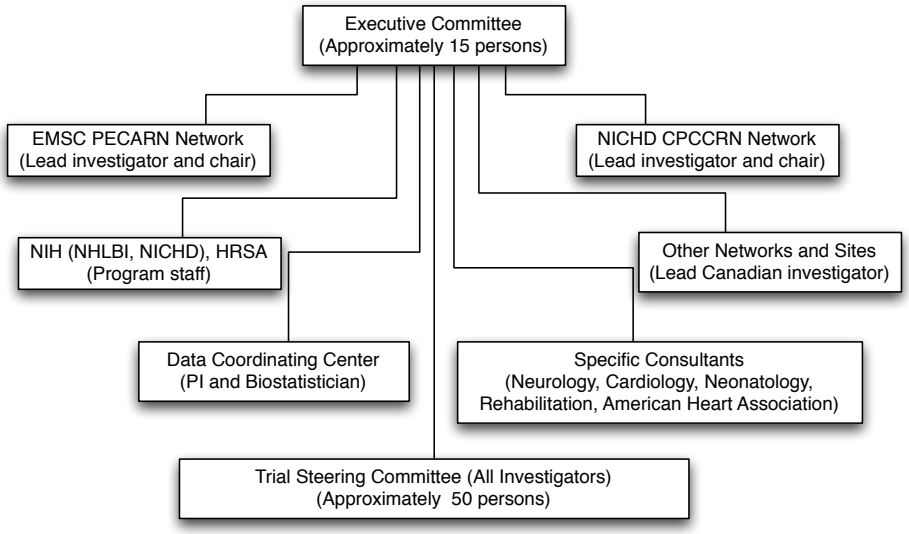

Figure 1: Organizational Chart for the THAPCA Study

3.2 Executive Committee

THAPCA will be governed by an Executive Committee (Figure 1). The Executive Committee will consist of the chairpersons of each of the two networks, a lead investigator from each of the two networks, a representative investigator from the current Canadian pilot study, two investigators from the Data Coordinating Center (DCC), and Federal representatives from the funding agency of this trial (NHLBI) and the funding agencies of the two networks. Consultants include a principal investigator from the NICHD

neonatal hypothermia RCT, a pediatric neurologist, and a pediatric cardiologist. Additional experts are anticipated to be consulted by the Executive Committee and may be added to the Executive Committee if deemed necessary by the members already listed.

The Executive Committee will be empowered to make all necessary decisions on behalf of the THAPCA Trials. It is anticipated that the Executive Committee will meet on a monthly basis, by teleconference or in person.

3.3 Steering Committee

The Steering Committee will consist of all investigators participating in THAPCA, as well as all members of the Executive Committee. Due to its large size, the Steering Committee is advisory to the Executive Committee. It is anticipated that the entire Steering Committee will meet at least twice annually, once in person and additional meetings by teleconference.

3.4 Study Coordinators

The research coordinators for this study will ideally meet twice per year to facilitate initial and on-going study training. One of these meetings may coincide with the Steering Committee, but logistical issues may make this impossible. The DCC staff will prepare all training materials, in conjunction with the lead THAPCA investigators, and will staff the training meetings.

The DCC staff will meet by teleconference with the research coordinators bi-monhtly or as needed to facilitate the execution of the project. After the trial has been underway for at least one year, the frequency of these meetings may be decreased at the discretion of the DCC staff.

3.5 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will be appointed by the National Heart, Lung, and Blood Institute (NHLBI). Its logistics will be handled by DCC. More details are provided in Section 11.1 on page 72.

4 Study Hypotheses and Endpoints

4.1 Study Hypotheses

The hypotheses of the THAPCA Trials are that (1) therapeutic hypothermia will improve survival and neurobehavioral outcome following out-of-hospital

cardiac arrest in children (THAPCA-OH Trial); and (2) therapeutic hypothermia will improve survival and neurobehavioral outcome following in-hospital cardiac arrest in children (THAPCA-IH Trial). These hypotheses will be tested independently.

4.2 Primary Endpoint

The primary endpoint of each THAPCA trial is survival with good neurobehavioral outcome at 12 months post arrest. The Vineland Adaptive Behavior Scales (VABS-II) will be used to provide a standardized, quantifiable measure of neurobehavioral function in survivors. Poor neurobehavioral functioning is defined as a standardized VABS-II score less than 70 at 12 months. Children with a pre-cardiac arrest baseline VABS-II standardized score less than 70 will be included in the trials but will be excluded from analysis of the primary outcome. Pre-cardiac arrest baseline VABS-II information will be completed retrospectively by the caregiver (as soon as possible after enrollment to decrease retrospective bias), and the 12 month VABS-II assessment will be conducted centrally by telephone interview by the Kennedy Krieger Institute (Johns Hopkins School of Medicine, Baltimore, MD).

4.3 Secondary Endpoints

Secondary endpoints of each THAPCA trial are:

1. Survival at 12 months post cardiac arrest;
2. Change in neurobehavioral function from pre-cardiac arrest baseline to 12 month measurement (VABS II);

For survivors only,

3. Neuropsychological scores at 12 month evaluation;
4. Neurological abnormality scores at 12 month evaluation.

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Safety endpoints of this study are:

1. All-cause 28 day mortality;

2. Incidence of culture proven infection (blood, urine, respiratory, or other) within 7 days of cardiac arrest;

3. Incidence of arrhythmias within 7 days of cardiac arrest;

4. Blood products required within 7 days of cardiac arrest. Blood products are defined specifically here to include red blood cells, platelets, fresh frozen plasma, and cryoprecipitate.

5 Patient Eligibility and Accrual

The study population is the pediatric population greater than 48 hours and less than 18 years of age who experience cardiac arrest for two minutes or longer with return of spontaneous circulation (ROSC/ROC).

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Patients will be eligible for enrollment if they meet *all* of the following inclusion criteria:

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- age greater than 48 hours (with a corrected gestational age of at least 38 weeks) and less than 18 years; AND
- patient requires continuous mechanical ventilation; AND
- the cardiac arrest was unplanned (i.e., not part of cardiac surgical procedure)

5.2 Exclusion Criteria

Patients will be ineligible for enrollment if *any* of the following exclusion criteria are met:

- the parent or legal guardian does not speak English or Spanish (the only two languages in which VABS II is standardized)
- randomization is impossible within six hours of ROSC; OR

- patient is on extracorporeal membrane oxygenation (ECMO) when arrest occurs; OR
- continuous infusion of epinephrine or norepinephrine at very high doses (≥ 2 μg/kg/minute) received immediately prior to randomization; OR
- Glasgow Coma Scale motor response of five (localizing pain or for infants less than two years, withdraws to touch) or six (obeys commands, or for infants, normal spontaneous movement) prior to randomization; OR
- history of a prior cardiac arrest with chest compressions for at least two minutes during the current hospitalization but outside the 6 hour window for randomization; OR
- pre-existing terminal illness with life expectancy < 12 months; OR
- lack of commitment to aggressive intensive care therapies including do not resuscitate orders and other limitations to care; OR
- cardiac arrest was associated with severe brain, thoracic, or abdominal trauma; OR
- active and refractory severe bleeding prior to randomization; OR
- near drowning in ice water with patient core temperature ≤ 32 °C on presentation; OR
- patient is pregnant; OR
- patient participation in a concurrent interventional trial whose protocol, in the judgment of the THAPCA investigators, prevents effective application of one or both THAPCA therapeutic treatment arms, or otherwise significantly interferes with carrying out the THAPCA protocol; OR
- patient is newborn with acute birth asphyxia; OR
- patient cared for in a neonatal intensive care unit (NICU) after arrest (ie, would not be admitted to PICU); OR
- patient has sickle cell anemia; OR
- patient known to have pre-existing cryoglobulinemia; OR

- central nervous system tumor with ongoing chemotherapy or radiation therapy; OR
- chronic hypothermia secondary to hypovolemic, pituitary, or related condition for which body temperature is consistently below 37 °C ; OR
- progressive degenerative encephalopathy; OR
- any condition in which direct skin surface cooling would be contraindicated, such as large burns, decubitus ulcers, cellulitis, or other conditions with disrupted skin integrity (NOTE: patients with open chest CPR should be included but placement of cooling mattresses will be modified as needed); OR
- previous enrollment in the THAPCA Trials.

5.3 Decision to Enroll Subject

Participation in THAPCA should be offered to all patients who meet inclusion and exclusion criteria, unless:

- the attending physician does not wish the patient to be offered the opportunity to participate in the study; OR
- the site investigator and/or study coordinator are unable to recruit an additional patient into the study at the time that a new eligible patient is identified.

Parents or legal guardians who are not approached because the attending physician does not wish the patient to be offered participation in the study will be tracked by the DCC in order to assure that enrollment bias does not occur. The attending physician will be asked for the specific reasons for not offering participation for the patient.

5.4 Subject Withdrawal

All patients withdrawn early from the study must have a reason for withdrawal recorded on the appropriate data collection form, and the circumstances leading to withdrawal must be described. All adverse events leading to withdrawal of study interventions must be fully documented and followed up as appropriate. This is particularly important when adverse events are

ongoing at the time of withdrawal, but the reason for withdrawal is not related to the adverse event.

If the study intervention is discontinued by the clinical care team because of adverse events, this does not constitute subject withdrawal from the study. All cases randomized in this study will be analyzed as an intention-to-treat.

If a subject's parents withdraw permission for the subject to continue in the study, all study interventions will be discontinued. The medical course of the subject will continue to be reviewed for adverse events until Day 14. If the subject experienced an Adverse Event from the time of randomization through Day 14 that has not resolved by Day 14, the Adverse Event will be followed until resolution or discharge, whichever is earlier. If the Adverse Event has not resolved by hospital discharge, please see section 11.2.6 of the protocol for further instructions.

5.5 Inclusion of Women and Minorities

The gender, ethnic, and racial composition of patients enrolled in the THAPCA Trials will be a function of the underlying referral population at each participating clinical center. Subjects from our retrospective chart review of cardiac arrest patients (Section 2.4 on page 20) were 47% white, 27% black, and 6% Hispanic. During this study, the DCC will monitor patient accrual by race, ethnicity, and gender.

5.6 Anticipated Recruitment and Study Duration

The planned duration of the study is six years; five years will be used for patient recruitment and one additional year for patient follow up. It is anticipated that participating sites will recruit between 5 and 20 patients annually. Based on HD044955 cohort pilot data and the size and number of sites participating in the current study, we anticipate enrolling between 150 to 250 patients per year for a total enrollment of 750 to 950 patients (300 to 350 out-of-hospital arrests and 450 to 600 in-hospital arrests).

5.7 Long Term Follow-up

Children who were enrolled in the THAPCA Trials represent a very valuable group to study for long term cognitive, developmental and medical sequelae. The subjects legal representative will be approached for consent to be contacted for future studies when deemed appropriate by the clinical centers IRB (i.e. at time of THAPCA consent, between 3 and 12 month visits or after the 12 month visit as appropriate).

6 Study Design & Methods

The THAPCA Trials are two prospective randomized controlled trials of therapeutic hypothermia after cardiac arrest in children. Each THAPCA Trial will be analyzed as an intention to treat study. The THAPCA Trials include one for out-of-hospital cardiac arrests (THAPCA-OH Trial), and one for in-hospital cardiac arrests (THAPCA-IH Trial) (see Figure 2). These trials will be analyzed separately, because etiologies and patient outcomes of these groups are substantially different (see Section 2.3.2 on page 18).

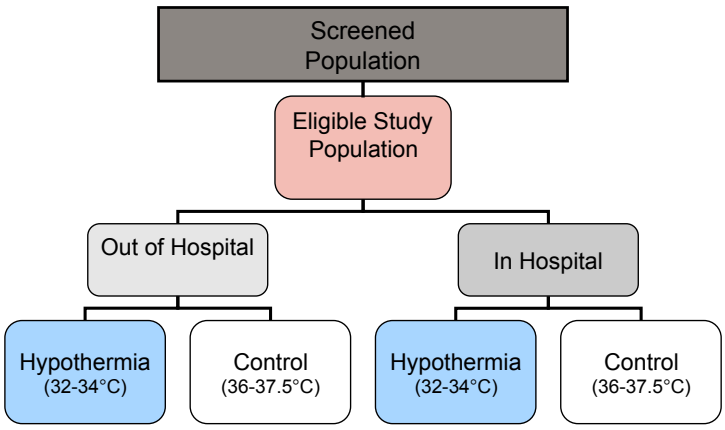

Figure 2: THAPCA Trials Diagram

The clinical care team (composed of physicians, nurses, and others) involved with direct patient care and the patient's family will not be blinded to the treatment group, because temperature is a routine vital sign required for patient care. However, individuals who conduct assessment of neurobehavioral outcome status at three and 12 months following CA will be blinded to the treatment group assignment.

6.1 Screening, Enrollment, and Randomization

Clinical investigators in each site will be pediatric critical care or emergency medicine specialists; in many sites, there will be an assigned investigator in the intensive care unit and in the emergency department. The THAPCA-OH (out-of-hospital) Trial will be enhanced by close cooperation between specialists in the emergency medicine and critical care.

For cardiac arrest cases occurring in the in-hospital (IH) setting, screening will be straightforward. The assigned study physician will be notified by the clinical team as soon as possible after the ROSC/ROC occurs. In the out-of-hospital (OH) setting, the emergency medicine (EM) staff will similarly notify the assigned study physician who performs screening of cases of any arrests occurring in or coming to the emergency department. In the event of a case at another facility, the PICU or EM clinical team arranging the transport will notify the study physician for screening.

The assigned study physician will screen/review each patient for potential eligibility. A screening log will be completed for all CA patients, whether eligible or not eligible. If a patient meets inclusion/exclusion criteria for study participation, the subject's parent(s)/guardian(s) will be approached for written informed permission for the child to participate in the appropriate THAPCA trial (see Section 10.2 on page 66). Following written permission, patients will be randomized to hypothermia treatment or normothermia control therapy. Patients must be randomized within six hours of ROSC/ROC.

Note: Pregnancy is a contraindication for participation in this study. All female patients of child-bearing potential must have a negative urine or blood pregnancy test prior to enrollment.

Randomization for each trial will be stratified by clinical center and patient age group (less than 2 years, 2 to 11 years, 12 years or older). The DCC will prepare randomization schedules using randomized blocks of varying length for each of these study strata. Patients within each stratum will be randomized in a 1:1 ratio to hypothermia or normothermia. Patient randomization will be accomplished using either an Internet connection to the DCC, or an interactive telephone service.

We expect participating centers to maintain equipoise with respect to the use of TH after CA in children. While we cannot prohibit the use of TH outside of the THAPCA Trials, we will track how many eligible patients were not approached for enrollment in the study by center. In addition, we will obtain information about the use of off study hypothermia as well as baseline cardiac status of all children meeting inclusion criteria but not enrolled in the study. If there are clinical centers in which the therapy is frequently offered outside of THAPCA, these centers will be dropped from the study due to concerns of enrollment bias.

6.2 Overview of Interventions

Patients will be randomly assigned to receive either therapeutic hypothermia or normothermia (control) therapy in a 1:1 ratio. See Figure 3 on the next page for an overview of the intervention timeline. Therapeutic hypothermia is defined as surface cooling to 32-34 degrees Celsius (°C), for a total duration of 48 hours. This will be followed by slow rewarming to normal temperature (36.0-37.5 °C range) over approximately 16 hours. The control group will have patient temperature maintained within the defined normothermic range (36-37.5 °C). Normothermia will be maintained in the control arm during the periods corresponding to cooling, hypothermia, and rewarming of the hypothermia arm. Both study groups will then have temperature maintained in the normal range (36-37.5 °C) until 120 hours post cardiac arrest ROSC/ROC. Thereafter, temperature will be maintained as is practiced routinely in the clinical center's PICU. See Section 7 on page 45 for a detailed outline of the interventions, patient monitoring, and concomitant therapies.

6.3 Laboratory Testing

Laboratory testing will be conducted throughout the intervention period (0 to 120 hours). The schedule of assessments is similar for the the two assigned treatment groups.

Electrolytes (sodium, potassium, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, chloride) will be monitored at the following timepoints:

For the Hypothermia Group:

- During Active Cooling and Re-warming: electrolytes will be completed at least every 6 hours. If electrolytes are drawn more frequently than once every 6 hours, all values will be recorded
- During Hypothermia and Normothermia: electrolytes will be completed at least every 12 hours. If electrolytes are drawn more frequently than once every 12 hours, those values drawn closest to 8 am and 8 pm will be recorded.

For the Normothermia Group:

- If active cooling/warming is required to get the subject to normothermic temperature; electrolytes will be completed at least every 6 hours. If electrolytes are drawn more frequently than every 6 hours, all values will be recorded.

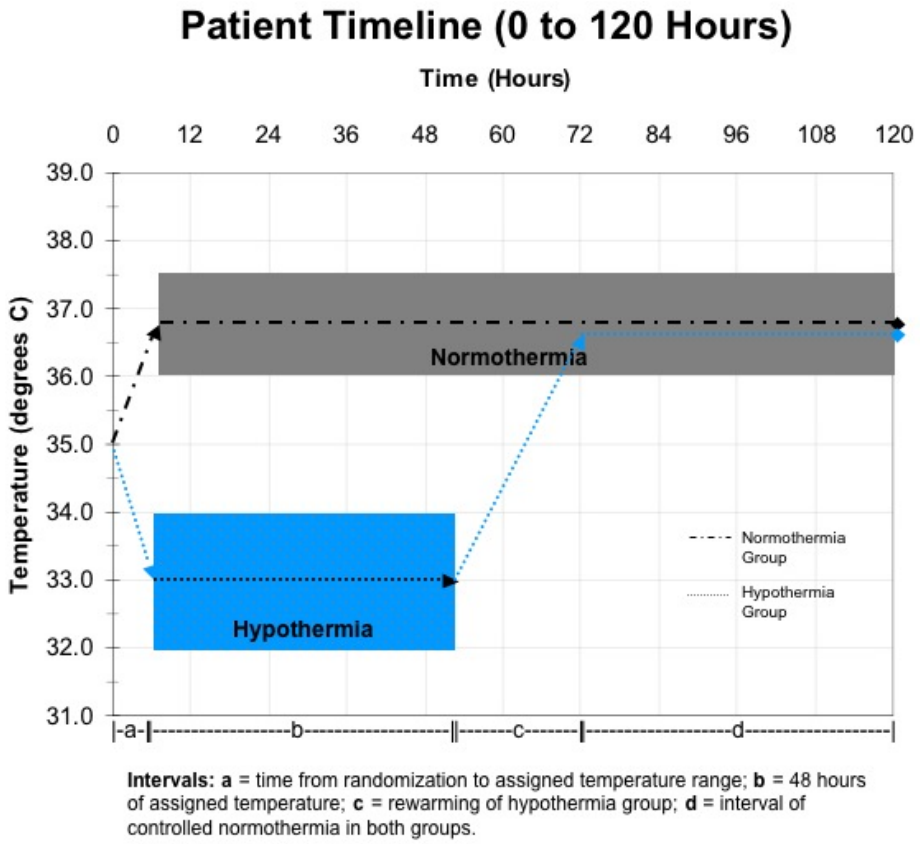

Figure 3: Timeline of Study Interventions

- During Normothermia: electrolytes will be completed at least every 12 hours. If electrolytes are drawn more frequently than once every 12 hours, those values drawn closest to 8 am and 8 pm will be recorded.

Other blood monitoring during the intervention period will include daily complete blood count (CBC), liver function tests (LFTs), specifically alanine aminotransferase (ALT),aspartate aminotransferase (AST), bilirubin (BILI), prothrombin time (PT) and International Normalized Ratio (INR), partial thromboplastin time (PTT), amylase, lipase, magnesium, calcium, and phosphorous. All values obtained during the intervention period (through 120 hours) will be recorded. These values should be obtained at a minimum of once per day.

Arterial blood gas (ABG) and lactate measurements will be monitored daily for the first 72 hours. Subjects are anticipated to have frequent ABG measurements. If there are multiple measurements during any study day, the measurement closest to 8:00 A.M. will be recorded.

Blood cultures will be obtained at the time of randomization and on days 1, 2, and 3. Days are defined as 24 hour periods from 12:00 a.m. to 11:59 p.m. Day 1 is the first full 24 hour period after randomization. Urine cultures will be obtained at the time of randomization and on days 2 and 4. The final results of all cultures sent within 7 days of enrollment will be obtained and recorded in the database.

Chest x-rays will be done daily during the intervention period in order to confirm temperature probe position. If multiple radiographic examinations are obtained during any study day, the examination closest to 8:00 A.M. will be recorded.

6.4 Monitoring of Safety Endpoints

Monitoring of the following events will occur:

Infections:

- Infection events associated with this study will be done by examination of all cultures (blood, urine, and respiratory) obtained from the time of randomization through Day 7 (168 hours).
- The final results of all cultures sent between the time of randomization and Day 7 will be obtained and recorded in the database.

Arrhythmias:

- All arrhythmias occurring from the time of randomization through Day 7 will be recorded.

Blood Products:

- In addition, blood products received from the time of randomization through Day 7 will be recorded.
- Blood products are defined specifically here to include red blood cells, platelets, fresh frozen plasma, and cryoprecipitate.
- In addition to blood products received,surgeries to treat bleeding will also be recorded from randomization through Day 7.

Mortality:

- Mortality will be recorded at 28 days post randomization for all enrolled patients.

6.5 Other Monitoring During and After Intervention

The total volume of fluids received and total urine output will be recorded on a daily basis (24 hour summary) from the time of randomization through the first 5 days (through the end of the intervention period).

Concomitant medications administered from the time of randomization through Day 7 will be recorded. Selected procedures and therapies, including new tracheostomies and placement of chronic feeding tubes will be recorded from the time of randomization through hospital discharge.

After the 120 hour intervention period, no study-specific interventions will occur as part of the THAPCA Trials. At the discretion of the clinical care team, the arterial line, the central line, and all probes for temperature monitoring may be discontinued when no longer needed for clinical care.

Temperature management after the intervention period will be according to the usual PICU clinical practice at each site. The minimum and maximum daily temperatures, including the measurement site, will be recorded through day 10.

The date of each study subject's PICU discharge and hospital discharge will be recorded. Assessments of neurological and functional status will be obtained within 72 hours prior to hospital discharge, and at three and 12 months post arrest. The three month follow up is intended to help with subject retention by maintaining contact with the family, as well as helping us to test our primary endpoint conclusions for robustness with respect to missing data. See Section 6.6 on the next page for a detailed description of neurological and neurobehavioral outcomes, and a schedule of assessments.

6.6 Neurologic and Neurobehavioral Outcomes

The instruments used to measure neurological and neurobehavioral outcomes for this study were selected to fulfill the following criteria:

- Sensitive to change after brain injury and over time
- Sensitive to multiple levels of outcome including impairment, activity, participation, and the quality of life of the child and family
- Sensitive to subtle differences in level of cognition, at both the mild and severe ends of the spectrum

These instruments are described below, and the overall schedule of assessments is provided in Table 2 on the following page. While some instruments will also be used at hospital discharge and 3 months, all primary and secondary outcome measures will be based on 12-month measurements. Data collected at earlier time points will be used for exploratory analyses.

6.6.1 Vineland Adaptive Behavior Scale (VABS)

The Vineland Adaptive Behavior Scale (VABS) was designed as a caregiver report measure to assess communication, daily living, social, and motor domains of adaptive behavior.[45] It has basal and ceiling criteria that allow for focused evaluation of each child's skill level, resulting in typical administration time of only 30 minutes. Normative data are available on children from birth through 18 years of age. Based on the normative data, standardized scores can be calculated that allow comparison of the child's functional status to other children of similar age. Moreover, the VABS-II[46] was revised and validated with more emphasis on young children. Like the VABS, the VABS-II has normative data available for children from birth through 18 years of age. The VABS-II is a continuous measure derived from developmental data using either a semi-structured, caregiver interview, or caregiver report form. Unlike other caregiver report measures of adaptive behavior, such as the Scales of Independent Behavior-Revised[47] and the Adaptive Behavior Assessment Scale-Second Edition,[48] the VABS-II has only one version of the test for the age range of interest (0 to 18 years), whereas the other tests have different versions for children of varying ages. Therefore, the VABS-II allows better comparison throughout the entire age range of this study. Additionally, the VABS-II has more items that capture behaviors of very young or low functioning children as compared to the other two measures. This is particularly important in this sample of children where there is the potential for many of the older children to be low functioning.

Table 2: Schedule of Assessments for Neurobehavioral Outcomes and Related Measures

Measurement	**Baseline**	**PICU Discharge**	**Hospital Discharge**	**Three months**	**Twelve months**
Pre-existing medical conditions	X				
Pre-existing developmental disabilities	X				
Family and household information	X				
Family function (FAD)	X				
Severity indicators (I.e. trach, vent, tube fed)	X		X	X	X
Location (acute hospital, rehabilitation, SNF, home)	X		X	X	X
Global function questions	X			X	X
POPC/PCPC	X	X	X	X	X
VABS-II	X			X	X
Family burden (ITQOL/CHQ)	X			X	X
Neuropsychological testing (Mullen or WASI)					X
Neurological abnormality assessment					X

Inter-interviewer reliability was high for the overall Adaptive Behavior Composite (.87 for children ages birth through six and .74 for ages 7 though 18 years).[46] While the VABS-II was not specifically designed to assess outcome after neurological injury, several studies have found the VABS to be sensitive to severity of neurological injury.[49, 50] Also, the VABS was used as a primary outcome in completed multicenter, randomized clinical trials in children with infantile spasms[51] and in children with Fragile X Syndrome.[52] It is currently being used as an outcome measure in several NIH funded clinical trials of pediatric patients with a variety of neurological disorders (clinicaltrials.gov). Deficits in functional skills, based on the VABS, have also been noted in several studies of children with cardiac arrest.[49, 53] While the VABS-II is not able to measure subtle differences in skills in very low functioning children, this is true of all measures of neurobehavioral outcome, and compared to other comparable measures,[47, 48] the VABS-II has a greater number of items to assess lower level skills.

Pre-cardiac arrest baseline information will be obtained with the caregiver rating form, and the 3 and 12 month VABS-II assessments will be obtained by interview. Agreement between the interview and caregiver rating form was found to be very high[46] and therefore the two methods can be compared directly.

Follow up interviews will be conducted by telephone. All follow up telephone interviews for VABS-II will be administered centrally by a trained clinician at the Kennedy Krieger Institute (Johns Hopkins School of Medicine, Baltimore, MD).

Telephone interviews, rather than in-person interviews were chosen for several reasons:

- The telephone interview allows for the administration of the VABS through a central site with expertise in outcome assessment. Administration at this central site will enable us to utilize select well trained professionals with direct ongoing oversight by a Psychologist (preferably a Ph.D. Neuropsychologist). This methodology is expected to decrease measurement variability and error.

- The telephone interview allows for increased participation rate for the primary outcome variable, as barriers to returning to a medical center are eliminated. This is especially relevant for those who are severely impaired and thus more challenging to transport. Systematic attrition of the more severely impaired could significantly impact the results of this study. Therefore, every provision is being made to ensure inclusion of these subjects in the primary outcome.

- The VABS is based solely on caregiver information and not on observation of the child, therefore direct observation of the child is not necessary for accurate completion of this measurement. Moreover, reliability between in-person caregiver interview and telephone caregiver interview is extremely high.[54]

- Also, when the VABS was used as a primary outcome in a successfully completed multicenter clinical trial in children with infantile spasms,[51] it was administered at one central site by telephone interview.

Although the primary outcome for this study is based on the VABS-II at 12 months post arrest, the baseline VABS-II score will be used to exclude those with a score less than 70 from analysis of the primary outcome. This approach will enable us to enroll a representative cohort of pediatric ICU patients and to take into account that functional decline may be difficult to quantify in subjects with severe pre-existing neurobehavioral deficits. However, change in VABS-II from baseline to 12 months follow up in survivors will be examined as a secondary outcome in all study subjects.

In order to assess interrater reliability of the VABS II telephone interviews, and prevent variance in ratings over time, the first 4 interviews and thereafter every 10th interview will be recorded for quality assurance. If there is less than 80% agreement on the scoring of the interview, the plan for the recordings will restart with the initial frequency (4 interview followed by every 10th interview). If there is a new interviewer, the frequency will also start with the initial frequency. Staff at KKI will listen to recordings and reconcile any discrepancies within 3 months of the interview. The recordings will be erased immediately after the review and adjudication. Recordings are to be stored in the same manner as all study related documents and will be destroyed as soon as quality assurance activities have taken place

6.6.2 PCPC/POPC

The Pediatric Cerebral Performance Category (PCPC) and the Pediatric Overall Performance Category (POPC) scales have been recommended for reporting outcome following cardiac arrest in children.[11] As a consequence, the PCPC and POPC have been used in all the major outcome studies of childhood cardiac arrest.[16, 17, 19, 55, 56] The PCPC provides a rating of neurological functioning, whereas the POPC provides a rating of overall health.

Both the PCPC and POPC can be reliably rated pre and post arrest based on a brief conversation with the child's family or medical record re-

view. Both measures were designed for children who experience cardiac arrest and are applicable to children who do not survive, those who survive in a vegetative state, and those survivors who are unable to cooperate with neuropsychological testing. These instruments provide a simple measure of overall severity and are correlated with other more lengthy measures of outcome, including the VABS.[57] The limitations of the PCPC and POPC are that they do not have normative data for different age groups. Moreover, the PCPC and the POPC do not allow for detailed measurement of functioning or measurement of subtle changes in function or cognition. Therefore, these measures are included for descriptive purposes only, to enable comparisons with results of other studies that used these measures, and are not a primary or secondary outcome of the study.

6.6.3 Neuropsychological Testing

In children, duration of cardiac arrest[49] and of circulatory arrest during heart surgery[58] have been associated with lower performance on measures of overall cognitive ability. Additionally, anoxic brain injury often significantly impacts specific neuropsychological skills, including attention, memory, executive functioning, processing speed and motor functioning.[59, 60] To more fully describe these cognitive outcomes and identify subtler but significant impairments, a brief battery of neuropsychological testing will be administered 12 to 16 months post arrest, by designated psychologists at each study site. Measures were chosen that are sensitive to brain injury, have adequate normative data for the age range, plus good reliability and validity. For all children 5 years 8 months or younger, the Mullen Scales of Early Learning will be employed at 12 months post arrest to obtain a measure of overall cognitive functioning. Since the Mullen only has available data through age 5 8/12th years, for children 5 9/12th through 5 11/12th years, testing will be delayed until they are six years old, which may be as late as 16 months post arrest.

For children 6 years of age or older neuropsychology testing will be administered if the child usually "follow instructions" (question 10, VABS-II Receptive Communication) or usually "point or gesture to indicate preference" (question 10, VABS-II Expressive Communication), or have higher level communication skills. For these children, the 2-subtest version (Vocabulary and Matrix Reasoning) of the Wechsler Abbreviate Scale of Intelligence will be administered to obtain a measure of general cognitive functioning (estimated full scale IQ score). In addition, a battery of specific neuropsychological measures to assess processing speed, attention, learning

and memory, executive functioning (ability to plan, organize, and engage in goal directed behavior), and visual motor functioning will be administered to these children

Processing Speed. Processing speed will be measured by coding on the Wechsler Intelligence Scale for Children-IV (WISC-IV) and digit symbol-coding on the Wechsler Adult Intelligence Scale Third Edition (WAIS-III). These are essentially the same task, but coding has normative data available for ages 6 though 16 and digit symbol has normative data available for ages 16 and older. In this study, the coding from the WAIS-III will be used for adolescents 17 years or older at the time of follow up. For this test, the individual copies symbols that are paired with simple geometric shapes or numbers. They use a key to draw the symbols in the correct boxes within a 2-minute time limit. This test is consistently more sensitive to brain damage than other Wechsler battery tests and it is the score that is most likely depressed even when damage is minimal.[61] The test-retest reliability (range 0.67 to 0.81) and interscorer agreement (0.98-0.99) is also good for this test. Coding has been shown to be sensitive to even mild TBI.[61]

Attention. Attention will be measured using the Digit Span subtest from the Wechsler Intelligence Scale for Children-IV (WISC-IV) and the Wechsler Adult Intelligence Scale Third Edition (WAIS-III).[62–64] Digit Span is a measure of auditory focused attention and working memory. Part one requires the subject to repeat strings of digits presented by the examiner. The strings are two to nine digits in length and are presented at the rate of one digit per second. For part 2, the examiner again presents increasingly longer strings of digits, but for these items the subject is required to reverse the order of the digits. On the WISC-IV, normative data for Digit Span are available for ages 6 through 16 years. For children 17 years and older at the time of follow up the WAIS-III Digit Span will be used. Research has indicated that digits forward span has been found to fall below normal limits in some patients following head injury, but it is also likely to show return to normal levels during subsequent years.[65, 66] Digit Span backwards has also been shown to be sensitive to many types of brain damage.[61] Digit Span demonstrates good test-retest reliability (0.81 for children and 0.75 for adults) and interscorer agreement (0.98-0.99).[62–64] Previous research has found Digit Span backward to be sensitive to TBI.[61, 65, 66]

Learning and Memory. The California Verbal Learning Test - Children's Edition (CVLT-C)[67] and the California Verbal Learning Test - Second Edition (CVLT-II)[68] are supraspan list-learning tasks, that will be used to measure verbal learning and memory. The CVLT-C is comprised of five recall trials of a 15-item word list; the list items belong to 3 semantic categories (Fruits, Clothing, Toys), whereas the CVLT-II is comprised of a list of 16 words in 4 semantic categories. For both tasks, there are five learning trials that followed by a single presentation of a distracter list, a second, novel word list. Learning and memory is assessed by number of words recalled over the 5 learning trials, after presentation of the distracter list (short-delay free and cued recall), after a longer 20-minute delay (long-delay free and cued recall), and on recognition. The CVLT-C has normative data available from ages 5 through 16 years, whereas the CVLT II has normative data available for ages 16 through adulthood. The CVLT-II will only be used in this study for adolescents 17 years of age or older at the time of follow up. According to the standardization manuals, the CVLT-C and CVLT-II have moderate to high internal consistency. In contrast, test-retest variability is variable, with improvement noted during the second administration due to learning effects. Moreover, the CVLT-C and CVLT-II have been associated with severity of brain injury.[68–70]

To measure visual memory, Rey Osterrieth Complex Figure (ROCF)[71, 72] will be employed. This task involves the child drawing a complex geometric figure from memory, after copying the figure. A standardized scoring system will be used to measure the accuracy of the recalled figure based on the overall shape and details of the figure. There is a short delay (approximately 3 minutes) and long delay (approximately 30 minute) recall trial. Additionally, after the 30-minute delay trial, there is a recognition trial in which the child will be asked to choose the correct details. The ROCF will be scored using the Meyers and Meyers Scoring System, which includes normative data for ages 5 years and older.[73, 74] The test has good inter-rater reliability (0.93 to 0.99).[73] Meyers and Lange found that brain injured adults performed significantly worse on the ROCF (immediate and delayed recall) compared to psychiatric patients and normal controls.[75]

Executive Functioning. We will measure rapid generation of verbal information using the Controlled Oral Word Association Test (COWA).[76] This test requires the individual to generate words that begin with a particular letter as quickly as possible during a one minute trial. Normative data are available for children ages 6 to 13[77] and then 15 to 20 years.[78] For chil-

dren, aged 14 at the time of the evaluation, the normative data for the next youngest group will be used. Test-retest reliability for the COWA is good.[79] Several studies have found the COWA to be highly sensitive among persons with brain injury.[80–82]

In addition to using the ROCF to measure visual memory (as above), we will use the ROCF copy trial to measure executive functions.[71–74] For this task, the child will be asked to copy a complex geometric figure, while the figure is directly in front of the child. A standardized scoring system will be used to measure the accuracy of the copy based on the overall shape and details of the figure. Normative data are available on this measure from age 5 to adulthood. Additionally, test retest reliability and interrater reliability were adequate.[73, 74] The ROCF correlates highly with other measures of visuoconstructional ability.[83, 84] Moreover, the copy of the ROCF has been found to be sensitive to the sequelae of brain injury in children.[85]

Visual-Motor Functioning. To measure fine motor dexterity bilaterally, the Grooved Pegboard Test[86] will be administered. This task requires the child to insert pegs into shaped holes on a board. Normative data are available for ages 5 and older.[87] For ages 5 through 8, children are only required to complete two rows of pegs. For older children, all rows are completed.

The Beery Buktenica Developmental Test of Visual-Motor Integration-Fifth Edition (VMI)[88] will be employed to assess ability of children to copy geometric figures of increasing complexity. Normative data are available for ages 2 through 18 years. The 18 year old normative data will be used to calculate standard scores for any individual 19 years of age at the time of the follow up evaluation. Overall odd-even internal consistency is adequate (.88). Inter-scorer reliability is also high (.92). The VMI correlates moderately with overall intellectual abilities. Also, children with neurodevelopmental disabilities associated with low birth weight and spina bifida perform poorly on the VMI compared to typically developing peers.[89, 90]

These measures are summarized in Table 3 on page 44.

6.6.4 Neurological Abnormality Assessment

A detailed standardized neurological exam will be performed in all 12 month survivors by a pediatric neurologist at each site. In order to compare outcomes between groups, and to take into account the different number of exam elements that can be evaluated among survivors of different ages and functional levels, two age-related systematic quantitative scoring sysems have

been devised. The scoring systems, Pediatric Resuscitation after Cardiac Arrest (PRCA1 for up to age 3 and PRCA2 for age 3 and older), are derived from the Pediatric Stroke Outcome Measure (PSOM) stroke scale, which is already being used successfully in a multi-center pediatric study of outcome after stroke (in children with sickle cell disease) (ref UO1-NS 042804). Since it is possible that the range in severity of deficits will be greater in the THAPCA study population than in pediatric stroke survivors, the PRCA1 and PRCA2 have an expanded scoring system. All elements of the evaluation represent integral components of age-appropriate neurological evaluation of children. These components include level of consciousness, behavior and mental status, language, cranial nerves, and motor skills. In addition to descriptive material, each exam generates two scores: a global assessment score (0-21 point range), and a normalized cumulative abnormality score.

6.6.5 Modifiers of Outcome and Severity Indicators

Since the range of developmental abilities is narrow in very young infants, it is difficult to define those subjects with pre-existing disabilities. Consequently, syndromes and medical conditions typically associated with developmental disabilities will be identified, to verify equal distribution between treatment groups.

Psychosocial variables including family resources[91–93] and family functioning[91, 94] have been consistently associated with outcome following traumatic brain injury. While the relationship between these psychosocial variables and outcome is not as well studied after CA, Bloom (1997) reported that higher socioeconomic status was related to higher cognitive function in both subjects after CA and in controls.[53] We plan to control for the impact of these variables in exploratory analyses. Pre-cardiac arrest baseline family functioning will be measured using the General Functioning Scale of the Family Assessment Device (FAD).[95] This 12 item scale is a self-reported measure with good internal consistency (range of 0.86 – 0.91).[96, 97] It discriminates well between healthy and poor functioning families.[91, 98–100]

Additional severity indicators such as medical or surgical interventions (e.g., need for tracheostomy or mechanical ventilation), rehabilitation services received, and the child's location or level of care needed (e.g., acute care hospital, rehabilitation hospital, nursing home or long term care facility, or at home). These data elements will be collected for descriptive purposes, according to the schedule of assessments outlined in Table 2 on page 36.

Table 3: Neuropsychological battery for subjects older than 6 years.

Domain	**Test Name**	**Constructs Measured**	**Test Variables**
Intelligence	WASI	Overall cognitive ability	Full scale IQ
Processing Speed	WISC-Coding or WAIS-Digit Symbol	Graphomotor speed	Number of symbols copied in time limit
Attention	WISC or WAIS-Digit Span	Attention span Verbal working memory	Total number of items recited correctly
Learning and Memory	CVLT-C or CVLT-II	Verbal learning Verbal memory	Number of words recalled in trials 1 to 5 Short term and long term recall
	ROCF - Recall and Recognition	Visual memory	Recognition memory Short term and long term recall Recognition memory
Executive Functioning	ROCF - Copy COWA	Visual organization Novel verbal generation	Total accuracy score Total number of words generated
Visual-Motor Functioning	Grooved Pegboard Test VMI	Fine motor dexterity Graphomotor accuracy	Time to place all pegs in the board Total accuracy score

6.6.6 Family Burden

To assess the impact of the child's health status on the family, the Child's Health Questionnaire (CHQ)[101] and the young child's version of this measure, the Infant/ Toddler Quality of Life Inventory (ITQOL)[102] will be used. On both measures, scales assessing the impact of the child's health condition on parent activities and the impact of the child's health on the parent's emotional status will be employed. Additionally, in the children 5 and older, a third scale assessing limitations in family activities as a result of the child's health status will also be employed. The total score for each of these scales will be converted to a score from 0-100 to allow for comparability between the two measures. The family activities and emotional burden scales of the ITQOL and CHQ have yielded significant differences between healthy children and those with a variety of disease states[103, 104] and between healthy children and children following traumatic injury.[105]

7 Detailed Study Interventions

The study interventions will begin in the intensive care unit as soon as possible after informed consent is received. Cardiac arrest patients in the emergency department will be expeditiously transferred to the PICU. Therapeutic hypothermia will not be induced in the emergency department. The setting of the patient's study cardiac arrest (IH vs OH) will be identified, after which the patient will be randomized to a study treatment group (hypothermia or normothermia) in the respective THAPCA Trial (THAPCA-OH or THAPCA-IH). The intervention time period covers the cooling, hypothermia, and rewarming time periods and the interval to 120 hours from the time intervention begins for both arms. Temperature control will be implemented with the Blanketrol III cooling unit (if the Blanketrol III is not available or is already in use, a Blanketrol II can be substituted) and appropriate patient size Maxi-Therm Lite mattresses. Temperature control will use the servo-control mode of the Blanketrol III. The Blanketrol III (and the Blanketrol II) cooling unit and blankets are manufactured by Cincinnati SubZero (CSZ), Cincinnati, OH, in accordance with all applicable Federal regulations. The Blanketrol II has been utilized safely in adult and neonatal clinical trials of therapeutic hypothermia (32 to 34 °C), and the Blanketrol III is the most current model. These prior populations represent the extremes of age ranges for the intended THAPCA Trial (Newborns and Adults vs Pediatric age groups). In prior studies there were no reports of significant skin injury or other complications associated with cooling using

Blanketrol II cooling units.

7.1 Hypothermia

Patients randomized to receive therapeutic hypothermia (hypothermia group) will have a target temperature of 33 °C plus or minus 1 °C (32 to 34 °C). Hypothermia will be induced using the Blanketrol III cooling unit and Maxi-Therm Lite blankets placed below and over each patient. No internal cooling procedures or devices will be used (e.g., gastric lavage, intravascular cooling catheter). Based on newborn and adult reports that used the Blanketrol II cooling unit, we expect to achieve the target temperature range within 1 to 4 hours of initiating cooling procedures.[30, 106] For the NICHD Neonatal study, cooling was achieved within 90 minutes[30] and in an adult TBI study, 2.8 hours (1.1 to 4.5 hr range) was reported.[106]

For patient safety, dual central temperature measurements will be performed. A temperature sensing esophageal probe and temperature sensing Foley catheter (or rectal temperature probe) will be placed for temperature monitoring prior to initiation of cooling. Please note: the esophageal probe is the preferred primary probe which will be connected to the Blanketrol unit. However, in the event that an esophageal probe is not judged to be feasible, the Foley catheter or rectal probe may be used as the primary probe and the remaining probe will be the secondary probe which will be connected to the bedside monitor. For patient safety, the *lowest* value will be assumed correct if there is a discrepancy in measurements. If there is a discrepancy of greater than 2 °C between the two measurements, the temperature probes should be inspected for proper positioning and function. The patient's temperature will be monitored continuously and recorded every 30 minutes until central temperature is 33 °C. If the patient is 33 degree at the time of therapy initiation, the temperature will be monitored every 30 minutes for at least one hour. Thereafter, the temperature will be recorded every hour until rewarming begins.

The hypothermia group will be sedated with midazolam and fentanyl. Other benzodiazepines and narcotics may alternatively be used at the clinical site's discretion. The hypothermia group will be paralyzed with vecuronium until the therapeutic hypothermia temperature range is achieved. Vecuronium for paralysis will be held after the initial cooling period and utilized only as needed for shivering unresponsive to the sedation/analgesia protocol described in Section 7.5 on page 49.

Once the patient has achieved the goal temperature (32 to 34 °C), the mattress placed on top of the patient may be moved, however, the mattress

underneath the patient will be left in place. Nursing staff will adjust the Blanketrol III unit as needed to maintain a temperature in the goal range. The hypothermia group will then be maintained in the goal temperature range for 48 hours. Rewarming will then occur over approximately 16 hours (0.7 °C every 4 hours) to normothermia (36.0 °C), which should occur at approximately 72 hours after intervention begins. Temperature will again be recorded every 30 minutes during the rewarming period.

From 72 hours or end of rewarming until 120 hours (end of day 5), the hypothermia group will be maintained in the normothermic range (36-37.5 °C) using the Blanketrol III, and temperature will be recorded every four hours. After 120 hours, temperature management will be according to the normal practice of the clinical care team.

7.2 Normothermia

Patients randomized to receive the normothermic control therapy (normothermia group) will have a target temperature of 36.75 (effectively 36.8) plus or minus 0.75 degrees Celsius (36.0 to 37.5 °C). Similar to the hypothermia group, each patient will be placed on a Blanketrol III cooling mattress (Maxi-Therm Lite) set to the appropriate temperature. Once the patient has achieved the goal temperature (36-37.5 °C), it will be maintained with the mattress.

For patient safety, dual central temperature measurements will be performed. A temperature sensing esophageal probe and temperature sensing foley catheter (or rectal temperature probe) will be placed for temperature monitoring. For patient safety, the *highest* value will be assumed correct if there is a discrepancy in measurements. If there is a discrepancy of greater than 2 °C between the two measurements, the temperature probes should be inspected for proper positioning and function. The patient's temperature will be monitored continuously and recorded every 30 minutes until central temperature is 36.8 °C. Thereafter, the temperature will be recorded every hour through 72 hours then every four hours through 120 hours. For study purposes, the temperature measurement closest to the hour should be recorded.

The normothermia group will be sedated with midazolam and fentanyl. Clinical shivering will be treated the same as with the hypothermia group with midazolam and fentanyl dosing as needed. Other benzodiazepines and narcotics may alternatively be used at the clinical site's discretion. See Section 7.5 on page 49 for a detailed description of sedation and neuromuscular blockade therapies.

Throughout the intervention period, nursing staff will adjust the Blanketrol III unit as needed to maintain a temperature in the goal range. The normothermia group will be maintained in the goal temperature range through 120 hours. This corresponds to the hypothermia, rewarming, and normothermia time periods for the hypothermia group. After 120 hours, temperature management will be according to the normal practice of the clinical care team until hospital discharge.

For subjects randomized to the normothermia group with central temperatures below the normothermic range at the time of randomization, slow rewarming to 36 °C at a rate not to exceed 0.5 °C per hour will be initiated. For patients with temperatures greater than 37.5 °C at the time of randomization, the Blanketrol III unit will be used to cool the subject to 37.5 °C. Ibuprofen or other non-steroidal anti-inflammatory drugs that interfere with platelet function are prohibited for use in patients under this protocol. Acetaminophen may be administered in a dose of 10-15 mg/kg if the clinical team determines there exists no contraindication to its use. If body temperature exceeds 38.0 °C in spite of acetaminophen and Blanketrol III cooling, the clinical care team will administer vecuronium (0.1-0.2 mg/kg) once to assist in cooling to normothermia.

7.3 Temperature Monitoring

Central temperature monitoring will be required during this study as alternative methods are not reliable. Core body temperature will be measured at two sites for safety, esophageal and either bladder or rectal temperature. In addition to monitoring subject temperature as described below, the water temperature of the Blanketrol III will be monitored and recorded at the same frequency as the subject central temperatures.

Esophageal probe placement will be in the distal third of the esophagus away from the airway. The appropriate sized esophageal temperature probe should be placed just prior to initiating cooling. Using the upper incisors as the marker, the following formula will be used to calculate the distance to insert the probe: 0.25 x ht (cm) + 4.5 (cm) = insertion distance in cm.[107] Proper position will be determined by chest x-ray. Repositioning will be done as needed.

NOTE: Temperature sensing foley catheters as well as temperature sensing esophageal catheters contain metal and may need to be removed prior to an MRI. Each site will need to establish MRI compatibility of temperature sensing catheters. If data are not available, the catheters will be removed at the time of MRI and replaced after leaving the MRI suite.

Temperature will be monitored continuously and recorded hourly through 72 hours and then every 4 hours thereafter through 120 hours. During the initial time to target temperature (hypothermia or normothermia) it will be recorded every 30 minutes. It will also be recorded every 30 minutes during the rewarming period for the hypothermia group. Temperature management after the initial 120 hours will be according to the usual PICU clinical practice at each site. Review of the minimum and maximum daily temperatures, including the measurement site, will be recorded through 10 days (240 hours).

7.4 Vascular Access

Secure venous access will be required to safely administer fluids and other medications such as inotrope/vasopressor infusions. The standard practice in PICUs is placement of a temporary central venous catheter. A variety of other central venous access type catheters will also be acceptable. A central venous catheter (CVC) may be pre-existing (acute or chronic line such as a Broviac) or peripheral inserted central catheter (PICC line) during the intervention time period so that intravenous fluids and medications may be administered as needed post arrest.

7.5 Management of Sedation and Analgesia

The use of sedatives and analgesia will be as similar as is clinically feasible in the hypothermia and normothermia groups. Previous adult clinical trials utilized midazolam with or without fentanyl for sedation and analgesia. These agents are well known to practitioners in emergency department and intensive care settings where they are commonly utilized for a variety of indications. Midazolam and fentanyl by continuous infusion supplemented by intermittent dosing will be used for the time intervals corresponding to initial cooling, 48 hours of sustained temperature, and 16 hours of rewarming for both groups.

After the period of cooling and rewarming, which will occur at approximately 72 hours in each group, sedation and analgesia use will be at the discretion of the primary clinical team caring for the patient. Information on agents utilized up to 120 hours (end of day 5) will be recorded.

7.5.1 Sedation

Midazolam is the sedative agent recommended, but not required, for use in this study. A loading dose of 0.1 mg/kg (100 mcg/kg)of midazolam will

be administered for both groups at the time the interventions are initiated. This will be repeated as needed to achieve a Ramsay score of at least 5 (sluggish response to light tap). A continuous IV infusion of midazolam at 100 mcg/kg/hr will be initiated and maintained at this rate or greater during the initial 4 hour period corresponding to time to cool in the hypothermia group. If required, up to two additional doses of midazolam 0.1 mg/kg (100 mcg/kg) may be given. The infusion rate can then be increased by 50 mcg/kg/hr as needed to achieve a Ramsay sedation score of 5.

If the Ramsay score is 6 (no response) after the first four hours of the intervention, the midazolam drip will be weaned by 50 mcg/kg/hr to achieve a Ramsay score of 5. Lowest infusion dose in the initial 24 hours will be 50 mcg/kg/hr. After 24 hours, the midazolam infusion may be weaned to off if there is no clinical shivering, patient temperature is in the appropriate target range, and the goal for sedation/analgesia is obtained (Ramsay score of 5).

Other benzodiazepines (e.g., lorazepam) may be used as an alternative to midazolam at the clinical site's discretion. However, the level of sedation should be based on the Ramsay targets outlined here.

7.5.2 Analgesia

Fentanyl is the analgesic agent recommended, but not required, for use in this study. A loading dose of 2 mcg/kg will be administered for both groups at the time the interventions are initiated. Continuous infusion of fentanyl will begin at 2 mcg/kg/hr and maintained at this rate during the initial 4 hour period corresponding to time to cool in the hypothermia group. If required, up to two additional doses of fentanyl 1 mcg/kg may be given. The infusion rate can then be increased by 1 mcg/kg/hr as needed to achieve a Ramsay sedation score of 5.

If the Ramsay score is 6 (no response) after the first four hours of the intervention, the fentanyl drip will be weaned by 1 mcg/kg/hr to achieve a Ramsay score of 5. The lowest infusion dose in the initial 24 hours will be 1 mcg/kg/hr. After 24 hours, the fentanyl infusion may be weaned to off if there is no clinical shivering, patient temperature is in the appropriate target range, and the goal for sedation/analgesia is obtained (Ramsay score of 5).

Other narcotics (e.g., morphine, remifentanil) may be used as an alternative to fentanyl at the clinical site's discretion. However, the level of analgesia should be based on the Ramsay targets outlined here.

7.6 Use of Neuromuscular Blockade

Vecuronium is the recommended, but not required, neuromuscular blocker for the THAPCA Trials. A paralytic loading dose of 0.1-0.2 mg/kg (100-200 mcg/kg) will be administered to patients randomized to hypothermia to facilitate cooling. Repeated doses of vecuronium will be administered as needed to maintain paralysis until the patient is cooled to the therapeutic range (32-34 °C).

Once therapeutic hypothermia is achieved, neuromuscular blockade is not required, except for as needed to control shivering resistant to sedative/analgesic agents and rewarming without clinical shivering. If a cooled patient begins to rewarm above 34.5 °C in spite of the absence of clinical shivering, vecuronium in a dose of 0.1-0.2 mg/kg (100-200 mcg/kg) would be administered immediately, and continued until the patient cools to the therapeutic range (32-34 °C). Neuromuscular blockade may also be used for other aspects of care at the discretion of the primary care team (such as ventilator asynchrony).

Other non-depolarizing agents may be used during cooling and to control shivering based on the above parameters at the clinical site's discretion.

7.7 Management of Glucose and Insulin

An explicit protocol for management of glucose and nutrition is not part of the current protocol at this time. We are aware that large clinical trials of explicit glucose control protocols are ongoing or planned in both adults and pediatric populations at this time. Should information from properly conducted clinical trials become available, which demonstrates efficacy and safety of a explicit protocol approach to glucose management in children, we will consider amending this protocol at that time.

The optimal glucose concentration range following pediatric cardiac arrest and in the more general pediatric critical care population is not known at the time of writing this protocol. It is not known, for example, whether a tight glucose range protocol utilizing insulin would be detrimental in a post arrest pediatric population. In adult populations, there is evidence suggesting hyperglycemia may be associated with poorer neurological outcome after various neurological insults.[108–113] Causality has not been established, however. Furthermore, RCTs in heterogenous adult ICU settings have so far reported conflicting findings related to tight protocol directed glucose control. Van den Berghe initially reported in a Belgium adult surgical ICU population, tight glucose control to be associated with reduced mortality.[114]

A more recent report by the same investigator reported glucose control not to be associated with reduced mortality in a medical ICU population.[115] A multicenter German RCT (VISEP) of intensive insulin therapy in severe adult sepsis population did not demonstrate efficacy.[116] Of note, this trial was stopped early because of no benefit and high rate of hypoglycemia in the treated group (12% versus 2%). No clinical trials have been conducted to assess explicit protocol directed glucose management and survival in a pediatric ICU population. In pediatric animal models, maintaining glucose levels in a low level range was not reported to improve neurological outcome.[117]

It should be noted that prior adult and neonatal hypothermia RCTs did not report glucose management protocols with the exception of Bernard[28] who stated a glucose less than 180 mg/dl was a goal. There are no animal or human data on the effects of tight glucose control combined with hypothermia on clinical outcomes. Hypothermia is known to be associated with both hyperglycemia and improved neurological outcome.

A potential safety issue exists with hypothermia and insulin use. Serum potassium measurements are known to decrease with therapeutic hypothermia cooling and then increase during the subsequent rewarming period. Insulin is known to significantly decrease serum potassium. If insulin is administered for hyperglycemia associated with hypothermia, it is likely to be associated with worsening of hypokalemia and require additional supplements of large amounts of potassium. On rewarming, this may result in a more exaggerated rise in serum potassium measurement. Therefore, the approach to be recommended for sites in the THAPCA Trials will be to pay special attention to serum potassium and glucose concentrations, and manage glucose, potassium, and insulin administration according to usual clinical practice for each PICU, avoiding extremes of glucose and potassium.

7.8 Hemodynamic Management

Blood pressure will be monitored by an arterial line. This is the usual standard practice in PICUs for a post arrest pediatric patient who would meet the study entry criteria. Secure cental venous access will be required for participation in this study. This is common practice for the majority of post arrest patients in order to be able to safely and reliably administer fluids, inotropic/vasopressor agents, etc.

It would be desirable to describe an explicit hemodynamic management algorithm for subjects enrolled in THAPCA, but this is untenable due to the diversity of the post arrest pediatric patient population, the multiple etiologies of cardiac arrest, and other comorbid conditions that would be

represented in a typical pediatric population. Of note, explicit hemodynamic protocols were not described in the adult and neonatal RCTs, which demonstrated efficacy of hypothermia for cardiac arrest or HIE.

In general, goal blood pressure for each case will be maintained in a range normal for age and optimized for other factors such as coexisting conditions as determined by the clinical care team. The clinical care team will determine the optimal preload, afterload, contractility and heart rate for each case enrolled in THAPCA. Fluids including blood products or diuretics will be administered as needed to optimize preload. Inotropic and/or vasopressor agents will be administered as clinically indicated for contractility and blood pressure augmentation. Optimal heart rate will also be determined by the bedside clinical care team. This includes treatment of cardiac arrhythmias. The effects of hypothermia on hemodynamics in adult and neonatal trials have usually been related to heart rate with little impact on blood pressure.[118] Bradycardia is commonly associated with decreased oxygen consumption in hypothermia treated cases.[119] In pediatric TBI trials tachycardia was observed in some hypothermia treated patients and responded to fluid administration.[34]

7.9 Management of Mechanical Ventilation

The requirement of mechanical ventilation support following cardiac arrest is a study inclusion criteria. It would be desirable to describe an explicit mechanical ventilator management algorithm for subjects enrolled in this study, but this is untenable because of the diversity of potential etiologies, clinical conditions, and comorbidities represented in a typical pediatric population. In general, hyperventilation should be avoided and PaCO2 should be maintained in a normal physiologic range for age unless the primary care team determines the patient would benefit from a different range. Arterial blood gas values will not be corrected for temperature and will reported at 37 °C . It is a common practice in the PICU setting to use a lung protective strategy by limiting tidal volume and peak inspiratory or plateau pressure. The optimal FiO2 and PEEP for the clinical case will be determined by the primary care team. The use of high frequency oscillation (HFO) after randomization is permitted. The clinical care team may administer other support therapies such as inhaled nitric oxide (NO) as clinically indicated.

7.10 Fluid and Renal Management

After cardiac arrest, patients are at high risk of renal injury that progresses to renal insufficiency or failure. In general, one would limit exposure to nephrotoxic drugs when other agents are available. Urine output less than 1 cc/kg/hr in infants and children and less than 30 cc/hr in adolescents may be inadequate. The primary caregiver team will determine the optimal preload range for a given patient and administer fluids and/or give diuretics as needed. Initiation and type of dialysis modalities if needed will also be determined by the clinical care team.

7.11 Seizure Management

The occurrence of clinical and electrographic seizures from the time of randomization through Day 7 will be recorded in the database. General guidelines for evaluation and treatment of either a clinical or an electrographic seizure are summarized as follows. A check of glucose, calcium, and electrolytes would generally be performed if not recently available. A benzodiazepine agent (i.e. lorazepam, midazolam, diazepam) would commonly be administered to stop acute seizure activity. Many patients would also receive a full loading dose of phenobarbital or phenytoin equivalent (20 mg/kg) to prevent recurrence or stop ongoing seizures. A follow-up EEG would be obtained as soon as feasible to verify that there are no on-going electrographic seizures. If there are electrographic seizures noted, these would usually be treated with additional anticonvulsant dosing, according to protocols or care management at each unit.

7.12 Special Issues of ECMO

Temperature regulation on ECMO does not require use of surface cooling (Blanketrol III unit with cooling mattresses). The desired temperature will be ordered and set by the bedside ECMO specialist by changing the temperature of the heat exchanger. Special considerations need to be made for the sedation, analgesia, and neuromuscular blockade of patients on ECMO during the intervention phase of the study. The bioavailability of midazolam and fentanyl may be reduced due to possible membrane oxygenator absorption. For patients on ECMO, lorazepam and morphine may be substituted for midazolam and fentanyl. Lorazepam will be given as a bolus of 0.1 mg/kg (100 mcg/kg) as needed to achieve a Ramsay score of 5. This will be followed by intermittent dosing of 0.1 mg/kg as needed.

Morphine will be administered as a bolus of 0.1 mg/kg (100 mcg/kg) as needed to achieve a Ramsay score of 5 or greater. Thereafter, morphine will be administered by continuous infusion beginning at 30 mcg/kg/hr. The infusion dose should be increased by 10 to 30 mcg/kg/hr only after 2 doses of morphine (0.1 mg/kg (100 mcg/kg)) are required.

Paralysis will not be required for ECMO patients unless clinical shivering is observed that is not responsive to sedation/analgesia with lorazepam and morphine.

Due to the propensity for bleeding in the ECMO patient, only one central temperature recording device is required in this population. Either a temperature sensing esophageal probe, Foley catheter or rectal probe can be used. If the clinical center has ECMO equipment that allows for the blood temperature to be measured within the circuit, then this can be substituted for a central temperature recording device (esophageal probe, Foley cathter or rectal probe).

7.13 Other Therapy Guidelines

All other therapies administered for both hypothermia and normothermia groups during the times corresponding to initial cooling, hypothermia maintenance, and rewarming periods will be according to the clinical care team.

8 Study Data Collection

Clinical data will be collected at the time of enrollment, throughout the intervention period, during the initial hospital stay and at the time of hospital discharge or death. Follow-up information including assessment of neurobehavioral outcomes will be collected at three and 12 months. This section provides a summary of the data that will be collected.

8.1 Screening, Enrollment and Randomization Period

Patients will be screened by the clinical investigator in the emergency department and in-hospital settings. Parents or legal guardians of potential subjects will be asked for permission to enter the trial, and the subject will be enrolled and randomized within six hours of ROSC/ROC. During this period patients will be evaluated for inclusion and exclusion criteria and demographic information will be collected. Demographic information will include: date of birth, gender, race, and ethnicity. If the patient meets all

inclusion and exclusion criteria and consent is obtained, the patient will be randomized into the study.

8.2 Baseline Period

Baseline data elements will be collected on all patients who have been enrolled and randomized into the study. Information to be collected during this period include a medical and surgical history, a physical examination, hospital and PICU admission information, cardiac arrest information, vital signs, evaluation of mental status, and infection status. Safety laboratories to measure serum chemistry, coagulation parameters, and hematologic parameters will also be collected at baseline.

8.3 Intervention Period (0 to 120 Hours)

Study interventions will begin after randomization. During the intervention period, vital signs will be monitored for all patients. Safety laboratories to measure serum chemistry, coagulation parameters, and hematologic parameters will also be collected. Information on daily chest x-rays will also be collected. Chest x-rays are performed routinely on patients after cardiac arrest to assess for signs of new infiltrates and to determine proper positioning of tubes including the esophageal temperature probe. The results of all blood, urine and respiratory cultures during the intervention period will be recorded. Adverse events, concomitant medications, and procedures and therapies administered will be recorded for both groups.

8.4 Post Intervention Through Discharge

After the intervention period, patients will be monitored according to standard PICU clinical practice for the participating site. Patients will be reviewed daily for their minimum and maximum temperatures through day 10 or hospital discharge, whichever is earlier. The results of all blood, urine and respiratory cultures conducted up to seven days after cardiac arrest will be recorded. Concomitant medications will be recorded from the time of randomization through day 7. Select procedures and therapies will be recorded through hospital discharge. Blood products received within seven days of arrest will be recorded. Adverse events will be recorded from the time of randomization through Day 14. Adverse events that have not resolved by Day 14 will be followed until resolution or hospital discharge, whichever is earlier. If the Adverse Event has not resolved at the time of hospital discharge, the Research Team should follow the guidelines for AE follow-up outlined

in section 11.2.6 of the protocol. PICU and hospital discharge information will be captured.

8.5 Day 28 Status

The vital status of the patient will be recorded on day 28. If the patient has been discharged to home prior to day 28, the parents may be contacted if all other efforts to determine patient mortality have been exhausted.

8.6 Three Month Follow Up

Caregivers will be contacted at three months post arrest and will be asked the status of the patient, location of the patient, and if the patient has undergone any additional procedures or therapies. The caregiver will be asked to provide information on family burden, the patient's global function, POPC, and PCPC. The VABS-II assessment will be done at this time. If the respondent is the child's treating healthcare professional the information on family burden will not be collected. All telephone follow up at three months will be conducted centrally by staff at the Kennedy Krieger institute (Johns Hopkins School of Medicine, Baltimore, MD) to assure uniform performance of the VABS-II assessment. In order to assess interrater reliability of the VABS II telephone interviews, and prevent variance in ratings over time, a subset of interviews (every 10th interview) will be recorded. Recorded interviews will be reviewed and rescored by Dr. Slomine. Discrepant scores will be adjudicated through discussion between Dr. Slomine and the psychometrician.

The three month follow up has several purposes. First, the contact will help with subject retention by maintaining communication with the family. Second, the three month assessment will be used to test our primary endpoint conclusions for robustness with respect to missing data (see Section 9.2 on Page 59). Third, it is of exploratory interest to determine if there is a trajectory of improvement between three months and 12 months.

8.7 12 Month Follow Up

Parents will be contacted at 12 to 16 months post arrest and will be asked the status of the patient, location of the patient, and if the patient has undergone any additional procedures or therapies. The parents will be asked to provide information on family burden, the patient's global function, POPC, PCPC, and VABS-II assessment. In addition to measures administered over

the phone, the patient will have a neuropsychological evaluation and neurological assessment performed at the study site at 12 to 16 months post arrest.

All telephone follow up will be conducted centrally by staff at the Kennedy Krieger Institute (Johns Hopkins School of Medicine, Baltimore, MD). In order to assess interrater reliability of the VABS II telephone interviews, and prevent variance in ratings over time, a subset of interviews (every 10th interview) will be recorded. Recorded interviews will be reviewed and rescored by Dr. Slomine. Discrepant scores will be adjudicated through discussion between Dr. Slomine and the psychometrician.

9 Data Analysis

9.1 General Analytic Issues

THAPCA will be analyzed according to the intention to treat principle, wherein all subjects randomly assigned to a treatment arm will be counted in that arm regardless of adherence to protocol or possible crossover to the other treatment arm. Therefore, this clinical trial will assess whether an initial strategy of hypothermia leads to different rates of death or poor neurological outcome than an initial strategy of normothermia. As THAPCA consists of two separate clinical trials, the alpha level for analysis of each trial is 0.05. All tests will be two-tailed.

9.2 Primary Analysis

The primary endpoint of each THAPCA trial is survival with good neurobehavioral outcome at 12 months post arrest. The Vineland Adaptive Behavior Scales (VABS-II) will be used to provide a standardized, quantifiable measure of neurobehavioral function in survivors. Poor neurobehavioral functioning is defined as a standardized VABS-II score less than 70 at 12 months. Children with a pre-cardiac arrest baseline VABS-II standardized score less than 70 will be included in the trials but will be excluded from analysis of the primary outcome. Pre-cardiac arrest baseline VABS-II information will be completed retrospectively by the caregiver (as soon as possible after enrollment to decrease retrospective bias), and the 12 month VABS-II assessment will be conducted centrally by telephone interview by the Kennedy Krieger Institute (Johns Hopkins School of Medicine, Baltimore, MD).

Differences between the two study arms with respect to this binary outcome will be evaluated using a chi-square test for each of the two THAPCA Trials separately. The rate ratio comparing survival with good neurobehavioral outcome in the hypothermia arm vs. the normothermia arm and its 95% confidence interval will also be described. Patients with a baseline VABS-II score less than 70 will be excluded from the primary analysis, but included in analyses of secondary and safety endpoints.

As all participating centers will be trained in the delivery of both arms of the study protocol, it is expected that any treatment effect should be reasonably consistent (while not uniformly so) across centers. Therefore, a secondary analysis will employ the Mantel-Haenszel test to quantify treatment effect adjusted by center. The Breslow-Day test (which we recognize will have limited power, as the number of subjects within most centers will be quite low) will be used to assess if there is evidence that treatment effect varies across center.

Missing data will be a non-negligible issue in the primary analysis. It is expected that vital status (alive or dead) will be known for almost all patients. The majority of missing data will consist of detailed neurobehavioral information. While the primary outcome analysis will use subjects with available data for the primary endpoint (complete patients), we will also report analysis results using various methods to estimate missing data including last observation carried forward (LOCF) and imputation approaches. The three month follow up will provide a better basis upon which to test our conclusions for robustness with respect to missing data. We will use the LOCF method using the three month observations, and if the three month and 12 month outcomes are highly correlated for complete patients, then the three month observation may enable a better multiple imputation-based robustness analysis.

9.3 Secondary Analyses

Secondary endpoints of each THAPCA trial are:

1. Survival at 12 months post cardiac arrest;
2. Change in neurobehavioral function from pre-cardiac arrest baseline to 12 month measurement (VABS II);

For survivors only,

3. Neuropsychological scores at 12 month evaluation;

4. Neurological abnormality scores at 12 month evaluation.

Mortality over time will be quantified and described using standard survival analysis techniques including generation of Kaplan-Meier curves and comparing these curves between treatment arms via the logrank test. Survival at 12 months will also be evaluated as a binary outcome using the chi-square test. We expect that almost all subjects will have vital status available at 12 months.

The overall change in VABS-II from baseline to 12 months will be evaluated using a linear regression model with 12-month VABS-II as the outcome, and assigned treatment as a predictor along with baseline VABS-II score. Because the distributions may be substantially skewed, we will examine significance levels and confidence intervals for the treatment effect achieved with the nonparametric Wilcoxon rank-sum test for consistency with the findings of the parametric approach. The Wilcoxon rank-sum test will be based on ranks assigned to the differenced scores (12 month minus baseline). If outcomes unexpectedly appear to have substantially differing distribution shapes between treatment arms, resampling techniques will be used to test significance of, and estimate magnitude of, differences in median outcome between treatment arms.

Neuropsychological testing results for the Mullen Scales of Early Learning (children $\leq$ 5 years 8 months) will be measured as continuous outcomes. Comparison between the study groups will employ a two-sample t-test if appropriate, or alternatively, the Wilcoxon rank-sum test if basic normality assumptions are not met. As detailed in Table 3 on page 44, for patients 6 years and older there is a battery of neuropsychological tests, with separate outcome measures for each test. Comparison between groups will be based on ranks and employ the Wilcoxon rank-sum test. Patients who do not meet minimum requirements to be tested will be assigned the lowest rank for a test; patients who are tested but are unable to meet the test's basal requirements will be given the second lowest rank for that test; all other patients will receive a rank based on the actual score achieved for that test.

The neurological abnormality scores will be measured as continuous outcomes for those who complete the exam. Comparison between the study groups will employ a two-sample t-test if appropriate, or alternatively, the Wilcoxon rank-sum test if basic normality assumptions are not met.

Narrative descriptors for each element of the PRCA (Section 6.6.4 on page 43) will also be analyzed by study investigators to characterize patterns of neurological dysfunction in survivors (e.g. specific movement disorders or

cognitive deficits).

9.4 Safety Analyses

Safety endpoints of this study are:

1. All-cause 28 day mortality;
2. Incidence of culture proven infection (blood, urine, respiratory, or other) within 7 days of cardiac arrest;
3. Incidence of arrhythmias within 7 days of cardiac arrest;
4. Blood products required within 7 days of cardiac arrest. Blood products are defined specifically here to include red blood cells, platelets, fresh frozen plasma, and cryoprecipitate.

Differences between the two study arms with respect to these binary outcomes will be evaluated using a separate chi-square test for each of the THAPCA Trials. Appropriate exact tests will be employed in the case of excessively small expected cell sizes. Rate ratios and 95% confidence intervals will also be described. A secondary analysis will employ the Mantel-Haenszel test to quantify the treatment effect adjusted by center, and the Breslow-Day test (which we recognize will have limited power, as the number of subjects within most centers will be quite low) will be used to assess if there is evidence that treatment effect varies across center.

9.5 Additional Exploratory Analyses

The primary goal of a randomized trial is to assess treatment effect with respect to various outcomes, and evidence for a treatment effect will be the focus of the primary publications from these trials. Predefined primary and secondary outcomes will be clearly noted as such in relevant reports. However, regardless of the primary study finding, THAPCA will generate a database of uniformly, carefully followed pediatric subjects after cardiac arrest, with details of their post-arrest management. Thus, it will be of interest to use this database to perform exploratory analyses of the trajectory of recovery (by comparing three month and 12 month VABS-II), or factors associated with outcomes. An example would be post hoc identification of patient characteristics, or patient management strategies, associated with a larger treatment effect. These studies will employ appropriate approaches including linear and logistic regression, Cox proportional hazards regression,

and appropriate variants of the mixed model to summarize outcomes over time. Assigned treatment will be included in these analyses as appropriate. Reports of these analyses will be clearly described as exploratory rather than formal hypothesis testing.

9.6 Power Analysis for Primary Outcome

As stated above, we believe it is appropriate to use an alpha level of 0.05 for each of the two THAPCA Trials, and that two-sided tests are appropriate for the study scenario. From previous studies, we would estimate primary outcome rates to be in the range of 80% for the out-of-hospital normothermia arm, while among the in-hospital subjects, a lower outcome rate would be expected, along the lines of 65% in the normothermia arm. Table 4 and Table 5 on the next page show the total number of subjects needed for the THAPCA-OH and THAPCA-IH Trials to achieve statistical power between 70% and 90% under various treatment effects. The treatment effect is noted as absolute effect size in these tables. Thus, for example in the out-of-hospital trial, an absolute effect size of 20% implies hypothermia improves the outcome rate from 80% to 60%, and in this instance 182 subjects would be required for 80% power. These numbers are not adjusted for interim data monitoring, but such adjustment is nearly negligible if conservative stopping boundaries are employed (Section 9.7 on the facing page).

Based on HD044955 cohort pilot data and the size and number of sites participating in the current study, we anticipate enrolling between 150 to 250 patients per year for a total enrollment of 750 to 950 patients (300 to 350 out-of-hospital arrests in the THAPCA-OH Trial and 450 to 600 in-hospital arrests in the THAPCA-IH Trial). This will give an effective sample size of 250 to 300 out-of-hospital arrests and 400 to 500 in-hospital arrests after adjustment for loss to follow up (10%) and excluding patients with a baseline VABS-II score less than 70. We therefore expect these trials to have substantial power (80 to 85%) to detect absolute treatment effects of 15% or greater among out-of-hospital subjects, and absolute treatment effects of 15% or greater in the in-hospital subjects.

Table 4: Sample Size Needed (Total) to Detect Various Treatment Effects, Assuming Event Rate in Normothermia Arm of 80% (Out of Hospital), Two-Sided Test with alpha=0.05

Absolute Effect Size	Power = 70% ($\beta = 0.3$)	Power = 75% ($\beta = 0.25$)	Power = 80% ($\beta = 0.2$)	Power = 85% ($\beta = 0.15$)	Power = 90% ($\beta = 0.1$)
5%	1800	2014	2266	2580	3600

continued on next page

Table 4: *continued*

Absolute Effect Size	Power = 70% ($\beta = 0.3$)	Power = 75% ($\beta = 0.25$)	Power = 80% ($\beta = 0.2$)	Power = 85% ($\beta = 0.15$)	Power = 90% ($\beta = 0.1$)
10%	500	558	626	710	822
15%	242	272	302	342	396
20%	148	162	182	204	236
25%	100	110	122	138	158
30%	74	82	90	100	116

Table 5: Sample Size Needed (Total) to Detect Various Treatment Effects, Assuming Event Rate in Normothermia Arm of 65% (In Hospital), Two-Sided Test with alpha=0.05

Absolute Effect Size	Power = 70% ($\beta = 0.3$)	Power = 75% ($\beta = 0.25$)	Power = 80% ($\beta = 0.2$)	Power = 85% ($\beta = 0.15$)	Power = 90% ($\beta = 0.1$)
5%	2392	2680	3020	3442	4016
10%	630	704	790	898	1044
15%	294	326	366	414	480
20%	170	188	210	238	274
25%	112	124	138	156	178
30%	80	88	98	110	126

9.7 Interim Analyses and Stopping Rules

This study will be monitored by the Data Safety Monitoring Board (DSMB) appointed by the funding institute (National Institutes of Health). The DSMB will have final jurisdiction regarding frequency of meetings, and appropriate formal monitoring boundaries for study stopping in terms of superiority. In this application, we present what we believe is an appropriate interim analysis plan. A detailed version of this plan will be submitted to the DSMB for approval and possible modification prior to the beginning of study enrollment.

Interim monitoring for superiority of one treatment approach over the other will clearly be appropriate in this study. While many investigators might expect hypothermia to be superior to normothermia, we believe that symmetric monitoring boundaries are appropriate as one cannot rule out a detrimental relative effect of either strategy.

Numerous clinical trials have found early treatment differences that diminished or even reversed as more subjects were enrolled. In a multicenter clinical trial, it is not unusual for early recruitment to be confined to a subset of centers that receive early IRB approval or have a smoother run-

in phase; the experience at these centers may differ from others. Also, a "learning curve" in delivering the study therapies, at some or all centers, is not inconceivable and has been specifically noted for therapies such as hypothermia.[120] Because of these issues, we strongly recommend monitoring boundaries that are conservative at the early looks at the data; we believe that O'Brien-Fleming-type boundaries,[121] implemented using the Lan-deMets flexible alpha spending function approach,[122] are appropriate for this study setting.

As this is an expensive study to conduct, early stopping of either or both of the THAPCA Trials for futility (low chance that a treatment effect is found if the trial continues) is a consideration. A conditional power approach, wherein the chance of the study finding a treatment effect (given the data accrued thus far in the study) under various assumed true scenarios is assessed, may be appropriate for the DSMB to address futility issues if this becomes necessary.[123] This approach, which requires careful consideration of what treatment effect scenarios are realistic given the study data themselves, encourages dialogue and discussion among DSMB members.

The projected accrual period in this study is five years. We assume that the DSMB will meet prior to study launch, and then twice per year during patient accrual. While flexible α spending will be used, we assume here for illustration purposes that there will be four meetings at which the DSMB will perform interim analysis, and that 10%, 25%, 50%, and 80% of study data (technically, of total statistical information for the primary outcome) are available at the respective meetings. Thus, in our illustration, there would be four interim analyses, with an additional final analysis of the study data if the study is not terminated early. While there is no doubt that the DSMB will integrate the results of the study in the out-of-hospital and in-hospital cohorts in their decision making, we generate stopping boundaries independently for these separately powered trials, in line with this study's analytic strategy.

It is helpful to simulate how many subjects will be required, since it is possible that enrollment for one or both trials (in-hospital and out-of-hospital arrests) will be curtailed early, because of evidence of superiority. As indicated in Section 9.6 on page 62, the precise effect size is not known. The discussions of stopping rules and properties below assume that the effect size for the primary analysis has been correctly estimated in the study power calculations. All calculations assume a two-sided $\alpha = 0.05$.

The possibility of stopping early is dependent on total information available at the time of each interim look. These chances of stopping early are identical for the THAPCA-OH and THAPCA-IH Trials, assuming each has

the same power and amount of information at a given look at the data. If the sample size is large enough to enable 90% power, it is more likely that a trial would be stopped early, because more statistical information is available than if the sample size is only large enough to enable 80% power. Table 6 shows the actual monitoring boundaries (expressed in terms of p-values), and expected probability of stopping the study (for benefit) at each look if the true effect size is precisely as postulated in the study power calculations.

It is important to note that sample size adjustments are required to adjust for the interim analyses, although these are so slight as to be nearly negligible. For example, if one of the substudies is designed to have 90% power and 500 subjects are required based on no interim analysis, the required sample size increases to 512 under the meeting schedule discussed above.

It is evident from these simulations that if the treatment effects are at least as large as expected *a priori*, the THAPCA Trials have a substantial chance of stopping early due to superiority, despite the conservative stopping boundaries that are pre-specified for each. Also, it should be noted that some "α spending" occurs from interim analyses, and if either trial is carried to completion, the final determination of overall significance of the primary endpoint at the $\alpha = 0.05$ level will require using a significance level of 0.0426 for the final analysis.

Table 6: Probability of Early Stopping at Interim Analyses

Analysis	Information	2-sided p value	Probability of Stopping, Power = 80% ($\beta = 0.2$)	Probability of Stopping, Power = 90% ($\beta = 0.1$)
First	10%	≤ 0.000000014	negligible	negligible
Second	25%	≤ 0.000015	0.2%	0.4%
Third	50%	≤ 0.003	16.7%	25.5%
Fourth	80%	≤ 0.0235	44.0%	49.0%
Final	100%	≤ 0.0426	19.2%	15.1%

10 Human Subjects Protection

10.1 IRB Review and Communications

This protocol, the parental permission, and child assent forms must be reviewed and approved by each clinical center's IRB before the study begins at that site. In addition, the Data Coordinating Center (DCC) must have

documentation of current IRB approval at all times during the study. The Data Coordinating Center must also have a copy of the informed permission and child assent forms that were approved by the IRB for each clinical center before enrollment will be permitted at the clinical center.

10.2 Informed Consent

10.2.1 Parental Permission

This protocol requires that parents or other legally empowered guardians sign a parental permission form. The parent or legal guardian will be informed about the objectives of the study and the potential risks.

10.2.2 Child Assent

Subjects who are eligible for THAPCA are comatose, and child assent will not be possible at the time of study enrollment. However, during follow up after discharge from the PICU, issues about assent become applicable. Children who are capable of giving assent and who are alert and competent, will be asked, following an age-appropriate discussion of risks and benefits, to give assent to the study for collection of follow up information. Assent will be waived if the child is too young, has a severely reduced mental age, decreased level of consciousness, psychological problems, or other legitimate reasons as judged by the Institutional Review Board at each site.

10.2.3 Subject Consent

Subjects who are eligible for THAPCA are comatose and under 18 years of age. If a subject attains the age of 18 years during the study intervention period, it will not be possible to obtain informed consent from the subject. During the follow up after discharge from the PICU, 18 year old subjects who are alert and competent and capable of giving consent will be asked, following an appropriate discussion of risks and benefits, to give consent to the study for collection of follow up information. Subject consent will be waived if the subject has a severely reduced mental age, decreased level of consciousness, psychological problems, or other legitimate reasons as judged by the Institutional Review Board at each site.

10.3 Risks and Benefits

Potential complications of hypothermia are addressed in the next two sections (Sections 10.4.1 on the next page and 10.4.2 on page 68). The potential

benefit of the intervention (hypothermia) is that it may improve overall survival, and may result in improved neurobehavioral outcome after pediatric cardiac arrest. Subjects assigned control(normothermia) therapy in this interventional trial may also benefit from having body temperature rigorously controlled in the normal range. In usual practice at most children's hospitals, central temperature is not rigorously monitored and controlled. To minimize the risks of this trial, all subjects will have their temperature controlled by the Blanketrol III cooling unit and appropriately-sized Maxi-Therm Lite mattresses.

10.4 Risk of Surviving with Worse Neurobehavioral Outcome

It is known that a significant number of children who have sustained cardiac arrest currently survive with neurological injury. It is expected that a significant number of children participating in THAPCA Trials will also survive with neurological injury regardless of whether they receive the actively maintained normothermic control therapy or therapeutic hypothermia. We do not know at this time whether the chance of surviving with brain injury is more likely in the cooled group or the normothermic control group. The informed consent shall reflect this information.

10.4.1 Complications Reported in Previous Studies

Several clinical trials have now been conducted in both newborn and adult populations that observed therapeutic hypothermia to be safe, so we do not expect clinically important complications associated with hypothermia to be observed in the THAPCA Trials.

Shankaran[30] reported an RCT of 205 newborns with birth asphyxia of which 102 were cooled with the Blanketrol II cooling unit for 72 hours. No increased occurrence of cardiac arrhythmia, bleeding, skin changes or death during the cooling period was observed. Additionally, there was no increase in blood stream infection during the hospital course. Other complications that were similar between the hypothermia and control groups were as follows: hypotension, persistent pulmonary hypertension, oliguria/anuria, hepatic dysfunction, disseminated intravascular coagulopathy, hypoglycemia, and hypocalcemia.

The neonatal CoolCap study[29] reported elevated glucose in hypothermia group vs control newborns (7.6 vs 5.4 mmol/L), which resolved spontaneously in 24 hours. Scalp edema occurred more commonly in head

cooled patients 32/108 vs. 1/110 controls, and resolved shortly after the end of cooling. There were no major cardiac arrhythmias, venous thrombosis, severe hypotension, or unanticipated serious adverse events reported. Other complications not increased in cooled cases included: hypotension, coagulopathy, prolonged coagulation times, abnormal renal function, hyponatremia, hypokalemia, platelet count less than 100,000/mcl, metabolic acidosis, respiratory distress, systemic infection, hemoconcentration, hypoglycemia, hypocalcemia, and clinical seizures. Liver function elevation was less in cooled cases.

Polderman reported a large adult experience of therapeutic hypothermia with the Blanketrol II cooling unit and mattresses. No increased risk of intracranial hematomas, acute renal failure, clinically significant cardiac complications, pulmonary complications, or deep venous thrombosis were reported.[106] The average duration of cooling was 4.8 days with a range of 1 to 21 days.

Bernard[28] reported an adult cardiac arrest RCT in which cooling was done with cold packs and cooling mattresses. No differences in platelet count or WBC during 12 hours of cooling in adult cardiac arrest cases were observed. Potassium levels were observed to be slightly lower at 6 hours in cooled patients compared to normothermic controls (3.6 vs. 4.0 mmol/L; p=0.06) and were stable during the period of cooling. On rewarming, potassium levels were greater in cooled patients (4.5 vs 3.9 mmol/L) at 24 hours. Glucose levels were also noted to be higher in cooled patients than normothermic cases (16.2 vs 10.5 mmol/L). The hyperglycemia resolved following rewarming.

10.4.2 Minimizing Risk of Complications in THAPCA Trials

There are several elements of this study design that will help minimize risks to subjects. The exclusion criteria eliminate certain populations that might be at higher risk for complications. These include patients on extremely high pressor infusions, sickle cell anemia, cryoglobulinemia, pregnancy, skin conditions, and patients with Glasgow Coma Score motor scale indicating an ability to localize pain or obey commands. Patients with terminal illnesses or progressive degenerative conditions will also not be eligible for enrollment.

Risk to subjects will also be minimized by the nature of the PICU clinical setting. Patients will be hospitalized in intensive care units and monitored closely for potential complications and adverse events as a part of usual clinical care. Patients will be assessed as per usual clinical care for development of skin injury or excessive cooling which could occur with use of the cooling

blanket. Each clinical site will be instructed to follow the instructions on the Blanketrol III unit and standard of care at their respective institutions. The study investigator will be contacted for central temperatures of 31.0 °C or less. The importance of temperature control will be emphasized in the training session and in the manual of operations. The Blanketrol III unit is equipped with a temperature control safety system that measures and controls the temperature which also will help protect the patient from harm. Temperature control will be implemented in all subjects using the servo-control mechanism available on the Blanketrol III.

We will provide training for clinical investigators and coordinators regarding potential complications of therapeutic hypothermia, study procedures, and the importance of temperature monitoring and maintaining therapeutic temperature ranges. Additional details on potential complications and the appropriate steps to be taken in the event of a complication are outlined below.

Excessive cooling below the therapeutic range. This complication will be treated by increasing the Blanketrol III temperature so that the patient warms to the therapeutic range (32 to 34°C). Excessive cooling below the therapeutic range in the THAPCA Trials could result in life-threatening cardiac arrhythmias. If cooling below the therapeutic range occurs in patients randomized to receive hypothermia, the patient will be rewarmed to the therapeutic range of 32 to 34°C immediately. Arrhythmias will be managed according to standard AHA PALS guidelines. Excessive cooling will be avoided by utilizing two central temperature probes (esophageal and bladder or rectal) and monitoring subject temperature on a continual basis. The temperature of the water in the Blanketrol III will also be monitored and recorded, and temperature control in all subjects will use the servo-control mechanism available with the Blanketrol III. The patient will not be cooled below 32-34 °C therapeutic range. The study investigator will be contacted for central temperatures of 31.0 °C or less. In the event that the temperature difference between central measures is greater than 1.0 °C, the study investigator will be also be notified.

Cardiac arrhythmias. Serious cardiac arrhythmias are not expected to occur unless the temperature falls well below 30 °C. If a clinically significant arrhythmia develops and persists, then the patient would be rewarmed to normal range if determined by the clinical care team to be necessary.

Infection. Infection rates are expected to be high in both groups of subjects (normothermia and hypothermia groups), based on our prior cohort study data of cardiac arrest patients. The clinical team will utilize antibiotics per their usual clinical site practice in the post arrest population. The THAPCA Trials will monitor both hypothermia and normothermia (control) groups for blood stream and urinary infections as outlined in Section 6.3 of the protocol. In the event of a positive culture or suspicion of possible infection, appropriate antibiotics will be initiated based on the clinical care team's hospital experience.

Bleeding. Bleeding will be monitored by measuring the volume per kg of blood products (red blood cells, platelets, fresh frozen plasma, cryoprecipitate) administered during the first seven days. We will also track the number of surgical interventions for bleeding during the first 7 days. Patients with life threatening bleeding or severe coagulopathies will not be eligible for this trial. Life threatening bleeding during the study will be managed per the clinical care team with rewarming to the normal range. Prior TBI studies did not observe bleeding to be more commonly observed in hypothermic patients compared to normothermic patients.

Alterations of Potassium. Initiation of cooling has been associated with slight reduction in potassium serum concentration measurement. Serum potassium levels will be measured at baseline and then at least every 6 hours during cooling and the rewarming period. Rewarming has been associated with mild increase in potassium serum concentration measurement. Therefore, the clinical team will remove potassium from the IV fluids during rewarming and supplement as needed during this period. Thereafter, the clinical care team will measure potassium based on their normal unit practice.

Multiple organ failure and death. Patients who have had cardiac arrests are at high risk for development of multiple organ failure and death. In our previous cohort study, the mortality rate was nearly 50%. Seizures following cardiac arrest varied between 14-26% for in-hospital and out-of-hospital cases. Blood stream infection was also high in the cohort study.

In summary, for the therapeutic hypothermia group of the THAPCA Trials, we do not expect higher rates of adverse effects to be observed based on findings from neonatal and adult RCTs using therapeutic hypothermia for HIE or cardiac arrest.

10.5 Data Security and Subject Confidentiality

All evaluation forms, and reports will be identified only by a coded number to maintain patient confidentiality. All records will be kept in a locked/ password protected computer. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring by the Federal funding institution (NHLBI), the DCC, or other governmental regulatory bodies.

The data coordinating center (DCC) at the University of Utah has a dedicated, locked server room within its offices, and the building has 24 hour on-site security guards. The DCC has a state-of-the-art computer infrastructure and coordinates its network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides the DCC with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Network equipment includes three high-speed switches and two hubs. User authentication is centralized with two Windows 2003 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using secure socket layer (SSL) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption. OpenClinca (OC) is the clinical trials software used at the DCC, and eRoom^{TM} is used for communications about the study. It is possible that a different electronic data capture system could be used in the future. OC, eRoom^{TM} and other web applications use the SSL protocol to transmit data securely over the Internet.

Direct access to DCC machines is only available while physically located inside the DCC offices, or via a VPN client. All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff are notified of intrusion alerts. Security is maintained with Windows 2003 user/group domain-level security. Users are required to change their passwords every 90 days, and workstations time out after 10 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group level access to databases, tables, and views in Microsoft SQL Server.

The investigators and staff of the data coordinating center are fully committed to the security and confidentiality of data collected for the THAPCA Trials. All personnel at the DCC have signed confidentiality agreements concerning all data encountered in the DCC. Violation of these agreements may result in termination from employment at the University of Utah. In addi-

tion, all personnel involved with DCC data systems have received Human Subjects Protection and HIPAA education.

10.6 Health Insurance Portability and Accountability Act

Data elements collected include the date of birth and date of admission. Prior to statistical analyses, dates will be used to calculate patient age at the time of the study events. The final data sets (used for study analyses and archived at the end of the study) will be de–identified, and will exclude these specific dates.

Data elements for race, ethnicity, and gender are also being collected. These demographic data are required for Federal reporting purposes to delineate subject accrual by race, ethnicity, and gender.

Each Clinical Center will be required to obtain informed consent from a legal guardian of eligible patients before the patient is enrolled in the study. For purposes of the DCC handling potential protected health information (PHI) and producing the de–identified research data sets that will be used for analyses, all study sites have been offered a Business Associate Agreement with the University of Utah. Copies of executed Business Associate Agreements are maintained at the DCC.

10.7 Record Retention

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)].

11 Data and Safety Monitoring Plan

11.1 Data Safety Monitoring Board (DSMB)

THAPCA will have a Data Safety Monitoring Board (DSMB) appointed by the Director of the National Heart, Lung, and Blood Institute (NHLBI). The

DSMB will have a charter, will approve the protocol prior to implementation, and will review interim analyses as described in Section 9.7 on page 63.

The purpose of the DSMB is to advise the Federal funding agency (NHLBI), the THAPCA scientific Principal Investigator (Dr. Moler), and the THAPCA Executive Committee regarding the continuing safety of study subjects and the continuing validity and scientific merit of the study. The DSMB is responsible for monitoring accrual of study subjects, adherence to the THAPCA protocol, assessments of data quality, performance of individual clinical sites, review of serious adverse events and other subject safety issues, and review of formal interim statistical analyses of treatment efficacy. The Data Coordinating Center will send reports relating to these topics to DSMB members ten days prior to each DSMB meeting. We propose that the DSMB will meet twice annually during patient accrual into the THAPCA Trials, although the DSMB will have the discretion to alter meeting timing and frequency. There are no planned DSMB meetings in the last year of the THAPCA project, during which no new patients will be enrolled (but 12 month follow-up will be conducted to obtain the primary outcome.)

The Data Coordinating Center will staff DSMB meetings. The DSMB Executive Secretary, appointed by NHLBI, will produce minutes of the meetings. The minutes will be approved by the DSMB Chairperson and sent to the Director, NHLBI, for acceptance of recommendations. The THAPCA Executive and Steering Committees will then receive the minutes.

11.2 Adverse Event Reporting

11.2.1 Definitions, Relatedness, Severity and Expectedness

Definition: An adverse event (AE) is any untoward medical occurrence experienced by a subject. An event constitutes a disease, a set of related signs or symptoms, or a single sign or symptom.

On each study day, the clinical site investigator will evaluate adverse events. Adverse events not previously documented in the study will be recorded on the adverse event record form. The nature of each experience, date and time (where appropriate) of onset, outcome, course, and relationship to treatment should be established.

Relatedness: The suspected relationship between study intervention (use of the temperature control blanket and/or hypothermia) and any adverse event will be determined by the clinical site investigator using the following criteria:

Not Related: The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Possibly Related: The event follows compatible temporal sequence from the time of application of the temperature blanket or changes in temperature, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Probably Related: The event follows a reasonable temporal sequence from the time of application of the temperature blanket or changes in temperature, and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Seriousness: The severity of clinical adverse events and laboratory abnormalities will be recorded by the clinical site investigator and categorized. A serious adverse event (SAE) is an adverse event that:

- results in death; or
- is life-threatening (the patient was, in the view of the clinical site investigator, in immediate danger of death from the event as it occurred); or
- requires inpatient hospitalization or prolongs and existing hospitalization; or
- results in persistent or significant disability or incapacity; or
- results in congenital anomaly/birth defect); or
- any other event that, based upon appropriate medical judgement, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Expectedness of the Event: All adverse events, including serious adverse events, will be evaluated as to whether their occurrence was expected or unexpected. An adverse event is considered expected if it is known to be associated with critical illness following cardiac arrest, the underlying medical condition of the subject, is directly related to study outcome (e.g. death), or is otherwise mentioned in the protocol, informed consent, or other study documents. For this protocol, expected events include:

- mortality (unless believed to be related to cooling)
- hemodynamic instability
- cardiac arrhythmias, including life-threatening rhythms
- electrolyte abnormalities
- metabolic acidosis
- sepsis, infections, or bacteremia
- fever
- bleeding
- seizures
- cerebral edema and other brain injury
- worsening neurological function
- renal dysfunction
- liver dysfunction
- reintubation
- hypoxia
- respiratory distress
- pleural effusions
- pulmonary edema
- anasarca (body edema)
- general pediatric problems related to ICU stay and cardiac arrest
- complications related to the condition that led to cardiac arrest

Treatment or Action Taken: For each adverse event, the clinical site will record whether an intervention was required:

- Intervention: Surgery or procedure
- Other Treatment: Medication initiation, change, or discontinuation
- None: No action taken

Finally, the clinical site will record the clinical outcome of each adverse event as follows:

- Death
- Recovered and the patient returned to baseline status
- Recovered with permanent sequelae
- Symptoms continue

11.2.2 Time Period for Adverse Events

For purposes of the THAPCA Trials, adverse events occur following randomization through Day 14. Specifically, events that occur following parental permission to participate in THAPCA, but prior to actual randomization, will be not be reported as adverse events. These should be recorded as baseline conditions. Events that occur following discharge from the hospital will not be reported as adverse events. Adverse events that occur between randomization and Day 14 that are not resolved by Day 14 will be followed until resolution or hospital discharge, whichever is earlier. If the event has not resolved by hospital discharge, please see section 11.2.6 of the protocol for further instructions.

11.2.3 Data Collection Procedures for Adverse Events

After patient randomization, all adverse events (including serious adverse events), whether anticipated or unanticipated, will be recorded according to the date of first occurrence, severity, and their duration, as well as any treatment prescribed. Any medical condition present at the time of randomization, recorded in the patient's baseline history at study entry, which remains unchanged or improves, will not be recorded as an adverse event at subsequent evaluations. However, worsening of a medical condition that was present at the time of randomization will be considered a new adverse event and reported.

Abnormal laboratory values that are clinically significant will be recorded as adverse events and the clinical site investigator will assess the severity and relationship to the study. Laboratory values that are abnormal at the time of randomization and that do not worsen will not be recorded as adverse events.

Adverse events will be coded using the MedDRA coding vocabulary. Coding will be done centrally at the DCC because this requires specific training.

11.2.4 Monitoring Serious Adverse Events

The Principal Investigator of the Data Coordinating Center (Dr. Dean) will act as the medical monitor for THAPCA. If Dr. Dean is unavailable, a qualified physician will be designated to fulfill this function. Clinical site investigators or coordinators will report a selected subset of expected serious adverse events to the DCC within 24 hours. A detailed completed report will be required to be sent to the DCC within 3 working days of the event,

and the medical monitor will assess these serious adverse events reported from clinical sites in THAPCA. For each of these serious adverse events, the clinical site will provide sufficient medical history and clinical details for a safety assessment to be made with regard to continuation of the THAPCA Trial. The medical monitor will sign each SAE report after review. All SAE reports will be retained at the DCC, and all SAE reports will be available for review by DSMB members and NHLBI staff via the eRoom^{TM} facility.

Serious adverse events that require a written notification of the DCC within 24 hours and a completed written report within three working days of the SAE, and subsequent review by the medical monitor, include the following:

- Mortality
- Infection diagnosed with positive bacterial or fungal culture
- Repeat cardiac arrest
- Life threatening arrhythmias
- Any SAE requiring early cessation of hypothermia
- Any SAE that the clinical site investigator believes should be reported with the supplemental written information.

The other expected serious adverse events that are listed in Section 11.2.1 on page 74 do not require written reporting, but should be recorded in the same manner as all adverse events.

In the unlikely event that the medical monitor believes an unexpected and study-related SAE warrants emergent cessation of enrollment in either or both of the THAPCA Trials, NHLBI staff and the DSMB chairperson will be immediately consulted. If these individuals concur with the judgment of the medical monitor, or if the NHLBI staff and the DSMB chairperson cannot be reached expeditiously, the Data Coordinating Center will notify all clinical site investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the THAPCA Executive Committee, the DSMB, and NHLBI staff.

11.2.5 Reporting Procedures

Assuring patient safety is an essential component of this protocol. Each participating investigator has primary responsibility for the safety of the individual subjects under his or her care. All adverse events will be evaluated by the clinical site investigator, and will be classified as noted in Section 11.2.1

. All adverse events occurring after study randomization through Day 14 will be recorded and entered into the electronic data entry system provided by the DCC.

The clinical site investigator will report all *serious, unexpected, and study-related* adverse events to the DCC within 24 hours. A detailed completed report will be required to be sent to the DCC within 3 working days of the event. After receipt of the complete report, the DCC will report such *serious, unexpected, and study-related* adverse events to the NHLBI Program Official or Project Officer in an expedited manner (within 24 hours). In accordance with local IRB requirements, the clinical site investigator may be required to report such events to the IRB in addition to notifying the DCC. In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in either or both of the THAPCA Trials, and NHLBI staff cannot be reached expeditiously, the Data Coordinating Center will notify all clinical site investigators to suspend enrollment in the trial. Resumption of enrollment will not occur without consent of the THAPCA Executive Committee, the DSMB, and NHLBI staff.

Unanticipated problems (UP) are defined as incidents, experiences, or outcomes that are unexpected, related to participation in the THAPCA Trials, and suggest that the research places subjects at a greater risk of harm than was previously known or recognized. The clinical site investigator will report unanticipated problems to the DCC within 24 hours. A detailed completed report will be required to be sent to the DCC within 3 working days of the event. After receipt of the complete report, the DCC will report these unanticipated problems to the NHLBI Program Official or Project Officer in an expedited manner (within 24 hours). In accordance with local IRB requirements, the clinical site investigator may be required to report such unanticipated problems to the IRB in addition to notifying the DCC. In the event that the medical monitor believes that the unanticipated problem warrants emergent suspension of enrollment in either or both of the THAPCA Trials, and NHLBI staff cannot be reached expeditiously, the Data Coordinating Center will notify all clinical site investigators to suspend enrollment in the trial. Resumption of enrollment will not occur without consent of the THAPCA Executive Committee, the DSMB, and NHLBI staff.

After notification of the NHLBI Program Official or Project Officer, and the DSMB chairperson, of *serious, unexpected, and study-related* adverse events or unanticipated problems (UP), decisions will be made whether to continue the study without change, and whether to convene the entire DSMB for an emergent meeting. If a decision is made to suspend enrollment in

either THAPCA trial, this will be reported to all THAPCA investigators, who will be instructed to report this to their local IRB.

The DSMB will review all adverse events (not necessarily serious, unexpected, and study-related) during scheduled DSMB meetings. The DCC will prepare a Summary Report of Adverse Events within 30 days of its meeting, and this report will be distributed to all THAPCA investigators to be forwarded to the local IRB. The Summary Report will contain the following information:

- A statement that a DSMB review of outcome data, adverse events, and information relating to study performance across all centers took place on a given date;
- A statement as to whether or not the frequency of adverse events exceeded what was expected and indicated in the informed consent;
- A statement that a review of recent literature relevant to the research took place;
- The DSMB recommendation with respect to progress or the need for modification of the protocol or informed consent. If the DSMB recommends changes to the protocol or informed consent, the rationale for such changes and any relevant data will be provided;
- A statement that if safety concerns are identified, the NHLBI Program Officer will communicate these promptly to all THAPCA investigators.

11.2.6 Follow-up of Adverse Events

All serious, unexpected and related adverse events, that are unresolved at the time of the patient's termination from the study or discharge from the hospital, will be followed by the investigators until the events are:

- Resolved, subject is lost to follow-up, the adverse event is otherwise explained or has stabilized; OR
- 12 months has passed from the time of randomization

Adverse experiences that begin after discharge from the hospital will not be reported as study adverse events.

12 Data Quality Assurance

12.1 Data Management

Data will be entered into an electronic data collection (EDC) system to be designed and implemented by the DCC. The Study Coordinator is required

to use hard copies of worksheets for data collection. The paper worksheets should be retained at the clinical center in a secure location until the study is complete and all study publications have been published.

12.2 Study Training

A formal training program for investigators and research staff will be held prior to the start of enrollment. The training program will cover regulatory topics including applicable device regulations and good clinical practice. The training will also provide in depth explanations regarding study procedures, device operation, clinical care, adverse event reporting, data entry procedures, quality assurance, site monitoring and the informed consent process. A manual of operations will be provided to each site investigator prior to the start of enrollment. The manual will detail specific information about the study procedures, regulatory information, safety reporting, and other necessary information. Updates and revisions to the manual will be made available electronically. The DCC, in collaboration with the principal investigator, will be the main contact for study questions. The DCC will coordinate phone conferences and/or web conferences at intervals throughout the study to address educational needs. It is also anticipated that the Steering Committee will meet at least twice per year, once in teleconference and once in person. At the physical meeting, it is anticipated that the research coordinators will also be present, and this setting may be used to facilitate ongoing study training.

A team of experts will also be on call to guide sites through enrollment of the first two patients in order to assure that correct study procedures are being followed, and to answer any questions related to administration of the interventions.

12.3 Site Monitoring

Clinical trials require monitoring commensurate with the degree of risk involved in participation as well as the size and complexity of the study. Site monitoring will be implemented with actual visits to each site, supplemented by remote site monitoring.

12.3.1 Physical Site Monitor Visits

Site monitoring visits are conducted during the study to review patient entry, data quality, and patient safety and to assure regulatory compliance. The ongoing site monitoring visits will include an on-site meeting of the monitor,

the investigator and his/her staff. A site monitor will visit each study site during the study period and review compliance with the study methodology and adherence to Good Clinical Practice guidelines. The site monitor will provide each site with a written report and sites will be required to follow up on any deficiencies.

It is anticipated that the study monitoring visits for this protocol will consist of a site initiation visit (prior to patient enrollment), interim visits, and a close out visit. The site initiation may take place as a group training of site investigators and research assistants.

Interim visits will take place depending on grant budget, site enrollment, and compliance issues identified. The first interim visit will take place when 1 to 5 subjects are enrolled. Subsequent interim visit triggers will be determined and outlined in the site monitoring plan. During interim visits, review of regulatory compliance and documentation, 100% review of consent documentation is anticipated, along with statistically controlled sampling for source verification.

Close out visits will take place after the last subject is enrolled at the site. The close out visit agenda would include resolution of outstanding queries and a review of adverse events, regulatory documentation, and archiving plan.

12.3.2 Remote Site Monitoring

The data center will supplement on-site monitoring with remote monitoring activities. Remote monitoring involves detailed review of the data entered by the site and telephone consultations with the site investigator or coordinator to review safety and data quality. The on site monitoring agenda generally includes source document verification of remote monitoring and the internal site QA performed.

12.3.3 Site Monitoring Plan

A supplemental study-specific monitoring plan, separate from the protocol, will be completed prior to the start of the study which outlines specific criteria for monitoring. This plan will include the number of planned site visits, criteria for focused visits, or additional visits, a plan for chart review, and a follow up plan for non compliant sites. The monitoring plan also describes the type of monitoring that will take place (e.g. sample of all subjects within a site; key data or all data), the schedule of when these activities are to take place, how they are reported, and a time frame to

resolve any issues found. For remote site monitoring, data elements and schedule of monitoring will be determined by the DCC.

12.4 Record Access

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. The medical record must be made available to authorized representatives of the DCC, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, Health Canada (the Canadian counterpart of the U.S. FDA), site local health authorities, the DCC and its authorized representative(s), the National Institutes of Health, and the IRB for each study site, if appropriate.

13 Publication of Data

Because a large number of sites and investigators will be involved in THAPCA, it is not reasonable to use a traditional authorship structure for study publications. Authorship for this study will be corporate, crediting the group's name (THAPCA Trial Investigators), and also including a byline to credit the participating research networks (PECARN and CPCCRN). Participant roles will be listed in the Appendix. All publications will be reviewed by the PECARN and CPCCRN according to applicable policies in these two networks, the THAPCA Executive Committee, and NHLBI requirements.

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