



# Rationale, Timeline, Study Design, and Protocol Overview of the Therapeutic Hypothermia After Pediatric Cardiac Arrest Trials

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**Objective:** To describe the rationale, timeline, study design, and protocol overview of the Therapeutic Hypothermia after Pediatric Cardiac Arrest trials.

**Design:** Multicenter randomized controlled trials.

**Setting:** Pediatric intensive care and cardiac ICUs in the United States and Canada.

**Patients:** Children from 48 hours to 18 years old, who have return of circulation after cardiac arrest, who meet trial eligibility criteria, and whose guardians provide written consent.

**Interventions:** Therapeutic hypothermia or therapeutic normothermia.

**Measurements and Main Results:** From concept inception in 2002 until trial initiation in 2009, 7 years were required to plan and operationalize the Therapeutic Hypothermia after Pediatric Cardiac Arrest trials. Two National Institute of Child Health and Human Development clinical trial planning grants (R21 and R34) supported feasibility

assessment and protocol development. Two clinical research networks, Pediatric Emergency Care Applied Research Network and Collaborative Pediatric Critical Care Research Network, provided infrastructure resources. Two National Heart Lung Blood Institute U01 awards provided funding to conduct separate trials of in-hospital and out-of-hospital cardiac arrest. A pilot vanguard phase that included half the clinical sites began on March 9, 2009, and this was followed by full trial funding through 2015.

**Conclusions:** Over a decade will have been required to plan, design, operationalize, and conduct the Therapeutic Hypothermia after Pediatric Cardiac Arrest trials. Details described in this report, such as participation of clinical research networks and clinical trial planning grants utilization, may be of utility for individuals who are planning investigator-initiated, federally supported clinical trials. (*Pediatr Crit Care Med* 2013; 14:e304–e315)

**Key Words:** cardiac arrest; in hospital; mortality; multicenter; outcome; out of hospital; pediatric; randomized controlled trial; targeted temperature control; therapeutic hypothermia; therapeutic normothermia

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Cardiac arrest (CA) is a tragic event that is often associated with high mortality and poor quality of life outcome in all age groups. Children who survive CA commonly sustain neurologic injury that may result in a lifetime of dependency for all aspects of care. The pathophysiology and outcome of pediatric CA differ greatly between those that occur out-of-hospital, commonly in healthy children, and those that occur in-hospital, typically in children with complex underlying disorders. There is a great need for neuroprotective therapies for both populations of pediatric CA survivors, and future randomized controlled trials (RCTs) must distinguish between cases occurring out-of-hospital and in-hospital (1).

In 2002, landmark RCTs in adults with out-of-hospital ventricular fibrillation or tachycardia (VF/VT) associated CA (2, 3) demonstrated improved survival with good neurologic outcome after therapeutic hypothermia (TH).

In 2005, newborns with birth-associated hypoxic ischemic encephalopathy (HIE) (4–6) were reported to have improved survival and neurobehavioral outcome following TH initiated within 6 hours of birth. There are, however, major differences in the etiology and pathophysiology of CA across age groups, and results in neonates and adults should not be extrapolated to children. Furthermore, a recent pediatric traumatic brain injury (TBI) RCT reported a strong trend for worse outcome in those receiving TH (7). No adequately powered RCT of TH has been conducted in the pediatric (nonnewborn) CA population, and such trials are urgently needed to guide current and future practice.

Our investigative team, which has worked together since 2002, has brought together two federally funded pediatric clinical research networks with a common data coordinating center (DCC) to conduct the Therapeutic Hypothermia After

Pediatric Cardiac Arrest (THAPCA) trials. The primary objective of these trials is to determine whether TH improves survival with good neurobehavioral outcome in children who have been resuscitated after CA in the out-of-hospital (THAPCA-out-of-hospital trial) and in-hospital (THAPCA-in-hospital trial) settings. This report describes the rationale, timeline, study design, and protocol overview of the THAPCA trials.

## MATERIALS AND METHODS

### Timeline: Key Milestones in the Development of the THAPCA Trials

**Background.** The simultaneous publication in 2002 of the landmark adult trials of TH for out-of-hospital CA provided the impetus for planning the THAPCA trials (2, 3) (Table 1). There are key differences between the typical out-of-hospital

**TABLE 1. Timeline for Therapeutic Hypothermia After Pediatric Cardiac Arrest Trials**

Year	Key Events
2002	PECARN originates and adult therapeutic hypothermia RCTs published <i>New England Journal of Medicine</i>
2003	National Institute of Child Health and Human Development R21 Request for Applications Pediatric Cardiac Arrest, Hypothermia RCT planning grant (HD044955) (July 2003) awarded
2004–2006	Cohort study conducted at 15 PECARN sites
2006	R34 (HD050531) awarded to support writing MOO (July 2006)
2006	Collaborative Pediatric Critical Care Research Network sites join PECARN sites to operationalize trials Protocol planning meeting in Washington, DC Other planning meetings in Toronto and Salt Lake City
2006	Prospective yield study at select sites using inclusion and exclusion criteria
2007	Draft MOO with “refined” protocol NHLBI contacted to submit application > ppg limit (1.5M) Letter (5-page study overview) to directors NHLBI— approved
2008	R01s submitted (February 2008) Study section review and council approved Budget and study design modifications by NHLBI (November 2008)
2009	HL094345 and HL094339 awards received (March 2009) Institutional Review Board materials and contracts to sites (April 2009) Vanguard (half of sites) selection (June 2009) Training (August 2009) Enrollment begins per schedule (September 1, 2009) Data Safety and Monitoring Board created
2009	Vanguard site enrollment (September 2009–August 31, 2010) Exceeds feasibility (minimum) goal 50 cases and expected goal 75 cases Actual enrolled: 90 cases
2010	Funding approved to add second cohort of sites (September 2010)
2012	37 total sites and enrollment of 389 cases as of May 29, 2012

PECARN = Pediatric Emergency Care Applied Research Network, RCT = randomized controlled trials.

adult and pediatric CA events: VF/VT shockable arrests in adults versus asystole/pulseless electrical activity (PEA) non-shockable arrests in children, emergency medical services resuscitation quality issues, impact of hypoxia and ischemic injury in the developing versus mature brain, and others. Such major differences provide a very strong argument that pediatric trials are urgently needed to determine if TH is effective in this age group.

**R21 Award: Preclinical Trial Cohort Study.** To determine the feasibility of a multicenter RCT of TH after pediatric CA, we planned a preclinical trial cohort study in conjunction with the Pediatric Emergency Care Applied Research Network (PECARN) <http://www.pecarn.org/> (8). Our application, in response to a National Institute of Child Health and Human Development (NICHD) Request for Applications (RFA) to support RCT planning related to CA (RFA-HD-02-026), resulted in an award (HD044955) to conduct the preclinical trial cohort study.

The R21 cohort study, conducted over 18 months at 15 PECARN sites, included 491 in-hospital and out-of-hospital CAs with return of spontaneous circulation (ROSC)/return of circulation (ROC) with extracorporeal membrane oxygenation (ECMO) (1, 9, 10). Approximately one third of the CAs were out-of-hospital and two thirds of the CAs were in-hospital cases; over half the children died during their hospitalization in each cohort (9, 10). When the in-hospital and out-of-hospital cohorts were compared, striking differences were observed (1). The most important finding was the unexpected difference in the cause of death; death was attributed to a neurologic indication in nearly 70% of out-of-hospital cases and only 20% of in-hospital cases. This remarkable difference made it imperative to conduct separate RCTs in these two populations. Sample size estimates, based primarily on information from this cohort, indicated that about twice as many sites as participated in the cohort study would be needed to conduct RCTs in 4 years of enrollment, with an additional fifth year for follow-up.

**R34 Award: Preparation of Investigator-Initiated Clinical Trials Application to NIH.** To complete planning for the THAPCA trials, we obtained a R34 (PA-04-008) award (HD050531) to support the development of the manual of operations and related materials. In 2006, a new PICU clinical research network, the Collaborative Pediatric Critical Care Research Network (CPCCRN) (<http://www.cpccrn.org/>), joined the existing PECARN sites in planning the THAPCA trials (11). Both networks use the same DCC (8, 11). Following protocol development meetings, we conducted a prospective examination of inclusion and exclusion criteria at clinical sites to obtain an improved estimate of the available sample sizes and site numbers required to conduct future RCTs. A major topic of discussion during initial protocol meetings was temperature management in the control group; there was consensus that there should be active temperature management to achieve normothermia in this group.

**NIH/NHLBI Special Application Process.** NHLBI requires that investigators, proposing multisite clinical trials with

direct costs of \$500,000 or more, obtain permission before submitting an application (<http://www.nhlbi.nih.gov/funding/policies/500kweb.htm>). As required, we met with NHLBI Program and Review staff to discuss the project and subsequently requested permission to proceed with an application. NHLBI granted approval to submit two linked R01 application in February 2008 cycle, one to support a DCC and a separate application to support 30 clinical sites to perform two separate parallel RCTs for in-hospital and out-of-hospital pediatric CA (THAPCA-in-hospital and THAPCA-out-of-hospital).

**NIH/NHLBI Review and Funding.** After review, the THAPCA clinical trials were funded (HL094345 and HL094339) and included some study design changes, budget modifications, and the implementation of a pilot Vanguard Phase, described elsewhere in detail (12). Funding began March 9, 2009, to allow 6 months to complete study launch activities followed by initiation of patient screening and enrollment on September 1, 2009.

## Study Design Overview

**Specific Aims and Hypotheses.** The primary objective of the THAPCA trials is to determine the efficacy of TH to improve survival with good neurobehavioral outcome in children who are resuscitated after CA in the in-hospital and out-of-hospital settings as separate RCTs. Specifically, the primary hypotheses of the THAPCA-out-of-hospital and THAPCA-in-hospital are as follows:

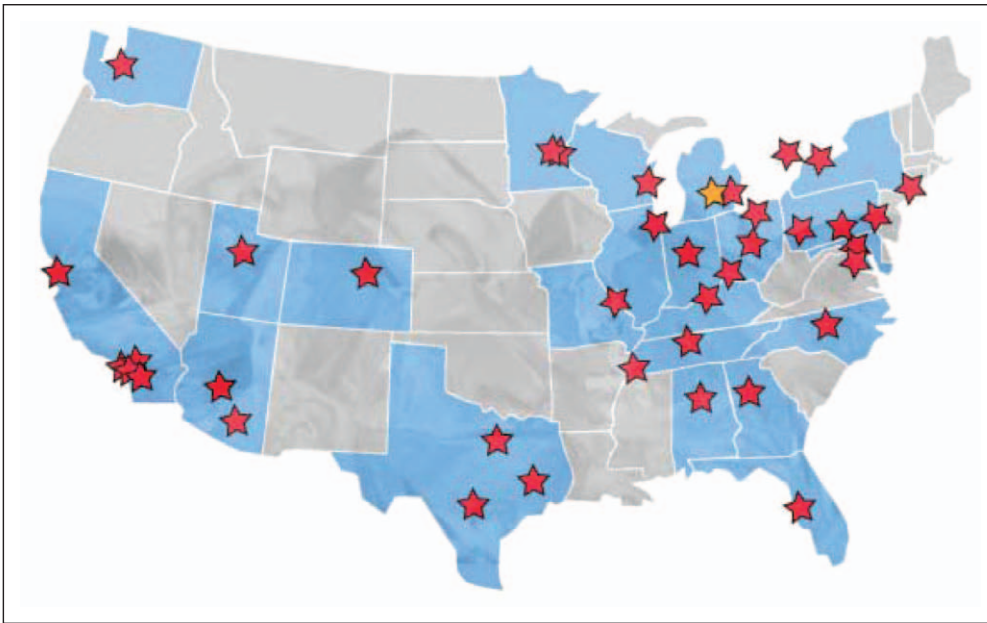
*Hypothesis 1:* Pediatric patients with *out-of-hospital* CA who are treated with TH will have higher survival with good neurobehavioral outcome at 12 months following resuscitation, compared with children who receive the normothermia control therapy.

*Hypothesis 2:* Pediatric patients with *in-hospital* CA who are treated with TH will have higher survival with good neurobehavioral outcome at 12 months following resuscitation, compared with children who receive the normothermia control therapy.

Key safety outcomes for both trials include all-cause 28-day mortality, risk of infection, arrhythmias, and bleeding.

**Study Sites and Organization.** THAPCA encompasses two separate phase III RCTs that investigate the efficacy of TH to improve survival and neurobehavioral outcome of children after CA in the in-hospital and out-of-hospital setting. THAPCA was planned to include 30 or more clinical sites in the United States and Canada with the majority of sites associated with the PECARN and CPCCRN research networks. Both networks used a common DCC at the University of Utah (Principal Investigator [PI], J. Michael Dean, MD, MBA). Additional PICUs at medical centers with strong interest in the project were successfully recruited (**Fig. 1**). The final study protocol was developed in partnership with PECARN and CPCCRN site investigators and consultants with special experience and interest in pediatric RCTs associated with TH.

**Patient Inclusion/Exclusion Criteria.** Children older than 48 hours old and up to age 18 years, who sustain a CA requiring chest compressions for at least 2 minutes, are eligible. Other



**Figure 1.** Site distribution map of the United States and Canada. See **Appendix 1** for site with site investigator listing.

inclusion criteria are need for mechanical ventilation following resuscitation and that CA is unplanned (not part of surgical procedure). Major exclusions are Glasgow Coma Scale motor component score of 5 or 6, preexisting terminal illness or lack of commitment to full support, CA associated with trauma, severe bleeding, and inability to obtain informed consent within 6 hours of ROSC. The full inclusion and exclusion list is provided in **Table 2**. Use of TH in children who are eligible for THAPCA but not randomized is discouraged; occurrence of such “off-study” hypothermia is monitored at all participating hospitals.

**Enrollment/Randomization Plans.** Site institutional review board (IRB) approved written informed consent is required and obtained from guardians of all subjects. For international readers who may have questions about indemnity in U.S. trials like THAPCA, all site IRBs have their own consent form description related to how each site handles this issue. The DCC has site PIs who sign statements related to conduct of the study and the lead site (University of Michigan) subcontracts to each site describes the site’s trial responsibility related to screening, enrollment, maintenance of equipment and execution of the study protocol and manual of operations.

Subjects are enrolled separately in the out-of-hospital and in-hospital settings (**Fig. 2**). Within each trial, randomization to TH or therapeutic normothermia (TN) occurs in a 1:1 ratio using randomized blocks stratified by clinical center and age at entry (younger than 2 yr, 2–11 yr, and 12 yr and older). Randomization is carried out using a telephone-based system. An Internet-based backup randomization system is available; each center is additionally provided with an envelope-based backup randomization to be used in “emergency” settings when neither remote system is available. Randomization is required within 6 hours of CA ROSC/ROC. Target total enrollments are 250 evaluable cases for THAPCA-out-of-hospital

and 504 evaluable cases for THAPCA-in-hospital. It is expected that over 800 total patients will be enrolled, as patients with suboptimal pre-arrest neurobehavioral status (discussed below) will not be included in the primary efficacy analyses.

In the planning of THAPCA, extensive discussions related to use of an Exception from Informed Consent occurred. It was concluded that informed consent with a 6-hour therapeutic window was necessary as animal studies had demonstrated a therapeutic window for neuroprotection after CA exists and also because U.S.

neonatal hypothermia for HIE trials used a 6-hour window for eligibility. If enrollment had been poor, it was planned to approach our Data Safety and Monitoring Board (DSMB) for permission to use the Exception from Informed Consent.

### Clinical Protocol Overview

With the exception of temperature-related management for each arm, all other monitoring and interventions described below are considered standard of care for the post-CA patient meeting THAPCA inclusion and exclusion criteria. Other therapies, administered during the times corresponding to the entire 120-hour intervention period, are in accordance with each site’s clinical practice.

**Interventions and Temperature Monitoring.** Following study enrollment and randomization to TH, children are initially paralyzed, sedated, and cooled (or warmed if indicated) by surface cooling using a Blanketrol III cooling unit with two appropriate-sized mattresses (Cincinnati SubZero, Cincinnati, out-of-hospital) applied anteriorly and posteriorly, to achieve and maintain a core temperature of 32–34°C for 48 hours. After 48 hours, the TH group is slowly rewarmed over 16 hours or longer to a target temperature range of 36–37.5°C, and this temperature is maintained through the remainder of the 120-hour intervention period. Following study enrollment and randomization to TN, children receive identical care except core temperature is actively maintained in a range of 36–37.5°C for 120 hours (**Fig. 3**). A servo-control mode (auto control or gradient variable mode) is used uniformly.

Dual central temperature monitoring is required during active temperature management. A primary central temperature probe is placed into the distal third of the esophagus, although other central sites (rectal or bladder) may be substituted. This probe is connected to the Blanketrol III unit for servo temperature control. A secondary central temperature probe is placed per rectum or

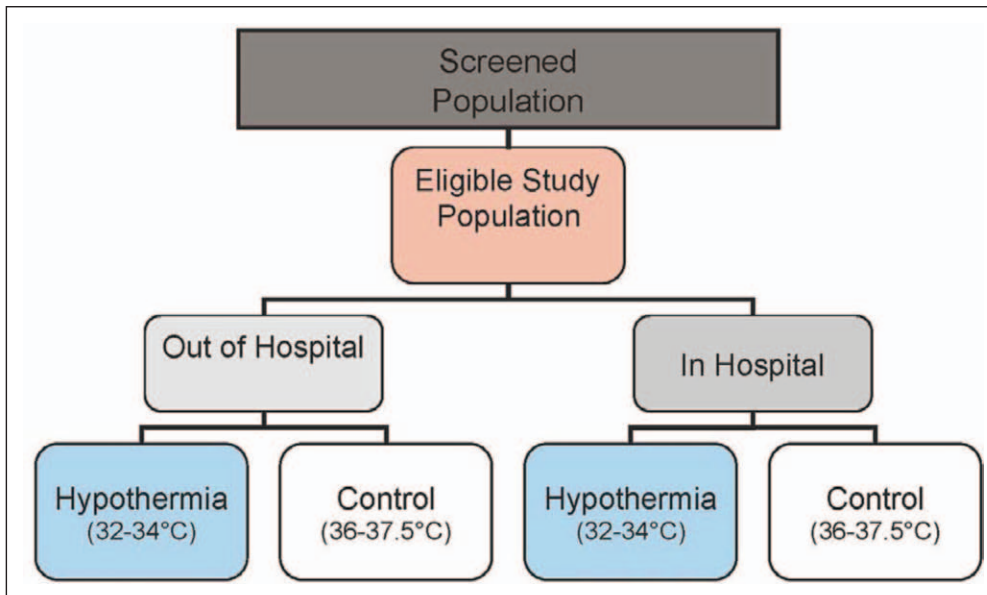
**TABLE 2. Therapeutic Hypothermia after Pediatric Cardiac Arrest Trials Inclusion and Exclusion Criteria**

Inclusion Criteria	Exclusion Criteria
Patients will be eligible for enrollment if they meet all of the following inclusion criteria	Patients will be ineligible for enrollment if any of the following exclusion criteria are met
Suffered CA requiring chest compressions for at least 2 min (120 s) with ROSC/return of circulation	The parent or legal guardian does not speak English or Spanish
Age > 48 hr (with a corrected gestational age of at least 38 wk) and < 18 yr	Randomization is impossible within 6 hr of ROSC
Patient requires continuous mechanical ventilation	Patient is on extracorporeal membrane oxygenation when arrest occurs
The CA was unplanned (i.e., not part of cardiac surgical procedure)	Continuous infusion of epinephrine or norepinephrine at very high doses ( $\geq 2 \mu\text{g}/\text{kg}/\text{min}$ ) received immediately prior to randomization
	Glasgow Coma Scale motor response of five (localizing pain or for infants less than 2 yr, withdraws to touch) or six (obeys commands, or for infants, normal spontaneous movement) prior to randomization
	History of a prior CA with chest compressions for at least 2 min during the current hospitalization but outside the 6-hr window for randomization
	Preexisting terminal illness with life expectancy < 12 mo
	Lack of commitment to aggressive intensive care therapies including do not resuscitate orders and other limitations to care
	CA was associated with severe brain, thoracic, or abdominal trauma
	Active and refractory severe bleeding prior to randomization
	Near drowning in ice water with patient core temperature $\leq 32^\circ\text{C}$ on presentation
	Patient is pregnant
	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
	Patient is newborn with acute birth asphyxia
	Patient cared for in a neonatal ICU after arrest
	Patient has sickle cell anemia
	Patient known to have preexisting cryoglobulinemia
	Central nervous system tumor with ongoing chemotherapy or radiation therapy
	Progressive degenerative encephalopathy
	Chronic hypothermia secondary to hypothalamic, pituitary, or related condition for which body temperature is consistently below $37^\circ\text{C}$
	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
	Previous enrollment in the THAPCA trials

CA = cardiac arrest, ROSC = return of spontaneous circulation, THAPCA = Therapeutic Hypothermia after Pediatric Cardiac Arrest.

via a temperature sensing Foley catheter into the bladder; this provides safety backup monitoring if the primary probe does not reflect central temperature. A difference between the primary and secondary probes of  $\pm 1^\circ\text{C}$  is considered acceptable.

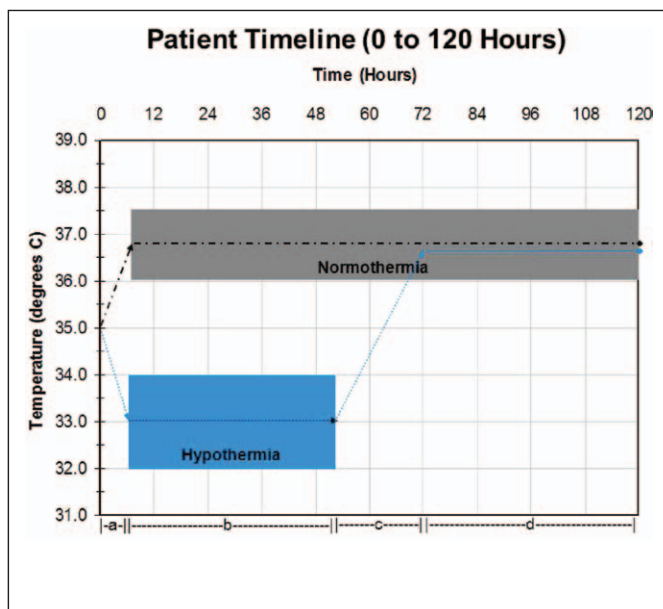
**Vascular Access.** Central venous access is required to safely administer fluids and other medications, such as inotrope/vasopressor infusions, and an arterial catheter is required for blood pressure monitoring. Use of central venous access



**Figure 2.** Overview of Therapeutic Hypothermia after Pediatric Cardiac Arrest trials.

and arterial catheters was considered standard of care in this population.

**Management of Sedation, Analgesia, and Neuromuscular Blockade.** The recommended sedatives and analgesia agents are benzodiazepines and opioids. Suggested agents are midazolam and fentanyl for both groups, as were used in the adult RCTs (2, 3). Midazolam and fentanyl administration by continuous infusion, supplemented by intermittent dosing, is suggested. After 72 hours, sedation and analgesia use is at



**Figure 3.** Therapeutic hypothermia and therapeutic normothermia temperature timeline 0–120 hr. *Dashed and dotted line* = normothermia group; *dotted line* = hypothermia group. Intervals: a = time from randomization to assigned temperature range; b = 48 hr of assigned temperature; c = rewarming of hypothermia group; d = interval of controlled normothermia in both groups.

the discretion of the primary clinical team. Vecuronium is the recommended, but not required, neuromuscular blocker to facilitate control of shivering. Other nondepolarizing agents to control shivering and facilitate temperature control in both the TH and TN groups may be used.

**Special Issues of ECMO.** Surface cooling is often not required for temperature regulation of children on ECMO. The desired temperature is titrated by the bedside ECMO specialist by changing the heat exchanger temperature. Only a single central temperature probe is required.

**Laboratory Testing.** Table 3 describes the minimum or required laboratory testing conducted throughout the intervention period (0–120 hr). Electrolytes, blood urea nitrogen, creatinine, and glucose are measured at least every 6 hours during the periods corresponding to active cooling and rewarming in the hypothermia group and at least every 12 hours during the remaining intervention period (up to 120 hr). Other blood monitoring during the intervention period includes daily complete blood count, liver function tests (specifically, alanine aminotransferase, aspartate aminotransferase, prothrombin time, partial thromboplastin time), amylase, lipase, magnesium, calcium, and phosphorus. Arterial blood gas and lactate are measured daily for the first 3 days. Blood cultures are obtained at the time of randomization and on days 1, 2, and 3. Urine cultures are obtained at the time of randomization and on days 2 and 4. Chest radiographs are done daily during the intervention period to confirm esophageal temperature probe position.

**Other Monitoring During and After Intervention.** The total volume of fluids received and total urine output are recorded daily for the first 5 days. Surgical procedures to treat bleeding postrandomization and concomitant medications and other procedures or therapies administered during the first 10 days are recorded.

There are no study-specific interventions after the 120-hour treatment period. Subsequent temperature management is according to the PICU clinical practice at each site; minimum and maximum daily temperatures, including the measurement site, are recorded through day 10. The dates of PICU and hospital discharge are recorded. All other therapies administered during the times corresponding to the entire intervention period are in accordance with each site's clinical practice.

**Data Collection and Confidentiality.** Clinical site personnel enter study data into a secure Web-based repository

**TABLE 3. Summary of Monitoring Required for Hypothermia After Pediatric Cardiac Arrest Trials**

<b>Physiologic Studies</b>
Arterial Line
Central venous catheter (or equivalent)
Temperature (central)
Esophageal (primary)
Chest radiograph (esophageal probe placement)
Rectal or foley (secondary)
Extracorporeal membrane oxygenation exception: 1 central temperature, any site
<b>Laboratory Studies</b>
Electrolytes (Na, K, Cl, HCO <sub>3</sub> , blood urea nitrogen, creatinine, glucose)
q 6 hr during cooling and rewarming
q 12 hr other times
Mg, PO <sub>4</sub> , Ca (q 24 hr)
Liver function tests (bilirubin, alanine transaminase, and aspartate transaminase) amylase, lipase (q 24 hr)
Coagulation (prothrombin time/international normalized ratio, partial thromboplastin time) (q 24 hr)
Complete blood count (q 24 hr)
Arterial blood gas (q 24 hr), lactate (q 24 hr) × 3 d
Cultures
Blood (d 0,1,2,3)
Urine (d 0,2,4)
Respiratory and other (as clinically indicated)

Minimal monitoring required for patients enrolled.

maintained at the DCC. All study data are identified solely via coded study identification number to maintain patient confidentiality.

### Study Monitoring

**Monitoring of Safety Endpoints.** Monitoring of infection events associated with these trials is accomplished by examination of all cultures obtained up to 7 days (168 hr) after the CA. Status of all cultures up to 10 days (240 hr) post-CA is recorded. All arrhythmias occurring during the first 7 days are also recorded. Blood products (RBCs, platelets, fresh frozen plasma, and cryoprecipitate) received during the first 7 days are recorded. Mortality, a key safety outcome, is recorded at 28 days post arrest for all enrolled patients (Table 4).

**Adverse Event Reporting.** Adverse events are recorded for 14 days after randomization or until hospital discharge, whichever occurs earlier. All adverse events are tabulated by study arm for review by the DSMB at their meetings. Serious adverse events are reviewed by the medical monitor of the THAPCA trials within 24 hours of notification of the DCC.

**Site Monitoring.** Trained site monitors were sent to clinical centers after the first three subjects were enrolled, and subsequently, they are sent for every five enrollments. Site monitors review regulatory documents, consent forms, and do selected source verification. Remote monitoring of selected data is done by DCC staff to complement the physical site visits.

### Study Outcomes

**Primary Outcome.** The primary efficacy endpoint is survival with good neurobehavioral outcome at 12-month follow-up, defined as an age-corrected standard score of 70 or greater on the Vineland Adaptive Behavior Scales-Second Edition (VABS-II) (13). The VABS-II is a caregiver report measure of functional skills, examining communication, daily living, socialization, and motor skills. The VABS-II is being collected via telephone by a trained interviewer blinded to assigned treatment from a central location. Enrolled children, whose reported prearrest VABS-II is less than 70 (based on data obtained within 24 hr of enrollment), will not be included in the primary efficacy analysis. Treatment effect will be assessed separately for the out-of-hospital and in-hospital trials.

**TABLE 4. Planned Outcomes of the Therapeutic Hypothermia After Pediatric Cardiac Arrest Trials**

Primary outcome
VABS $\geq$ 70 at 12 mo post CA
Secondary outcomes
All cases
Survival at 12 mo following CA
Change in neurobehavioral function from pre-CA baseline to 12-mo measurement (delta VABS-II)
Tertiary outcomes
Survivors only
Neuropsychological battery score at 12-mo evaluation
Neurologic abnormality scores at 12-mo evaluation (modified Pediatric Resuscitation after Cardiac Arrest Neurological Outcome Measure pediatric stroke scale)
Safety outcomes
All-cause 28-d mortality
Prevalence of culture-proven infection within 7 d
Blood
Urine
Respiratory
Other
Blood product requirement within 7 d post CA
Arrhythmias within 7 d

VABS = Vineland Adaptive Behavior Scales, CA = cardiac arrest.

**Secondary, Tertiary, and Safety Outcomes.** A list of secondary, tertiary, and safety outcomes is summarized in Table 4. Outcomes assessed only among survivors have been designated tertiary, as the comparability between treatment arms provided by randomization will not be guaranteed in the patients who survive to 1 year.

**Outcome Follow-up Overview.** At 3 and 12 months, the VABS-II is obtained via telephone interview by a trained clinician blind to treatment group at a single-designated site (Kennedy Krieger Institute, Baltimore, MD). Mortality status is also determined at 12 months. Additionally, 1 year after CA, all survivors participate in an onsite neurologic evaluation. All survivors under the age of 6 years at the 1-year follow-up also participate in an onsite neurobehavioral evaluation. For survivors 6 years old and older, only those who are sufficiently responsive (based on specific criteria obtained in the VABS-II 12-month interview) are scheduled to participate in a neurobehavioral assessment. Children who are not determined to be sufficiently responsive are assigned the lowest possible scores for the test battery.

**Sample Size Calculation.** For power calculations, rates of the primary outcome are estimated to be 15% to 35% for out-of-hospital and 35% to 55% in in-hospital CA (in the TN arm). The target sample sizes (subjects available for the primary analysis) of 250 out-of-hospital and 504 in-hospital will

provide 80% to 90% power to detect an absolute treatment benefit of hypothermia, with respect to the binary primary outcome above, in the range of 15% (hypothesized magnitude of benefit in in-hospital setting) to 20% (hypothesized benefit in out-of-hospital setting) at an alpha level of 0.05 for each study, accounting for interim efficacy monitoring by the DSMB. Total enrollment projections are higher to account for loss to follow-up and exclusion from the primary analysis of children with a baseline neurologic deficit (VABS-II below 70). In five neonatal and adult TH RCTs for CA or HIE conducted so far, observed absolute treatment effects ranged from 16% to 32% and total study enrollment ranged from 70 to 300 cases.

**Interim Monitoring.** An independent NHLBI-appointed DSMB meets twice yearly to assess study safety, efficacy, and performance issues. The DSMB operates according to a charter that mandates regular interim review of study efficacy outcomes, with prespecified, conservative O'Brien-Fleming boundaries for early stopping in the setting of observed treatment superiority (14). Per the DSMB charter, early trial termination in the setting of futility may also be considered if conditional power (chance of detecting a significant treatment effect if the trial were continued) is very low.

**Efficacy Analysis Plan.** The primary analysis, performed separately within each trial, will use a chi-square testing approach to compare proportions of patients with good



neurobehavioral outcome (alive with VABS-II at least 70) at 12 months following resuscitation, among enrolled patients with prearrest VABS-II of at least 70. Two secondary within-trial analyses will compare proportions of all enrolled patients alive at 12 months following resuscitation, as well as compare change in VABS-II from prearrest to 12 months among all patients. The latter analysis, performed using nonparametric rank-based approaches, will treat patients deceased at 12 months as having the worst possible deterioration from their prearrest state. For each trial, the primary analysis will use a two-sided chi-square test with alpha level of 0.05. The two secondary outcomes will be analyzed by chi-square test (survival) and Mann-Whitney test (change in neurobehavioral status), with a joint alpha level of 0.05. The statistical tests above will be stratified using the age categories that were used as randomization strata. A statistical analysis plan (SAP) is in place and will be adhered to for all study analyses; any analyses not specified a priori in the SAP will be explicitly described as exploratory in study reports.

### Trial Organization including Research networks

**Research Network Resources.** The PECARN network has supported this project since 2002 with its DCC, subcommittees, and steering committee to support conduct of RCTs. The NICHD-sponsored CPCCRN uses the same DCC and has supported and participated in the development of the trial since 2006. Both networks have experience in multicenter RCTs. The investigative team is multidisciplinary and includes experts in Pediatric Critical Care Medicine, Neonatology, Neuropsychology, Emergency Medicine, Physical and Rehabilitative Medicine, Neurology, Cardiology, TH, and conduct of RCTs in children.

**Data Safety and Monitoring Board.** THAPCA has an independent DSMB, which was created according to NHLBI guidelines. The DSMB meets at regular intervals to assess study safety, efficacy, and performance issues.

**Executive Committee.** An Executive Committee oversees the conduct of the THAPCA trials. Members also evaluate proposals for ancillary studies that are linked to the parent trials and review and make recommendations concerning trial issues that arise (see **Appendix 2** for membership composition).

**Steering Committee.** Steering committee meetings of the site PIs occur monthly via conference calls and in-person at an annual 3-day training meeting. During the monthly meetings, screening and enrollment by site are reviewed, updates on amendments and other information are shared, best practices by sites are presented, and case discussions occur. The DCC and PI have weekly conference calls to overview study progress and planning of all phases of study.

**Site Information.** As of May 29, 2012, the THAPCA trials had 35 active sites (two sites inactive) in the United States and Canada (**Fig. 1**). Three additional sites were pending activation.

## DISCUSSION

TH improves survival with better functional outcome in a wide range of animal models including CA (15–17), stroke (18,

19), TBI (20, 21), birth asphyxia (22, 23), and other conditions (24). In 2002, landmark RCTs in adults with out-of-hospital VF/VT CA were the first reports showing improved outcomes for a TH intervention in a specific human condition (2, 3). However, after nearly a decade, no additional RCTs of TH for adult CA have been reported, and important questions remain concerning the generalizability of the original trials' findings. One key unanswered question concerns the efficacy of TH in nonshockable CA rhythms, such as PEA or asystole; such cases were excluded in the initial RCTs. Recently, a French registry report described improved outcome associated with TH for out-of-hospital VF/VT CA; however, patients with initial asystole or PEA CA did not benefit from TH (25). Another vital question concerns whether TH benefit is generalizable to in-hospital CA cases; no trials have been conducted in this population. Another issue is the optimal duration of TH; no trials have investigated TH for adult CA longer than 24 hours.

The only nonneonatal pediatric condition in which TH has been studied in adequately powered RCTs is TBI. Although small preliminary studies showed promise for TH improving TBI outcomes (26–28), subsequent larger RCTs in adults and children have not demonstrated efficacy (7, 29). The largest pediatric trial to date (Hypothermia Paediatric Head Injury Trial [HYP-HIT]) reported not only a lack of efficacy of TH for TBI but also a very strong trend for higher mortality in the TH-treated group (7). A subsequent NIH-sponsored multicenter RCT (Cool KIDS trial) of TH for TBI was designed to address some potential shortcomings in the HYP-HIT trial and was recently terminated because of futility to demonstrate a difference in the primary study outcome (30).

A major shortcoming of both the adult out-of-hospital VF/VT trials and neonatal HIE trials reported so far concerns the control group temperature management; fever was often not successfully prevented in controls. In post-RCT publications from both the adult CA and neonatal HIE trials, fever commonly occurred in control cases and was associated with much worse outcomes (31, 32). This trend supports both experimental findings in animal models and studies of human brain injury that report a strong association of fever with worse neurologic outcomes (33). International resuscitation guidelines for both pediatric and adult CA strongly recommend aggressive management to avoid fever (34). However, TN requires similar interventions to those required for TH (35), and THAPCA is the first RCT that compares the efficacy of TH and TN in survivors of CA or HIE. An adult RCT currently registered on clinicaltrials.gov is examining whether TH is superior to TN in adult CA survivors (36).

Thus, there is great uncertainty concerning the use of TH in the pediatric CA population until adequately powered RCTs are performed that demonstrate or exclude benefit. The suggestion of lack of benefit in adults with asystole or PEA is extremely concerning, as these arrhythmias are much more common in children with out-of-hospital CA (25). Additional caution is warranted based on findings of pediatric TBI trials that observed a trend of higher mortality with TH (7). TN, as

an alternative therapy in contrast to usual temperature management that commonly does not prevent fever, has not been adequately examined.

By the time the results of the current THAPCA trials are reported, over a decade will have elapsed since the original adult clinical trials of TH for out-of-hospital CA were published in 2002. This lag time is attributable to the challenges inherent in determining the feasibility of conducting RCTs in U.S. pediatric hospitals, time required to prepare a successful application for a large NIH-sponsored clinical trial, and complexity inherent in conducting these trials. A unique feature of THAPCA is the concurrent conduct of two separate RCTs (in-hospital and out-of-hospital) with little incremental impact on study cost, as the same protocol and infrastructure resources are being used. To this date, no RCT has been conducted of TH for in-hospital CA in an adult or pediatric population.

After THAPCA findings are reported, gaps in our knowledge will remain. For example, the optimal duration of TH in both of our trials will not be known. The selection of 120 hours of temperature control with 48 hours as duration of TH in THAPCA trials was based on an expert majority consensus of a multidisciplinary group in critical care, emergency medicine, neurology, and others in 2006. Of note, the duration of TH selected for the THAPCA trials was intermediate between the longest administration of TH in adults and neonatal trials available in 2006 (24 and 72 hr). Whether the duration of TH should be titrated (longer or shorter) based on some biomarker(s) or other measurement(s) will not be established during the THAPCA trials. We will only be able to establish whether 48 hours of TH, initiated within 6 hours of ROSC and followed by TN through 120 hours, is superior to 120 hours of TN in two populations. Additionally, our trials will likely be underpowered to determine whether TH has differential effects in subgroups, such as shockable versus nonshockable rhythms. In contrast to out-of-hospital adult CA, children with out-of-hospital CA often have nonshockable rhythms, which have worse prognosis. We anticipate that the majority of our in-hospital CA population will be children with congenital heart disease, and our findings may not be generalizable to all in-hospital CA cases.

We have described some of the key events in the planning and operationalization of our two complex RCTs in a critically ill pediatric population. We anticipate that lessons learned from our experience with THAPCA may be of value to other investigators who are planning complex interventional RCTs in PICU or emergency department settings. Clinical trials in these settings present significant challenges, as described recently (12). Multicenter participation is commonly required to achieve adequate sample size to attain statistical power with reasonable effect size, and multicenter trials may also provide stronger evidence of generalizability of findings compared with single-center studies.

Finally, until the completion of the THAPCA trials, the use of TH should be considered experimental in children after CA in both the in-hospital and out-of-hospital settings, as there have been no RCTs that suggest efficacy and some reports have suggested no benefit or possible harm in other settings (i.e., TBI). During the planning and conduct of THAPCA, many

individuals from nonparticipating sites in the United States and international sites have inquired about using our clinical protocol to administer TH. We have denied all requests and explained that the protocol requires extensive training and has not been shown to be safe and efficacious at this time. Our perspective is that this intervention should not routinely be used outside the setting of ongoing clinical trials at this time.

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