STUDY PROTOCOL

P-ICECAP: Pediatric Influence of Cooling duration on Efficacy in Cardiac Arrest Patients

A multicenter, randomized, adaptive allocation clinical trial to identify the optimal duration of induced hypothermia for neuroprotection in comatose survivors of cardiac arrest

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Protocol Version 3 (17 March 2023)

Protocol Signature Page

I have reviewed and approved this protocol. My signature assures that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

17 MAR 2023

Sponsor's Signature | Date of Signature (DD MMM YYYY)

I have read this protocol and agree that it contains all the necessary details for carrying out the study as described. I will conduct this protocol as outlined herein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the interests of the study participants.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practices (GCP).

Investigator's Signature | Date of Signature (DD MMM YYYY)

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For updated contact information, including the Emergency 24/7 Toll Free Contact Number, please refer to the P-ICECAP study website or the study Manual of Procedures.

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Table of Abbreviations

AE	Adverse Event
BP	Blood Pressure
CCC	Clinical Coordinating Center
CNS	Central Nervous System
co-I	Co-Investigator
co-PI	Co-Principal Investigator
CIRB	Central Institutional Review Board
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events Version 3.0
DPHS	Department of Public Health Sciences
DCC	Data Coordinating Center
DCR	Data Clarification Request
DCU	Data Coordination Unit
DRC	duration-response curve
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
PED	Pediatric Emergency Department
ECMO	Extracorporeal membrane oxygenation
EEG	Electroencephalogram
EMS	Emergency Medical Services
ET	Endotracheal tube
FDA	Food and Drug Administration
GCMS	Glasgow Coma Motor Score
ICH	International Conference on Harmonization
IHCA	In-Hospital Cardiac Arrest
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
kg	Kilogram
KKI	Kennedy-Krieger Institute
LAR	Legally Authorized Representative
mg	Milligram
Min	Minute
mL	Milliliter
mm	Millimeter
MoP	Manual of Procedures
MSM	Medical Safety Monitor
MUSC	Medical University of South Carolina
NIH	National Institutes of Health

O2	Oxygen
OHCA	Out-of-Hospital Cardiac Arrest
OUS	Outside of United States
PCPC	Pediatric Cerebral Performance Category
PedsQL	Pediatric Quality of Life Inventory
PICU	Pediatric Intensive Care Unit
POPC	Pediatric Overall Performance Category
PRCA	Pediatric Resuscitation after Cardiac Arrest (PRCA) score
PI	Principal Investigator
ROSC	Return of Spontaneous Circulation
ROC	Resuscitation Outcomes Consortium
SAE	Serious Adverse Event
SIREN	Strategies to Innovate Emergency Care Clinical Trials Network
SSL	Secure Socket Layer
SOP	Standard Operating Procedures
THAPCA	Therapeutic Hypothermia After Pediatric Cardiac Arrest
TTM	Targeted Temperature Management
UAP	Unanticipated Problem
VABS-3	Vineland Adaptive Behavior Scales – Third Edition
VABS-II	Vineland Adaptive Behavior Scales – Second Edition

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BRIEF SYNOPSIS

Protocol Title	Pediatric Influence of Cooling duration on Efficacy in Cardiac Arrest Patients
Acronym	P-ICECAP
Clinical Trial Phase	Phase II/III
Study Design	Randomized, response-adaptive, duration/dose finding, comparative effectiveness clinical trial with blinded outcome assessment
Sites/Enrollment Period	About 45 children's hospitals / 5 years
Study Population	Comatose pediatric (2 days to <18 years) survivors of out-of-hospital cardiac arrest (OHCA) who have already started targeted temperature management using a definitive temperature control device.
Primary Study Objectives	To characterize the duration response curve for hypothermia and determine: i. whether increasing durations of cooling are associated with better outcomes ii. the shortest duration of cooling that provides the optimal treatment effect (based on a standardized neurobehavioral function test score and mortality one year later)
Sample Size	Maximum of 900 participants
Inclusion Criteria	Age 2 days to <18 years with corrected gestational age of at least 38 weeks; coma or encephalopathy after return of spontaneous circulation (ROSC) following out-of-hospital cardiac arrest; requiring mechanical ventilation; definitive temperature control device started; informed consent from legally authorized representative (LAR) including randomization within 6 hours of ROSC; intent to maintain life support for 120 hours.
Exclusion Criteria (Major)	Glasgow Coma Motor Score (GCMS) of 6, severe hemodynamic instability; pre-existing condition confounding outcome determination, pre-existing terminal illness; planned early withdrawal of life support before 120 hours; pre-existing contraindication to cooling; CPR duration > 60 minutes; prisoner; pregnancy
Study Intervention	The intervention will be random allocation to duration of cooling from 0 to 96 hours using FDA cleared surface cooling devices.
Primary Outcome	The primary outcome is titled the Vineland Adaptive Behavior Scales – Third Edition (VABS-3) Mortality Composite Score. It is defined as the VABS-3 (age-standardized neurobehavioral function measure) assessed at 1 year after OHCA in survivors and adjusted for mortality (death score = 0).
Statistical Analysis	Modeling of the duration response for the primary outcome. Identification of the shortest duration of cooling that provides the maximum treatment effect.

1. STUDY OBJECTIVES

1.1 Primary Objectives

The primary objectives of this project are:

A. To determine whether increasing durations of cooling are associated with better outcomes.

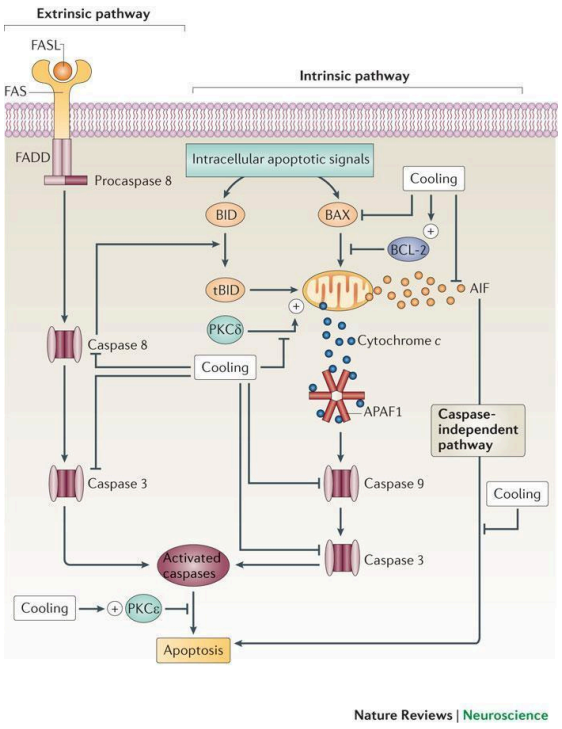
B. To determine, in pediatric comatose survivors of out-of-hospital cardiac arrest (OHCA), the shortest duration of cooling that provides the maximum treatment effect as determined by Vineland Adaptive Behavior Scales – Third Edition (VABS-3) Mortality Composite Score at one year.

1.2 Secondary Objectives

The secondary objectives of this project are:

i. To characterize the effect of duration of cooling on a global function measure, the Pediatric Cerebral Performance Category (PCPC).
ii. To characterize the effect on a standardized neurological outcome measure, the Pediatric Resuscitation after Cardiac Arrest (PRCA) score
iii. To characterize the overall safety and adverse events associated with duration of cooling
iv. To characterize mortality of varying durations of cooling
v. To determine if age group, etiology of CA, or initial GCS motor score influence primary outcome
vi. To characterize the effect of cooling on family reported quality of life

2. BACKGROUND



Cooling affects several aspects of extrinsic, intrinsic, and direct mitochondrial apoptotic cell death pathways (white boxes). FAS=cell death receptor. FASL=FAS ligand. DISC=death-inducing signaling complex. FADD=FAS associated death domain protein. BAK=BCL-2 antagonist/killer. BAX=BCL-2-associated X protein. BOK=BCL-2-related ovarian killer protein. BID=BH3-interacting domain death agonist. APAF1=apoptosome with apoptotic protease-activating factor 1. PKC=Protein kinase C. PKC family members can be either pro-apoptotic (PKCδ) or anti-apoptotic (PKCε). *Yenari and Han, 2012, Nature Reviews Neuroscience 13:267*

2.1 Rationale

Neurological death and disability are common outcomes in survivors of cardiac arrest. Therapeutic hypothermia to treat comatose patients resuscitated from shockable rhythms has been shown in two randomized controlled trials to markedly increase the rate of good neurological outcome, but the optimal duration of therapeutic hypothermia has not been investigated. P-ICECAP is a randomized adaptive clinical trial to characterize the duration-response curve of therapeutic hypothermia in comatose survivors of OHCA and to determine the optimal duration of cooling. There are a total of 10 possible treatment arms exploring 0 through 96 hours of cooling duration. Participants will initially be randomized to 24, 48, or 72 hours of cooling. After the first 150 participants have been enrolled, response adaptive randomization will allocate participants to additional durations from 0 through 96 hours. A zero hour cooling duration treatment arm will be opened for enrollment if there is not an increase in the treatment effect across the durations. Alternatively, longer durations (84 or 96 hours) will be opened for enrollment if the treatment effects are increasing (rather than plateauing or decreasing) through 72 hours. Comatose pediatric survivors of OHCA that have already been on

a definitive temperature control device will be enrolled. The primary outcome will be a VABS-3 Mortality Composite Score at 12 months that includes all cases by incorporating the measured VABS-3 scores in survivors and the assigned score of zero for non-survivors.

The overarching goal of this project is to identify clinical strategies (duration of cooling) that will improve the neurobehavioral outcomes of children after OHCA. We hypothesize that longer durations of cooling may improve either the proportion of children that attain a good neurobehavioral recovery or may result in better recovery among the proportion already categorized as having a good outcome. 2.2 Supporting Data

Pre-clinical data on efficacy of cooling

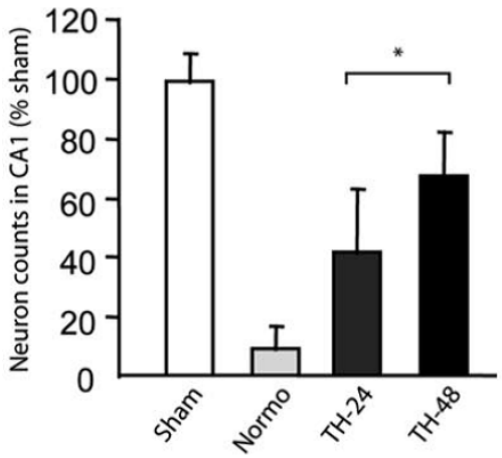
After cardiac arrest, brain neurons experience damage and ultimately death through a variety of pathophysiological pathways (Lipton, 1999). These processes occur differentially over a number of time periods and involve both immediate necrosis and apoptosis. Clinically, in humans rapidly resuscitated from cardiac arrest, neuronal injury from brief ischemia and reperfusion tend to lead to damage that predominates through the apoptotic pathway. As such, a therapeutic window exists for neuroprotection in ischemic brain injury states such as global cardiac arrest.

In preclinical models of both global and focal ischemia, hypothermia is consistently one of the most effective treatments to reduce neuronal damage. In seminal work on this subject, rats were subjected to intra-ischemic brain temperatures of 36, 33, and 30 degrees Celsius (°C) (Busto, 1989). Release of glutamate and dopamine were substantially reduced, without affecting ischemia-induced cerebral blood flow reduction or free fatty acid accumulation. In a systematic review of various neuroprotectant strategies for focal ischemia in the preclinical space (the majority drugs or biologics), hypothermia performed exceedingly well, and was one of only three treatments to receive a perfect 10 on the Stroke Treatment Academic Industry Roundtable (STAIR) quality score out of 1,026 treatments (O'Collins, 2006).

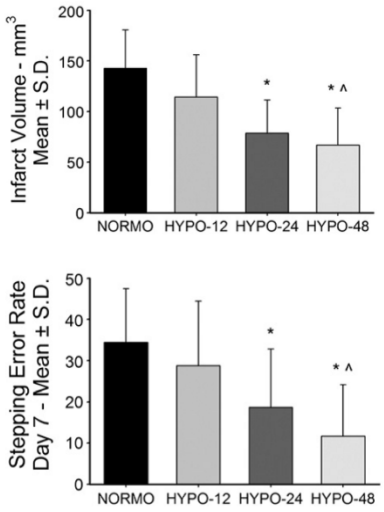
The overall preclinical evidence base for neuroprotection from hypothermia is extremely (perhaps uniquely) robust. An exhaustive review in 2006 reviewed preclinical data from 1,026 experimental treatments for ischemic brain injury (O'Collins, 2006). The authors compiled 7,554 experimental results from 3,500 papers. Hypothermia was the most thoroughly studied intervention, having been evaluated for efficacy in 244 studies, 105 of which were models of global cerebral ischemia (with the others being models of focal ischemia or hypoxia-glucose deprivation in cell culture). Hypothermia had the highest STAIR score of any neuroprotective strategy reflecting the reproducibility of efficacy across models, species, outcome metrics, and severity of injury. Preclinical investigations of hypothermia in cerebral ischemia have continued at a high rate with a PubMed search of “hypothermia cerebral ischemia” limited to animal investigations demonstrating an average of 58 publications per year since 2003, the end of the search period included in the 2006 review. Despite the robust study of hypothermia in animal models, the experimental space dedicated to the effects of varying durations of therapy are limited, largely due to the difficulty of clinically realistic modeling of multiple days of intensive care.

Pre-clinical data on duration of cooling

Preclinical models of global cerebral ischemia demonstrate that neuroprotection has a dose-response with increasing efficacy with longer durations of hypothermia and suggest potential mechanisms to explain this effect. Previous work compared 12 hours of hypothermia versus 24 hours in a gerbil model of 5 minutes of global cerebral ischemia and evaluated hippocampal CA1 cell counts at 30 days (Colbourne, 1994). Animals were cooled to 32 degrees and cooling was initiated 1 hour after the period of ischemia. They demonstrated dramatically greater neuronal protection versus untreated controls (90%) with longer duration of hypothermia compared to the neuronal protection seen with the 12-hour duration (15%). In a subsequent study this group demonstrated that the histopathological findings in this model reflected behavioral deficits with 24 hours of cooling even with initiation of therapy at either 1 or 4 hours post ischemia (Colbourne, 1995). In 2011, Che compared 24 hours to 48 hours of hypothermia in a rat model of global cerebral ischemia from 10 minutes of cardiac arrest (Che, 2011). Cooling was initiated at 0, 1, 4, or 8 hours after ischemia and animals were cooled to 33 degrees. Hippocampal CA1 cell counts at 7 days in this model of more severe injury again showed improved neuronal preservation with longer durations of hypothermia, with 68% (+/-15%) preservation at 48 hours compared to 42% (+/-22%) at 24 hours ($p < .0001$), see figure. This effect was independent of time of initiation.



Che – Cardiac Arrest Global Ischemia

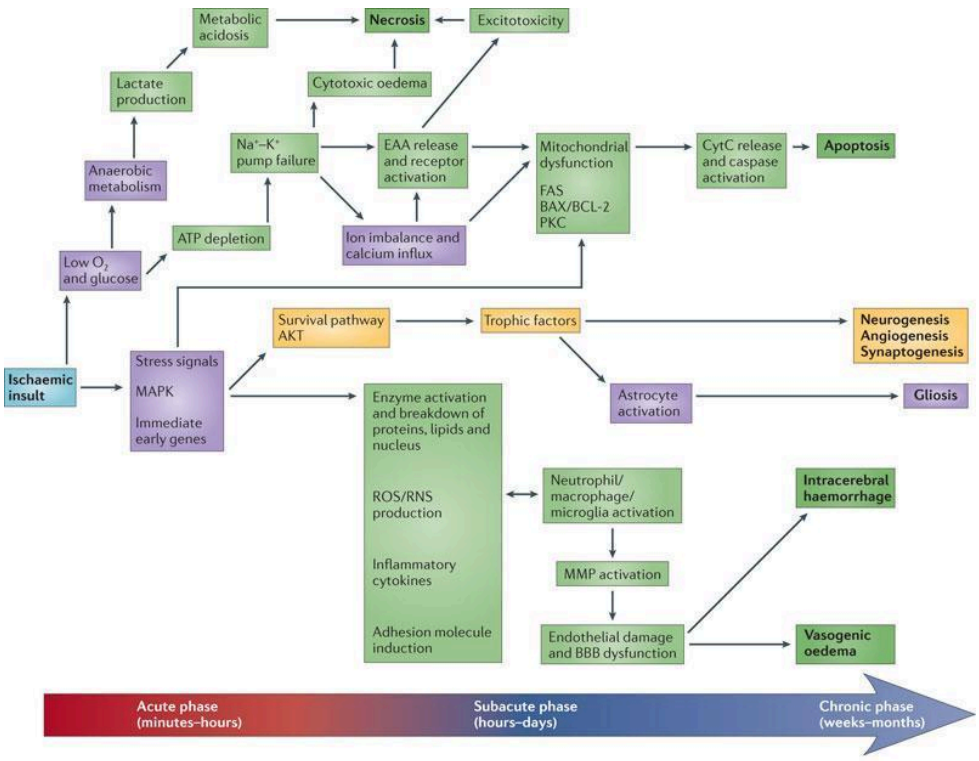


Clark – MCAO Focal Ischemia

It is less clear whether the duration response curve seen in these two studies between 12 and 24 hours and 24 and 48 hours also exists over much shorter (less clinically relevant) durations of hypothermia. Ye et al compared 2, 5, and 8 hours of cooling to 33 degrees initiated 7 minutes after an 8-minute cardiac arrest in a rat model and found no duration response in behavioral outcomes (Ye, 2012). However, Zhang et al compared

0.5, 1, 2, and 4 hours of cooling to 32 degrees initiated immediately after 20 minutes of 4-vessel occlusion in a rat model and found robust duration response on oxidative and cytokine markers of injury (Zhang, 2008). Unfortunately, both experiments only recovered for short durations and neither obtained histological outcomes, so only limited conclusions can be drawn.

Increased neuroprotection with increasing duration of hypothermia at 12, 24, and 48 hours is reproducible across models or transient or permanent focal cerebral ischemia (Clark, 2008, Clark, 2009). Benefit from prolonged durations of 48 hours of hypothermia has also been confirmed in focal cerebral ischemia in aged rats (Florian, 2008, 180). Benefit was seen in anatomic, histopathologic, biochemical, and behavioral outcomes across these models.



Effect of therapeutic hypothermia on ischemic mechanisms change over time. Hypothermia suppresses or inhibits processes indicated by green boxes, whereas yellow boxes show events that are increased or enhanced by hypothermia. Purple boxes indicate events that are not affected by cooling. BAX, BCL-2-associated X; BBB, blood–brain barrier; CytC, cytochrome c; MAPK, mitogen-activated protein kinase; PKC, protein kinase C; ROS/RNS, reactive oxygen species/ reactive nitrogen species. *Yenari and Han, 2012, Nature Reviews Neuroscience 13:267*

Yenari et al have speculated on the mechanisms for enhanced neuroprotection with prolongation of hypothermia and suggest that even longer durations may be needed to optimize recovery (Yenari, 2013). They note that in both global and focal models of cerebral ischemia there is an increase in neuronal neurogenesis when hypothermia is given for 24 hours, but that this effect is not present in models of short

durations of cooling. In rats with global forebrain ischemia, Silasi et al reported a 60% increase in the number of BrdU/NeuN-positive dentate gyrus neurons at 4 weeks in rats receiving 24 hours of hypothermia relative to normothermic rats ($p<0.0001$) (Silasi, 2011). Similarly, Xiong et al demonstrated neurogenesis, evidenced by significantly increased BrdU+ stained immature and mature neurons at 2 weeks, after 24 hours of hypothermia in a rat model of focal cerebral ischemia as compared to controls (Xiong, 2011). In contrast, in the rat global forebrain ischemia model, Lasarzik et al found no evidence of alteration of post-ischemic neurogenesis on BrdU staining at 4 weeks in animals cooled to 33 degrees for only 45 minutes, as compared to normothermic controls (Lasarzik, 2009). Increased efficacy with prolongation of hypothermia could be mediated by these and other regenerative mechanisms including not only neurogenesis, but neuronal connectivity, angiogenesis, and gliogenesis.(Yenari, 2013, 122)

Clinical Trials in Humans

Five moderate to large RCTs in adult populations have evaluated the benefit of therapeutic hypothermia and target temperature management (the latter broader term encompassing the use of advanced temperature management to enforce low normal targets or hypothermia) following cardiac arrest. The first two, utilizing surface cooling in ventricular fibrillation/pulseless ventricular tachycardia patients with OHCA were published in 2002. The Hypothermia After Cardiac Arrest (HACA) trial was a multicenter trial of cooling versus no cooling in 273 comatose survivors of out of hospital cardiac arrest (HACA Group, 2002) HACA demonstrated improved neurological outcomes (55% versus 39% - statistically significant) in the group receiving hypothermia to 33°C for 24 hours versus a group with no temperature control as measured by the Cerebral Performance Score of 1 or 2 at 6 months. In the same issue of the New England Journal of Medicine, a similar, smaller trial of 77 participants by Bernard in Australia demonstrated a 49% rate of good neurological outcome in patients receiving hypothermia to 33 °C for 12 hours as compared to 26% in the normothermic control group (Bernard, 2002).

The Targeted Temperature Management (TTM) trial was a large, randomized controlled trial performed nearly ten years later. TTM randomized OHCA patients with presumed cardiac etiology to a target of either 33 or 36°C (Nielsen, 2013). The target of 36°C was chosen to avoid re-warming patients who usually presented to the ED with nominally lower body temperatures following cardiac arrest, and to prevent patients from developing hyperthermia which has previously been demonstrated to likely be injurious in numerous observational and animal studies. In addition, both treatment groups in this two-arm trial were exposed to an excellent prognostication protocol that provided safeguards against premature withdrawal of life support in potentially salvageable individuals. This extremely well conducted and conceived trial had 939 patients included in the final analysis; about a quarter had temperature management with an endovascular device (as this was left to the discretion of sites). About half of the patients in both groups had a favorable neurological outcome (measured by either the modified Rankin scale or the CPC) at 180 days. This finding closely matched the observed outcomes in the cooled groups of the HACA and Bernard trials, although the TTM trial included about 20% patients with non-shockable rhythms of presumed cardiac origin and excluded those with shockable rhythms but not presumed to be of a cardiac cause. In this large trial, the safety of both regimens

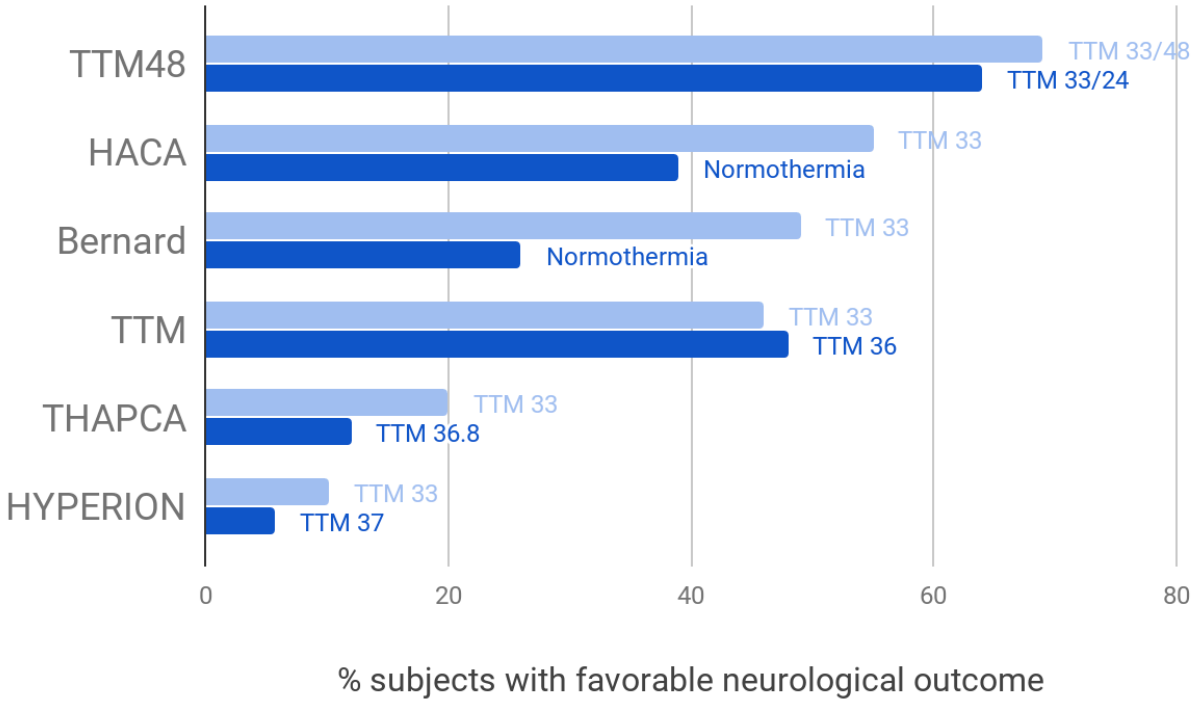
was effectively identical (of pre-specified serious adverse events, only hypokalemia was observed in a higher proportion of the 33°C group). The meaning of the TTM is unclear. To many, the 36°C group resembles normothermia, and the lack of benefit compared to 33°C is interpreted as lack of overall benefit from cooling beyond using advanced temperature control devices to prevent hyperthermia. To many others, however, using advanced cooling devices to maintain a target of 36°C is still cooling, albeit to a higher temperature (a lower dose of cooling). In this context, TTM is interpreted as showing that two doses of hypothermia are equally effective. This reinforced the importance of having another study like the Influence of Cooling duration on Efficacy in Cardiac Arrest Patients (ICECAP) to more robustly confirm efficacy of cooling or to restore sufficient uncertainty in the larger clinical community to permit a future trial with a normothermic control arm.

Recently in 2019, the HYPERION trial enrolled 584 comatose survivors of predominantly out of hospital cardiac arrest with non-shockable rhythms and randomized participants to treatment with 24 hours of targeted temperature management to 33°C versus 37°C in 25 French ICU's (Lascarrou , 2019). This trial found a clinically and statistically significant improvement in favorable neurologic outcome in the 33°C group (10.2%) as compared to the 37°C group (5.7%), assessed on day 90 after randomization with the use of the Cerebral Performance Category (CPC) scale. Although the population was adult, the non-shockable rhythm of the trial was a first and it is comparable to the usual pediatric out of hospital cardiac arrest population where over 90% of cases have non shockable initial rhythms.

Additional Context

Prior clinical trials have created a sometimes confusing, sometimes nihilistic context relevant to the ongoing adult ICECAP trial from which P-ICECAP evolved to study the pediatric population. The HACA and Bernard trials published in 2002 compared 33 °C to usual care in which some patients were febrile and showed marked efficacy of cooling, but had methodological flaws.(Bernard 2002; Hypothermia after Cardiac Arrest Study Group 2002) The European TTM trial published in 2015 compared 33 to 36°C and found that 36°C was neither more or less effective.(Nielsen 2013) Outcomes in both arms were similar to the cooling arms in the prior trials. TTM also showed that 36 °C was neither safer nor easier than 33°C . However, the 36°C arm in the TTM trial had better outcomes than the usual care control groups in the HACA and Bernard trials. Nevertheless, TTM resulted in some clinicians rejecting the 33°C target, but changes in practice using higher target temperatures, or no target temperatures, have been problematic and associated with worse outcomes in observational studies (Bray 2017). Two other related trials have also affected understanding. Into this milieu, THAPCA, the first and only pediatric OHCA study comparing 33 to 36.8°C was published in 2015 (Moler, 2015). THAPCA was a neutral study despite observing point estimates with 8% absolute (66% relative) higher rates of survival with good neurological outcomes with hypothermia for 48 hours. Then the TTM48 trial was published in 2017, comparing 33°C for 24 hours to 48 hours (Kirkegaard, 2017). TTM48 demonstrated outcomes far better than prior trials in both groups, but also observed point estimates with 7% better survival and 5% better neurological outcomes in the longer 48 hours of 33°C arm, with no difference in adverse event rates. All of this has evoked confusion and frustration in the clinical community. Clinicians are left to wonder if depth of cooling is even important, and whether nothing ever works, or whether the trials are all just underpowered to detect

meaningful differences. To the first question, we conclude that all trials have found 33°C to be as good or better than their control arms, such that it remains a promising standard target to be used in P-ICECAP. Despite the neutral results of the TTM2 trial, alternative depths are unlikely to prove scientifically or clinically impactful in the long run. To the latter question of nihilism, we offer a smarter study designed to be convincing and not ambiguous, regardless of the direction of its findings.



THAPCA-OH provides evidence of the promise of therapeutic hypothermia in children after OHCA

There are major differences in the etiology, human developmental physiology, and pathophysiology of CA across age groups, and therefore results in neonates and adults cannot be reliably extrapolated to children. In children, non-shockable rhythms occur in about 90% of OHCAs. The THAPCA-OH trial (Moler, 2015) compared therapeutic hypothermia to controlled normothermia and did not find a statistically significant difference in the primary neurobehavioral outcome measured at one year (VABS-2 ≥70) (therapeutic hypothermia 20% vs. controlled normothermia 12 %, difference 7.3%; p=0.14) and survival (therapeutic hypothermia 38% vs. controlled normothermia 29 %, difference 9.1%; p=0.13). However, THAPCA-OH was not powered to demonstrate a 7-8% effect size for the primary outcome, which would be of substantial clinical significance. It did show longer survival time in the hypothermia arm in a planned secondary analysis (p=0.04) suggestive of survival benefit. A Bayesian reanalysis of THAPCA-OH data found "the probability of any benefit from hypothermia was 94% for both the neurobehavioral outcome and survival at 1 year." (Harhay, 2022) In 2019 the HYPERION trial enrolled nearly 600 adults with predominantly OHCA and non-shockable arrest rhythms (which is the predominant rhythm in children). It reported better neurologic outcome with 24 h of therapeutic

hypothermia versus controlled normothermia [10.2% vs. 5.7%, difference 4.5%, p=0.04]. This statistically significant 4.5% difference in HYPERION, compared to a 7.3% difference in THAPCA-OH, further suggests that THAPCA-OH was underpowered.

THAPCA-OH had several other limitations: (i) The consensus protocol excluded mildly encephalopathic participants with any purposeful motor response (Glasgow Coma Score motor response = 5); yet, many children in this group incurred significant neurological injury. Clinical observations revealed that these survivors often had poor outcomes, and this population may well have benefited substantially from hypothermia. (ii) The time to achieve goal temperature from return of spontaneous circulation (ROSC) was delayed to about 7.5 hours because informed consent was required prior to initiation of cooling; this delay may have contributed substantially to attenuation of efficacy. (iii) Another protocol limitation was the duration of cooling (48 hours); this duration was selected by expert group consensus (a compromise between the 24 hours of cooling used initially in adults, and the 72 hours used in neonates) but without any specific supporting data. Yet, longer or shorter durations may be superior, and these options will be systematically evaluated in P-ICECAP.

The International Liaison Committee on Resuscitation (ILCOR) consensus statements and American Heart Association Pediatric Advanced Life Support Guidelines (de Caen, 2015, Duff, 2019, Kleinman, 2018) have identified scientific knowledge gaps and clinical research priorities in pediatric cardiac arrest resuscitation research. These priorities include the need for further studies to determine 1) whether therapeutic hypothermia is superior to controlled normothermia and 2)the duration of targeted temperature management. P-ICECAP will not include a discrete “controlled normothermia” control arm throughout its implementation. Therefore, while it may further inform the comparison of outcomes with controlled normothermia and therapeutic hypothermia, P-ICECAP will not specifically address the first priority of determining whether therapeutic hypothermia is superior to controlled normothermia.

3. STUDY DESIGN

The study is a randomized, response-adaptive, duration (dose) finding, comparative effectiveness clinical trial with blinded outcome assessment. The ideal range of durations to explore is unknown. Only in newborns with birth asphyxia associated hypoxic ischemic encephalopathy (HIE) have long durations been assessed. In this population, 72 hours was demonstrated to be superior to 96 hours duration of cooling. For adults and children, the longest duration of cooling reported in trials has been 48 hours. Because of this duration uncertainty, the P-ICECAP trial design, like the ICECAP trial, explores a broad range of durations. The design of this trial is based on a statistical model of the primary endpoint, the VABS-3 Mortality Composite Score, across the treatment arms. This is the duration-response model and all conclusions about the treatment arms are based on this model. The duration-response model is flexible and able to fit many different shapes for the duration-response curve. Specifically, it is parameterized to identify up to two change-points in the treatment effect across arms, allowing it to fit an increasing, decreasing, flat, plateau, or U-shape duration-response curve. The fit of the model is updated frequently with the emerging trial data and is used to adaptively randomize participants across the (up to) 10 treatment arms. The adaptive randomization algorithm effectively searches for the durations that provide the optimal treatment effect while also allocating participants to learn overall about the shape of the duration response curve.

Studies of the efficacy of therapeutic hypothermia in adults with OHCA used short durations of cooling. Cooling was maintained for 12 hours in one trial and for 24 hours in the two other trials. In newborns with birth asphyxia associated HIE, 72 hours is the standard of practice cooling duration. For the pediatric population, only one moderately large multicenter trial has been conducted. A duration of 48 hours was investigated which was midway between the adult 24 hours and neonatal 72 hours. For P-ICECAP, the study design will initially allocate participants to only the durations of 24 hours (the usual adult duration), 48 hours (the pediatric duration reported as safe as controlled normothermia) and 72 hours (the current standard neonatal HIE duration). As the trial continues, if the data suggest increasing efficacy with increasing duration, then the study design incrementally allocates to longer durations of cooling (up to 96 hours). Alternatively, if the data does not indicate increasing efficacy with increasing duration (or suggests an inverse relationship), the study design weights randomization toward shorter durations of cooling, including no additional cooling (controlled normothermia). This design minimizes the possibility of participants being allocated to durations of cooling that are too risky by virtue of being too short or too long and allows the study to consider a broad range of durations of cooling that would not otherwise be considered in a trial requiring fixed allocations to all treatment arms. There will be frequent interim analyses to stop the trial early for futility if no treatment arm offers a larger treatment benefit than the 0-hour duration arm.

3.1 Clinical Sites

At all participating sites, the usual clinical practice during the course of P-ICECAP for comatose pediatric OHCA survivors will be rapid initiation of TTM to a target within the local temperature range on arrival in the

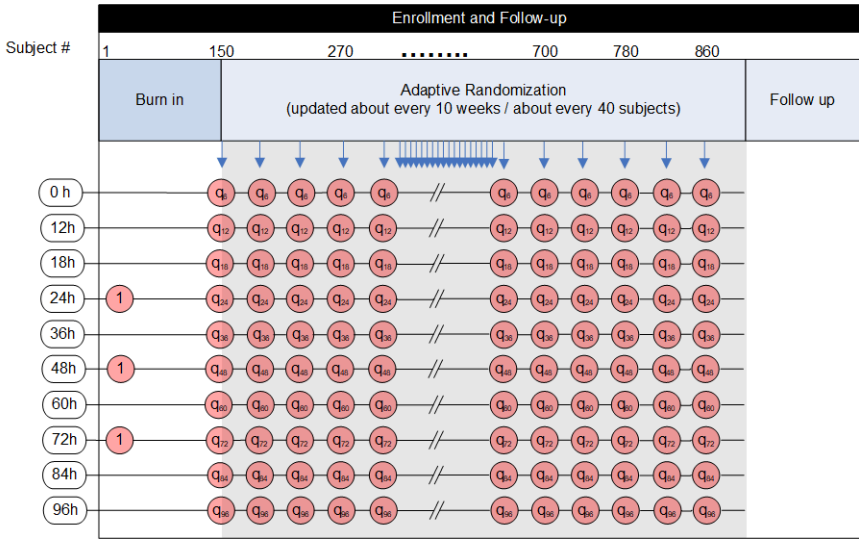
pediatric intensive care unit (PICU); any definitive servo-regulated surface temperature control device may be used. Approximately 70 percent were former sites in the THAPCA trials. Approximately 45 hospitals are anticipated to each enroll an average of 4 participants per year. The enrollment period is anticipated to be 5 years (estimated accrual rate of 15 participants per month).

3.2 Randomization and allocation

Central computerized randomization by web-based interface will be used. Participants will be potentially randomized over the course of the trial to the following possible durations of cooling (in h): 0, 12, 18, 24, 36, 48, 60, 72, 84 and 96. The first 150 participants will be randomized 1:1:1 to the 24, 48, and 72-hour durations only. After this initial "burn in" period, response adaptive randomization will be used to allocate participants to other durations if the emerging duration-response curve (DRC) suggests that the largest treatment benefit might be on those durations. Randomization probabilities will be updated about every 10 weeks. At an expected accrual rate of 15 participants per month, 37 (range 30-45) interim participants would be projected. The 3-month VABS-3 Mortality Composite Score will be used in longitudinal modeling for adaptive randomization until the 12-month value is obtained. We have previously reported the 3- and 12-month VABS-II to be highly correlated (r=0.95) in the THAPCA trials (Slomine, 2019).

After the burn in period, the trial can open all arms. Allocation procedures are described in greater detail in Section 9 and in the Statistical Design appendix. Arms where the model proposes less than 5% allocation will be temporarily set to zero until the next interim look.

All of the possible durations that will be tested from 0 to 96 h are shown in the white shapes on the left in figure. The sequential columns of red circles represent randomization vectors as the trial progresses and participants accrue in the trial. After the burn-in period, shorter, longer, and interspersed arms may receive some allocation depending on the shape of the emerging DRC. The blue arrows at the top indicate automated "looks" at the data about every 10 weeks. At each look, there is a test for efficacy and futility and then calculation of the new randomization vector.



3.3 Blinding / masking

The primary outcome assessment in this trial will always be performed centrally by a study team member at the Kennedy-Krieger Institute (KKI), who is blinded to treatment as done in the THAPCA-OH trial. Participants themselves will be comatose during the intervention period. It is not practicable to blind the clinical care team or the participant's family to the duration of cooling. Study procedures to prevent inadvertent unblinding of the KKI include minimized contact between study team members involved in the study intervention and those performing follow up at 3 and 12 months through the use of centralized outcomes assessment. Participants and their family members will be instructed not to communicate any knowledge of the treatment group to the person assessing outcomes at any follow up visit. In addition, trial clinical leadership, as well as research teams, will be blinded to the outcome distribution by treatment arm, as well as to the updated allocation probabilities.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

Comatose pediatric survivors of OHCA who have already had initiation of a definitive temperature control device (e.g. Arctic Sun, Blanketrol III, etc.) will be considered for enrollment.

At all participating sites, the usual clinical practice during the course of P-ICECAP for comatose pediatric OHCA survivors will be TTM to targets of 33-37 °C on arrival in the PICU; any definitive servo-regulated surface temperature control device may be used. Families of patients who meet inclusion criteria will be approached for enrollment; cases with any initial presenting cardiac rhythm are eligible.

The inclusion and exclusion criteria detailed below stem both from actual clinical trial experience gained in the THAPCA-OH trial and modifications incorporated to broaden the scope of the P-ICECAP trial population (Moler, 2015).

4.1 Inclusion Criteria and Rationale

Inclusion Criteria

- Age 2 days to < 18 years with corrected gestational age of at least 38 weeks
- Chest compressions for at least 2 minutes
- Coma or encephalopathy after resuscitation from OHCA
- Requires mechanical ventilation through endotracheal tube or tracheostomy
- Definitive temperature control device initiated
- Randomization within 6 hours of ROSC
- Informed consent from LAR including intent to maintain life support for 120 hours*

Rationale for selected eligibility criteria - Inclusions:

Age

Age 2 days to <18 years with corrected gestational age of at least 38 weeks, incorporates the age group excluded from the adult ICECAP trial. The efficacy of different durations of therapeutic hypothermia in pediatric patients surviving cardiac arrest is unknown and is to be studied in this P-ICECAP trial. Brain recovery and outcome from cardiac arrest in children is markedly different from adults and likely represents a distinct medical condition. Furthermore, outcome markers used in the adult ICECAP trial are not validated or readily interpretable in young children.

Chest compressions for at least 2 minutes with coma or encephalopathy

Chest compressions for a minimum of 2 minutes combined with coma or encephalopathy indicate significant injury following pediatric OHCA. This was an inclusion criterion in the THAPCA-OH trial and identified a population with high mortality and high morbidity with approximately 13% found to have good outcomes within 1 standard deviation of baseline at 12 months post cardiac arrest (Moler 2015). The in-hospital pediatric population is excluded from P-ICECAP because there was no trend seen in the THAPCA-IH trial for benefit with cooling compared to normothermia. Additionally, this population has many comorbidities which are difficult to adjust for while pediatric OHCA is largely from a group that has normal baseline function.

Patient requires mechanical ventilation with a stable airway

For safety reasons, all post OHCA patients who are cooled require mechanical ventilation via a stable airway (endotracheal tube or tracheostomy) since deep sedation with or without neuromuscular blockade is commonly required for induction and maintenance of cooling to decrease shivering.

Definitive temperature control device applied

Inclusion requires that a definitive temperature control system be applied to ensure that participants are maintained at the target temperature for the allocated duration. Without such systems temperature lability is common and potentially dangerous in the range less than 32°C, but especially less than 30°C. Inability to maintain the target range would result in unplanned crossovers that add unnecessary variability and may dilute treatment effect. See 5.1.2 for the definition of definitive device.

Randomization within 6 hours of ROSC.

All participants will be randomized within 6 hours of ROSC and after the initiation of targeted temperature management. Enrollment is defined as the time of randomization.

Informed consent from a legally authorized representative (LAR) including intent to maintain life support for 120 hours.

Patients (comatose children) in this study meeting eligibility criteria are, by definition, unable to consent for themselves. The time window for the intervention in this study (randomized allocation to the duration of cooling, i.e., when rewarming will be initiated), however, makes it practicable to contact and engage in a consent process for enough eligible participants. Therefore, consent must be obtained from an LAR

(usually a child's parent) to enroll a pediatric patient in the study. LARs are also the surrogate decision makers in clinical practice regarding choices related to the timing of withdrawal of life support in the days following resuscitation. In the pediatric population unlike in adults, parents generally do not withdraw life support early, but wait many days to make end of life decisions. Nonetheless, the timing of withdrawal of life support is potentially a major confounder in the evaluation of duration of cooling after cardiac arrest. To reduce variability from this issue, the timing of potential withdrawal of life support under relevant scenarios must be discussed prior to enrollment. The principles guiding the timing of withdrawal of life-sustaining care for participants on the P-ICECAP protocol are intended to minimize bias by allowing each participant a similar exposure to the intervention, and a similar duration of intensive care and opportunity to awaken. Implementation of these principles will be detailed in the trial's clinical standardization guidelines. Only those patients whose LAR intend to maintain life support for 120 hours are to be enrolled.

4.2 Exclusion Criteria and Rationale

Criteria

Exclusion Criteria

- Glasgow Coma Motor Score (GCMS) = 6
- LAR does not speak English or Spanish
- Duration of CPR > 60 minutes
- Severe hemodynamic instability requiring continuous infusion of epinephrine or norepinephrine of 2 µg/kg/minute or initiation of ECMO
- Pre-existing severe neurodevelopmental deficits with PCPC =5 or progressive degenerative encephalopathy
- Pre-existing terminal illness, unlikely to survive to one year
- Cardiac arrest associated with brain, thoracic, or abdominal trauma
- Active and refractory severe bleeding prior to randomization
- Extensive burns or skin lesions incompatible with surface cooling
- Planned early withdrawal of life support before 120 hours
- Sickle cell anemia
- Pre-existing cryoglobulinemia
- Non-fatal drowning in ice covered water
- Central nervous system tumor with ongoing chemotherapy
- Previous enrollment in P-ICECAP trial
- Prisoner
- Chronic hypothermia
- New post-cardiac arrest diabetes insipidus
- Pregnancy

Rationale for selected eligibility criteria - Exclusions:

Participants with GCMS of 6 lack evidence of brain injury and are outside the scope of this trial.

Legally authorized representative (LAR) does not speak English or Spanish is excluded because the VABS-3 is not available in other languages.

Participants with OHCA CPR duration of >60 minutes are expected to have profound brain injury and may not benefit from hypothermia.

Severe hemodynamic insufficiency requiring high vasoactive doses or ECMO and/or ECMO during CPR to achieve return of circulation for OHCA is associated with very high mortality and is not offered at many hospitals.

Several pre-existing conditions may confound the outcome determination. Examples include participants with severe baseline neurodevelopmental deficits (PCPC =5) would likely not have measurable changes in VABS-3 except for death.

A progressive, degenerative encephalopathy may lead to worsening by the time the primary outcome is assessed independent of the intervention.

Patients with preexisting terminal conditions would not be able to contribute outcome data if they are not expected to survive to the one year neurological outcome assessment.

Severe trauma raises concern for exacerbating hemorrhage. Cooling for treatment of severe head trauma has been studied previously and had no benefit on patient outcome.

Planned early withdrawal of life support will not allow completion of the intervention and/or outcome determination.

Certain conditions may contraindicate cooling. Since patients need to be cooled prior to enrollment in P-ICECAP these are unlikely. Some examples include sickle cell anemia and cryoglobulinemia which may be exacerbated by cooling.

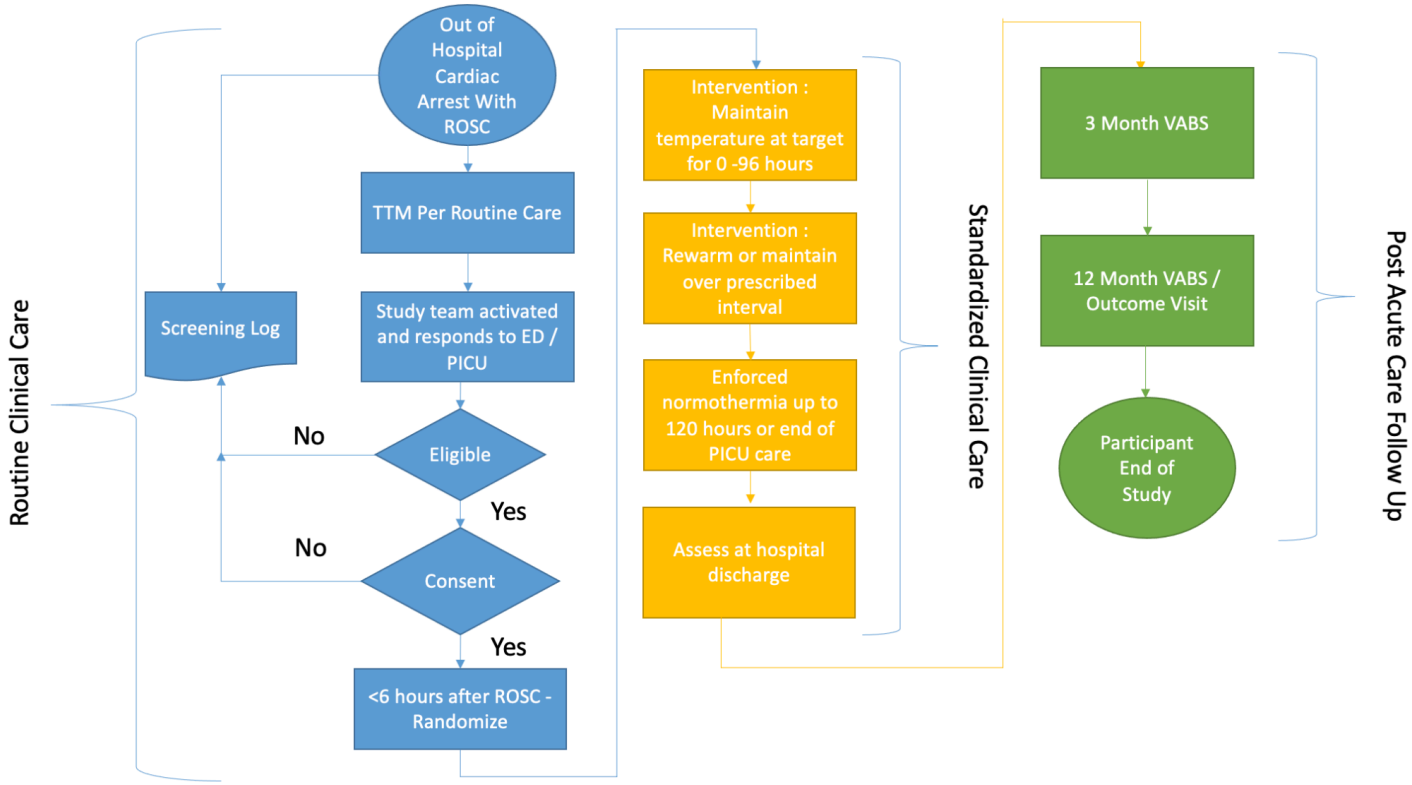
Prisoners are a vulnerable population.

New post arrest diabetes insipidus is a marker of profound and irreversible neurologic injury and may not benefit from hypothermia.

Patients with chronic hypothermia live at a lower temperature and the intervention may be no different than their baseline.

Patients who are pregnant are excluded given insufficient information to address whether there are reasonably foreseeable risks from trial participation to the pregnant person and fetus, and insufficient literature on the risks and benefits of targeted temperature management in pregnant people. Few, if any, pregnant people would have been anticipated to enroll in the trial, and the trial would be unable to specifically inform use and duration of targeted temperature management in this population. For these reasons, FDA has requested exclusion of pregnant patients.

4.3 Study Enrollment Procedures



The on-call P-ICECAP study team will respond to the PICU clinical team's notification to screen survivors of OHCA for eligibility, engage eligible patient's LAR in an informed consent process, coordinate with the clinical care team, and randomize eligible participants. Enrollment case report forms will be completed in the PICU, where the study teams will determine and identify the sources for the times of arrest. Of note, this is routine information obtained by transport teams, pediatric emergency medicine specialists, and pediatric intensivists who care for children after OHCA.

The study team will follow each enrolled participant daily until day 10 for data collection and shepherding of clinical standardization through ICU stay. There is additional data collection at hospital discharge, and the follow up assessments at 3 and 12 months. P-ICECAP will use strategies described in THAPCA-OH that achieved a 98% one-year follow-up success rate (Gildea, 2020).

A screen log that includes all patients with a PICU diagnosis consistent with OHCA (ICD-10 code of I-46, I-46.2, I-46.8, I-46.9, I-49.01, I47.2, R95, R96, R98, R99, or equivalent codes in another diagnostic system) that are treated in the PICU but not enrolled will be completed at all sites.

4.4 Consent Process

Because eligible participants for this study will be comatose children, the informed consent process will be conducted with the patient's LAR (usually parent) as defined by prevailing local law or regulation. During this process the LAR will receive a verbal explanation of the purpose of the study, the scientific basis for hypothermia as a neuroprotectant, the randomization process, the process of temperature management, and the follow-up examinations expected. The specific risks of participating will be outlined. The LAR will be informed that therapeutic hypothermia has not been identified to be of greater benefit than controlled normothermia. The LAR will be informed that the optimal duration of hypothermia has not yet been determined, participation is completely voluntary, and declining to participate will not adversely affect their loved one's care. A discussion of goals of care and intent to maintain life support for 120 hours will also be part of this process as discussed in the eligibility section. Those choosing to enroll their loved one will sign an informed consent document. Because the primary outcome is only available in English or Spanish, only participants with a LAR speaking these languages will be eligible for P-ICECAP. The SIREN Network has a standardized operating procedure for electronic consent or "e-consent" (available at the website http://siren.network under "Resources – Standard Operating Procedures.") SIREN uses an e-consent process that is 21 CFR part 11 compliant.

4.4.1 Parents and legally authorized representatives

Some participant information collected will refer to the parents (demographics, socioeconomic status, etc.) and the consent form notes this. Although these data involve others, we still consider these data to be participant information, and do not consider the parents themselves to be participants in the trial. The risk-to-others from collecting these data are low and are adequately managed by the confidentiality protections offered through the participant's enrollment. Additionally, parents can decline to answer specific questions or instruments and still continue with the study.

4.4.2 Change in guardianship

If at any point during the trial, a change in guardianship occurs and/or a participant reaches the age of majority and regains capacity for research decision-making, the new LAR and/or adult participant will be offered the

opportunity to withdraw from the trial and the informed consent process will be repeated. The consent by the new LAR and/or “adult” participant will be obtained using the written informed consent form approved by the IRB and documented in accordance with 21 CFR 50.27(a).

The desire of an LAR or a participant to withdraw from the study will be honored and does not require the LAR or participant to sign any documentation.

4.4.3 Assent from minors

The trial does not require written documentation of the assent of the participating child. No eligible participant will have capacity to assent during the phases of intervention. During follow up assessments, it is anticipated that participants will be asked for their permission to be examined or asked questions, but the trial does not require documentation of this permission. The trial has prepared informative documents that can be optionally used by sites to document assent to continue in the trial and perform these follow up assessments if desired or locally required. These participant facing materials will be approved by the IRB for this optional use.

4.4.4 Withdrawal from study

Altering the allocated intervention duration or declining some surveys is not considered withdrawing from the research study. However, if a parent, LAR, or eligible minor wishes to withdraw fully from the study, data collection will stop at that point in time. Data collected prior to that point, however, cannot be removed from the database as it is safety data in an FDA regulated device trial unless relevant local regulations or laws supersede FDA regulation.

4.5 Randomization Process

The objective of participant randomization is to prevent possible selection bias by providing random treatment assignment to each participant and to prevent accidental treatment imbalances for the known prognostic variables.
Randomization will be conducted through the web interface of the WebDCU™, the clinical trial management system used for P-ICECAP. The randomization process will be blind to study team members except as needed to perform essential functions. The unblinded statistical team will have access to the randomization information to oversee quality control of the computer program.

4.6 Pregnancy

Participants of childbearing potential cannot be randomized until a pregnancy test is negative.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The intervention will be random allocation to duration of cooling after cardiac arrest, inclusive of a duration of no additional cooling (controlled normothermia) where the participant is set to a normothermic target after randomization. Cooling in the study will be by a definitive temperature control method to a target temperature of 33°C. Any FDA cleared surface temperature control device with closed loop feedback (servo regulated) will be allowed. Duration of cooling will be measured from the time that cooling is started as indicated by activation of a definitive cooling device (see 5.2 for definition) set to a target of 33°C (targets from 32- 34°C and maintained continuously prior to randomization also qualify as start of cooling). Sites are required to set the target temperature to 33°C within 15 minutes of randomization. Sites are required to have participant temperature below 34°C within 120 minutes of randomization. The constant practice seen in the THAPCA-OH trial was that 70% of pediatric OHCA cases were transported directly from outside community hospitals directly to the Pediatric ICU of the study site. For the remaining 30% of cases coming directly to the study site emergency department, the pediatric patients were resuscitated and if ROSC was achieved, these patients were transferred promptly to the PICU. On arrival to the PICU, arterial and central venous access were rapidly established, and targeted temperature management was initiated. In P-ICECAP, after the allocated duration of cooling is completed, controlled rewarming will be performed. Slow rewarming to a temperature of 36.8°C will occur over approximately 16 hours for those participants assigned to cooling durations greater than zero. After rewarming, a normothermic target will be used until 120 hours from device being set to the hypothermic target (see figure in section 4.3 above).

Participants assigned to no additional cooling (controlled normothermia) will have their target set to normothermia after randomization. Participants assigned to this arm will be rewarmed promptly per routine clinical practice, and will not be rewarmed using the 16 hour procedure for the arms that receive therapeutic hypothermia for 12 to 96 hours. Duration of controlled normothermia will be 120 hours from the time the device is set to a normothermic target. Definitive cooling devices may be used for maintenance of normothermia after rewarming is complete if the participant remains intubated and mechanically ventilated.

5.2 Definition of Definitive Device

Definitive device is defined as a closed loop feedback (servo regulated) surface cooling device that can be used 1) to induce body temperature to a target of 33°C, 2) to maintain therapeutic hypothermia within a range of 32 to 34°C, and 3) to slowly rewarm or maintain at a normal temperature range (36-37.5°C). The device must be a FDA cleared device.

5.3 Temporary or Permanent Early Cessation of Cooling

In certain instances, it may be necessary to disconnect the participant from the definitive cooling device such as during participant transport to and from diagnostic or therapeutic procedures. Interruptions in active

temperature management should be minimized but brief periods of less than 30 minutes are allowed if monitored with central temperature monitoring. For longer periods of potential interruption, the definitive cooling device should accompany the participant and be re-instituted as soon as possible, during the procedure to avoid temperature excursions. MRI would be an exception. Core temperatures should be monitored continuously and documented at least every 30 minutes during interruptions in cooling. The clinical team along with parents or legally authorized representatives may alter the depth and duration of cooling, although this is discouraged without a clinical reason.

5.4 Clinical Standardization

A clinical standardization guideline will be followed to reduce the effects of practice variability subsequent to randomization. Key physiologic and practice variables will be tracked and compliance with clinical standardization and deviation from physiologic targets reported back to study teams. Clinical standardization guidelines will include but may not be limited to the following: avoiding hypotension, avoiding hypoxia, treatment of seizures, management of sedation and paralysis, and defining and treating infections. Additional parts of clinical standardization may include monitoring of chemistries, CBC, coagulation tests and blood gases. Clinical standardization guidelines state that neurologic prognostication leading to withdrawal of life support is only allowed after 120 hours. The exception is when a participant meets the full brain death criteria at the clinical site. Recently, guidelines for post resuscitation management have been published by an expert international multidisciplinary group (Topjian, 2019, e194).

6. OUTCOMES

6.1 Primary Efficacy Outcome

Primary Efficacy Outcome. The primary outcome will be the “VABS-3 Mortality Composite Score” in which enrolled participants who die before the 12-month outcome are scored 0 and the age-adjusted standardized VABS-3 composite score is assigned for the survivors (Sparrow , 2016). Measured VABS-3 composite scores range from 20-140 (mean=100, SD=15). The VABS-3 Mortality Composite Scores will be compared across treatment groups at 12 months after OHCA. The VABS-3 measures three core domains of neurobehavioral function (communication, daily living, socialization). These 3 core domains yield age-corrected standardized scores that contribute equally to an overall adaptive behavior composite score. The VABS-3 is applicable from birth through adulthood and has strong reliability and validity in children of all ages. Of note, no NIH toolbox neurobehavioral outcome measures are validated for children under age 3, and the measures for pre-school children function poorly for those with significant impairments.

The previous version of the Vineland (VABS-II) (Sparrow, 2005) was used as the primary outcome for the THAPCA trials and is no longer available. The new VABS-3 has updated content to reflect changes in everyday

life (e.g., new technology) and provides an online administration format using a computer or tablet that guides the examiner in the structured interview process by tracking item content and applying basal and ceiling rules.

In survivors, VABS-3 data will be obtained, using this format for structured telephone interviews, scheduled at 3 and 12 months after OHCA. Data will be collected by a trained interviewer, unaware of treatment allocation, at a central outcome center (KKI) with extensive experience and familiarity with this tool and method of data collection. Each interview is expected to take 30 to 45 minutes. The VABS-3 item content is available in English and Spanish. Spanish speaking interviewers will interview Spanish speaking caregivers.

Analysis of THAPCA-OH VABS-II scores revealed very strong correlations (r=0.95) of 3 and 12-month composite scores, even in infants (r=0.88); these findings support use of the 3-month VABS-3 scores to inform adaptive allocation until the 12-month outcome scores are available (Slomine, 2019). We anticipate that most enrolled OHCA cases will be under age 2 years; in such young children, sole reliance on performance at 3 months after OHCA as the primary outcome would be difficult to justify to many stakeholders (clinicians and families). Inclusion of a 12-month recovery period will likely strengthen the generalizability and acceptance of the P-ICECAP findings.

In THAPCA-OH, pre-OHCA functioning was evaluated within 24 h of enrollment using VABS-2; >90% had broadly normal function. Based on these data, coupled with feedback from the Collaborative Pediatric Critical Care Research Network (CPCCRN) – Family Network Collaborative that a lengthy structured interview within the first day after OHCA would be viewed unfavorably, no baseline VABS-3 score will be obtained. Pediatric Cerebral Performance Category data (see below) will be used to verify that baseline pre-OHCA function does not differ among treatment groups (Fiser, 1992).

6.2 Safety Outcomes

The primary safety outcome is all-cause mortality at 30 days. All-cause mortality is selected because it incorporates the most severe irreversible safety consequences across many potential adverse events. Safety problems that are not reflected in either neurological recovery (the efficacy outcome measure) or mortality (the primary safety measure) do not generally cause any permanent morbidity and are therefore secondary. In THAPCA-OH 28-day mortality was used and trended lower in the hypothermia group than normothermia group (57% vs. 67%; p=0.08) (Moler, 2015). In THAPCA-OH the most common cause of death was brain death or severe neurologic injury occurring in approximately 80% of both groups.

6.3 Secondary and Exploratory Efficacy Measures

Secondary Measures – Global Functioning. The Pediatric Cerebral Performance Category (PCPC) and Pediatric Overall Performance Category (POPC) (Fiser, 1992) are 6-point categorical rating scales that include death in the scaling (range normal =1 to death =6). The PCPC rates neurological functioning, whereas the POPC rates

overall health. These scales were included in the 1995 Pediatric Utstein template of recommended guidelines for reporting outcomes of pediatric advanced life support (Perkins , 2015) and have been used extensively to measure CA outcomes (Moler , 2009; Moler , 2015; Sparrow , 2005; Topjian , 2008; Andersen , 2015; Matos , 2013). Most recently, the PCPC was recommended as part of the core outcome set for pediatric cardiac arrest research (Topjian , 2020). The PCPC and POPC will be collected based on review of medical record and caregiver interview within 24 hours of admission for baseline score, and at hospital discharge or at day 30, whichever is first (Topjian , 2020). Age-appropriate PCPC/POPC rating instructions, developed for the THAPCA trials, will be provided to ensure consistent ratings across sites. PCPC/POPC will also be scored at 3 and 12 months by the P-ICECAP neuropsychologist (BS) based on the VABS-3 interview responses. The change in PCPC score from 12 months minus baseline (delta PCPC) will be evaluated.

Neurological Functioning. At 12 months, survivors will undergo a neurological evaluation at their local site. Neurologists will describe the findings of a detailed age-appropriate neurological exam and provide global scores (from 0, normal, to 3, severe impairment) in 7 domains (total score range: 0-21), using the Pediatric Resuscitation after Cardiac Arrest (PRCA) measure, which was adapted from the Pediatric Stroke Outcome measure. PRCA scores obtained in THAPCA were strongly correlated with the VABS-II scores; 16/75 OHCA survivors had normal neurological exams (score “0”) (Ichord , 2018). Motor function in P-ICECAP will primarily be assessed by this measure. Deaths will be assigned the worst score, 21.

Survival at 12 months. Survival status is a standard outcome reported in cardiac arrest trials (Topjian , 2020).

Quality of Life (QL) and Family Burden (exploratory). In survivors, the PedsQL caregiver-report measures will be collected at 3 and 12 months to measure quality of life and family burden. To measure quality of life, caregivers of participants 2-18 years will complete the physical, emotional, social and school functioning scales of the PedsQL generic core measure (53) and supplemental cognitive function and daily living scales (Varni , 2002; Varni , 2006). Caregivers of participants who are still <2 years at 3 and 12 month time point will complete the infant version (Varni , 2011) which consists of 5 scales (adding Physical Symptoms and replacing “School” with Cognitive Functioning). Reliability and validity are adequate across numerous health conditions (Uzark , 2008; McCarthy , 2005). Family burden will be measured using the family impact module of the PedsQL which includes caregiver self-ratings of physical, emotional, social, and cognitive functioning, communication, and worry as well as the impact of their child’s health condition on daily activities and family relationships (Varni , 2004).

From THAPCA-OH we reported findings for each of the above outcomes (Moler , 2015 Slomine , 2019; Ichord , 2018; Slomine , 2016; Silverstein , 2016; Meert , 2016) and results included follow up in 98% of survivors at 12 months for the primary outcome measure. Methods used to achieve this high rate have been reported (Gildea 2020).

6.4 Schedule of Assessments

Measures	Domain	Hospital Day One	Hospital Days Two - Discharge	Hospital Discharge	30-days post OHCA	3-months post OHCA	12-months post OHCA
Demographics (10-20 minutes)	Child/Family Factors	X					
VABS-3 Mortality Composite Score (20-60 minutes)	Neurobehavioral Functioning					X	X
All-cause mortality	Survival				X	X	X
PCPC/POPC (5-10 minutes)	Global neurological and overall functioning	X		X*	X*	X	X
PRCA (40-60 minutes)	Neurological Exam Findings						X
PedsQL (20 - 40 minutes)	Quality of Life and Caregiver Burden	X				X	X
Clinical data / adverse events	Medical Information from chart	X	X	X			

*PCPC/POPC assessed at hospital discharge OR 30 days after OHCA, whichever is earlier

7. MANAGEMENT OF ADVERSE EXPERIENCES

Monitoring of safety is critically important, and among the most central responsibilities of the investigator. The definitions of adverse events (AEs) and serious adverse events (SAEs), expectedness, severity classification, and determination of relatedness are detailed in the extensive Safety Monitoring Plan in the Manual of Procedures.

7.1 Adverse Event Recording

All non-serious AEs occurring through 120 hours from setting the temperature control device to the assigned target and all serious adverse events (SAEs) occurring until participation in study has ended are recorded on the AE case report form (CRF) through the WebDCU™. The Site PI or Study Coordinator or designee is responsible for entering any and all AEs and SAEs into the database as soon as he/she becomes aware of the event and updating the information (e.g., date of resolution, action taken) in a timely manner. All non-serious AEs occurring through 120 hours must be recorded on the electronic AE CRF within 5 days from the time it was discovered by the site study personnel. For SAEs, the data entry must take place within 24 hours of discovery of the event. The NCI Common Terminology Criteria for Adverse Events (CTCAE) (see MoP) will be used to define severity of events.

The Site PI is responsible for the monitoring and follow-up of AEs until resolution or establishment of a new baseline and appropriate documentation in the participant research record. In addition to performing protocol-specified follow up, the participating PI must review all previously reported ongoing AEs to evaluate the current status. Upon completion of the study protocol by the participant, premature withdrawal from the study by the participant, or participant's death, all information regarding each AE must be completed, if not done so earlier.

7.2 Serious Adverse Event Recording and Reporting

All Serious Adverse Events (SAEs) occurring during a participant's study participation will be recorded. All SAEs must be entered into the WebDCU™ system within 24 hours of first knowledge of the SAE by the study team. Additionally, all current study data for that particular participant must be entered to allow for timely review by the medical safety monitors (MSMs). Medical safety monitoring will be conducted as detailed in the P-ICECAP manual of procedures (MoP). The Project Manager forwards all SAE to an internal quality reviewer, and then an independent MSM, within WebDCU™.

7.3 Formal Definitions of Selected or Anticipated Adverse Events and Safety Outcomes

The outcomes and events defined below as adverse events are anticipated and will be closely tracked. The expected incidence data is based on events tracked in the THAPCA-OH Trial. Events tracked daily as primary safety outcomes in THAPCA-OH are indicated by an asterisk *. When applicable, some but not all of the tracked outcomes below would be serious adverse events. The below events are based on study defined definitions of these occurrences, as outlined in the MOP.

Selected or Anticipated Adverse Events and Safety Outcomes	Expected Incidence
*Pneumonia, Blood Stream Infection, or Urinary Tract Infection	39-46%
*Cardiac arrhythmias requiring intervention	9-11%
Neurological worsening	40-60%.
Hypokalemia	14-23%
Neutropenia	1-3%
Thrombocytopenia	1-10%
Seizures	35-41%
Repeat cardiac arrest	7-9%
*Any blood-product use	54%
Cryoprecipitate	8-9%
FFP	30-33%
PRBCs	42-43%
Platelets	9-12%

7.4 Unanticipated Problems

An Unanticipated Problem (UAP) generally includes any incident, experience or outcome that meets all of the following criteria: (1) Unexpected in terms of nature, severity or frequency, (2) related or possibly related to participation in the research and (3) suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. All UAPs will be reported to the IRB and/or FDA according to standard reporting guidelines.

8. TRAINING

The SIREN network utilizes multiple methods to optimize education and training of site personnel including both virtual and face-to-face training at investigator meetings employing audience interaction systems to identify comprehension of topics in real time, instantly remediate topics as required, and certify based on individual competency. Online training modules and certifications are also employed when appropriate for re-training or training of additional personnel.

At all P-ICECAP enrollment locations, the site principal investigator, study teams, treating physicians, inpatient nursing staff, and outcome assessment investigators will receive appropriate training prior to study initiation. There will be training meetings either virtually or in person annually including one meeting prior to any trial enrollment. Training decay will be minimized with scheduled recertification and/or refresher training of study and clinical staff. Personnel responsible for outcomes assessment will be recertified frequently to ensure inter-rater reliability.

Clinical principal investigators from the study leadership will evaluate each site prior to initiation to provide and assess adequacy of training and organization. Investigator and research coordinator meetings will occur monthly. In addition, P-ICECAP includes the following specific training programs:

Hypothermia administration: Approximately two-thirds of the study sites were former THAPCA trial sites that used a standardized protocol for therapeutic hypothermia temperature management for Induction, Maintenance, Rewarming and Normothermia phases. At training meetings to be conducted prior to the start of enrollment and then annually thereafter; a review of the physiology of cooling, target temperature management phases, and best practices will be conducted. The CCC will evaluate the existing protocols of study sites as part of site initiation. Additionally, as was done in the THAPCA trial, there will be 24/7/365 coverage by an experienced investigator to assist any site PI or bedside clinical team with questions related to cooling or the study protocol. For sites that did not participate in THAPCA, the site PI will contact the on-call study investigator at the time of enrollment and then daily through 120 hours for the first two enrollments. A daily review of the study protocol will be required with the on-call expert. Special emphasis related to the details of the rewarming period will be reviewed prior to each participant entering this phase of targeted temperature management. Note that in the THAPCA trials all sites were required to call the expert on call to discuss enrollment for the first two enrolled cases, so the P-ICECAP investigators have much experience in this real-time training.

Clinical standardization: A training program will teach the consensus standardization guidelines created for P-ICECAP to clinical care teams at participating sites to reduce variability in standard practice. Updated AHA guidelines on pediatric post arrest care by an expert group lead by one of the P-ICECAP PIs was recently published and will provide the framework (Topjian, 2019).

Outcomes assessment training: To address the need for certification in the patient reported outcome

measures, training will be done by the P-ICECAP Kennedy Krieger Institute outcome center and involve didactic and hands-on training with the tablet computer testing equipment.

Periodic investigator meetings: To address any impediments to participant enrollment, discrepancies in treatment between centers, and protocol violations of concern, we will hold meetings including investigators and site research staff. In addition, this will afford an opportunity to discuss any changes in the standard of care during the study period.

9. STATISTICAL CONSIDERATIONS

This trial will enroll a maximum of 900 participants. The primary outcome will be the "VABS-3 Mortality Composite Score" in which enrolled participants who die before the 12-month outcome are scored 0 and the age-adjusted standardized VABS-3 composite score is assigned for the survivors. The design of this trial is based on a statistical model of the mean VABS-3 Mortality Composite Score, i.e. the duration response curve. All participants will be receiving targeted temperature management at the time of enrollment as a condition of inclusion and will then be randomized to one of ten possible treatment arms for the duration of cooling. The ten possible treatment arms are 0, 12, 18, 24, 36, 48, 60, 72, 84, or 96-hours of cooling.

Participants will be adaptively randomized to a cooling duration, inclusive of a no additional cooling arm (controlled normothermia). The trial will determine the shortest duration of cooling that provides the maximal treatment effect and whether increasing durations of cooling are associated with better neurological outcomes. Regardless of whether participants are ever allocated to the no additional cooling arm (or have possible exposure to some pre-randomization cooling), an increasing treatment effect across some set of durations may imply a dose (duration) response effect. In this section we provide a detailed overview of the statistical design and operating characteristics. Further details are provided in the Statistical Analysis Plan (SAP).

9.1 Primary Endpoint

The VABS-3 ranges from 20 to 140 (mean age-corrected standardized score of 100) where higher scores indicate better cognitive outcomes. Deaths are assigned a score of 0. The VABS-3 Mortality Composite Score will analyze the combined deaths and survivors in a single analysis.

9.2 Primary Analysis

The primary analysis of the trial will model the mean VABS-3 Mortality Composite Score at 12 months for each treatment arm. The primary analysis is conducted on the intent to treat (ITT) population. The primary analysis will address two objectives: 1) to determine whether increasing durations of cooling are associated with better outcomes (Objective A); 2) identify the most likely target duration, where the target duration is the shortest duration that achieves the maximum treatment effect (Objective B). If increasing durations of cooling are

associated with an increasing treatment benefit in at least one part of the duration-response curve, then this may demonstrate a dose (duration) response effect in improving neurological outcomes.

9.3 Statistical Models

9.3.1 Duration-Response Curve Model

We model the mean 12-month VABS-3 Mortality Composite Score across the ten treatment arms with a duration-response model. All conclusions about each treatment arm will be based on a duration-response model. The duration response model restricts the shape of the duration response curve to have 3 phases – an increasing phase, a plateau phase, and a decreasing phase. We create a parametric family for this inverted-U duration response model.

Let Y_i be the primary composite outcome measured at 12 months for the i^{th} participant. We model the outcomes as

$$Y_i \sim N(\theta_{d_i}, \sigma^2)$$

where θ_d is the mean response for arm d .

The U-shaped dose-response model allows for an initial increase in the mean with dose, followed by a leveling out of the mean, then a decrease. The dose-response curve can be characterized in four different regions of the dose space:

$$\theta_0 = \begin{cases} \theta_0 + \delta\left(\dfrac{d}{p_{min}}\right)^{\alpha} & 0 < d < p_{min} \\ \theta_0 + \delta & p_{min} < d < p_{min} + p_{width} \\ \theta_0 + \delta\left(1 - \dfrac{d - (p_{min} + p_{width})}{w_{width}}\right)^{\beta} & p_{min} + p_{width} < d < p_{min} + p_{width} + w_{width} \\ \theta_0 & d > p_{min} + p_{width} + w_{width} \end{cases}$$

where d corresponds to the duration of cooling index (1 through 10). For the lowest dose region near 0 hours ($d = 1$), the dose-response curve is modeled as (potentially) increasing. The next region is the plateau, where the dose-response curve is assumed constant. For the third region, the dose-response curve is decreasing. For the final region, the dose-response curve is again constant, at the same level as the zero-dose. Since some participants will be cool prior to randomization, the controlled normothermia arm is considered to be longer than zero in the above equation.

9.3.2 Longitudinal Model of 12-month VABS-3 Mortality Composite Score

At each interim analysis there will be participants who have not yet reached 12-months and will therefore not have a final outcome. We use the 3-month VABS-3 Mortality Composite Score as possibly predictive of the 12-month score, allowing participants with this earlier measurement to be included in the analyses of the 12-month measurement. This modeling is referred to as the longitudinal model. The longitudinal model allows for learning the relationship between the 3-month and 12-month VABS-3 Mortality Composite Scores as the accruing empirical data is used to determine the strength of the association between the two values. The observed 12-month values are augmented by multiple imputations from the longitudinal model (simple linear regression) for participants with an unknown 12-month value.

9.4 Adaptive Randomization

The first 150 participants will be equally randomized to the 24, 48, and 72-hour arms. After this initial randomization period, adaptive randomization will begin. Randomization probabilities to each treatment arm are weighted according to the weighted average of two posterior probabilities: the posterior probability that each treatment arm produces the maximum treatment effect (25% weight) and the posterior probability that each treatment arm produces 95% of the maximum treatment effect (75% weight). The target duration and randomization probabilities will be updated approximately every 10 weeks. The goal of the adaptive randomization is to allocate participants to the arms most likely to be the target duration, but also to learn effectively about the duration-response curve.

9.5 Interim Monitoring for Efficacy and Futility

Interim analyses begin after 150 participants have been enrolled and will occur approximately every 10 weeks. At each interim analysis, the trial may stop accrual for expected futility if the 0-hour cooling period has at least an 85% probability of being the cooling period with maximum treatment benefit. At each interim analysis, the trial may stop accrual for expected success if the 96-hour cooling period has at least a 95% probability of being the cooling period with maximum treatment benefit. If a futility or efficacy stopping rule is met at an interim analysis, then a final analysis will be conducted after all currently enrolled participants have been followed to their final endpoint.

9.6 Sample Size

This trial will enroll a maximum of 900 participants. If the trial is not stopped early for futility or efficacy, it will continue to enroll to the maximum sample size. Extensive numerical simulations of the design were conducted over a range of potential scenarios to characterize the trial's Type I error and the power for the primary analysis provided by a maximum of 900 participants. Sensitivity of operating characteristics to a range of sample sizes was also simulated.

9.7 Power and Type I Error Control

For trials with adaptive features like those presented here, asymptotic formulas are not available to calculate operating characteristics (e.g., power, expected sample size). We evaluate the proposed design through trial simulation. We hypothesize several possible underlying true settings (referred to here as scenarios) for the mean response. For each of these scenarios, we generate data according to the true distribution in the scenario and run through the entire design as specified above. We repeat this process to create multiple virtual trials, tracking the behavior of each trial and then summarizing characteristics over the many simulations. The assumed effect sizes in these scenarios were based on historic THAPCA-OH observed effects as well as effects seen in other cooling studies. Additional information can be found in the SAP.

To demonstrate the variety of duration-response scenarios considered in the simulation study, seven examples are provided in TABLE 9.7.A. A name briefly describing each scenario, the overall VABS-3 Mortality Composite Score, and the survival and average VABS-3 among survivors are presented. In the scenarios described by plateau at 48 and 72 hours, constant upslope, and (inverted) U-shape, the effect size is an increase in survival of 10% and an increase of 10 on the VABS-3 among survivors. This corresponds to an increase from 29.3 to 41.3 (12 units) on the VABS-3 Mortality Composite Score. The different scenarios reflect when/how we might observe those peaks. The scenario described by a plateau at 72 hours with a larger effect corresponds to an increase of about 19 units on the VABS-3 mortality composite score.

Table 9.7.A: Scenarios evaluated for operating characteristics in P-ICECAP

Scenario	Outcome Component	Arm (Cooling Duration in Hours)									
		0[0]	12	18	24	36	48	60	72	84	96
Null	Overall	29.3	29.3	29.3	29.3	29.3	29.3	29.3	29.3	29.3	29.3
	Survival (%)	45	45	45	45	45	45	45	45	45	45
	VABS-3	65	65	65	65	65	65	65	65	65	65
Plateau at 48 hours	Overall[1]	29.3	31.5	33.8	36.2	38.7	41.3	41.3	41.3	41.3	41.3
	Survival (%)	45	47	49	51	53	55	55	55	55	55
	VABS-3[2]	65	67	69	71	73	75	75	75	75	75
Plateau at 72 hours	Overall[1]	29.3	31.0	32.4	33.8	35.6	37.4	39.3	41.3	41.3	41.3
	Survival (%)	45	47	48	49	50.5	52	53.5	55	55	55
	VABS-3[2]	65	66	67.5	69	70.5	72	73.5	75	75	75
Plateau at 72 hours (larger effect)	Overall[1]	29.3	30.9	32.6	35.0	38.1	41.3	44.6	48.0	48.0	48.0
	Survival (%)	45	46.5	48	50	52.5	55	57.5	60	60	60
	VABS-3[2]	65	66.5	68	70	72.5	75	77.5	80	80	80
Constant Upslope	Overall[1]	29.3	31.5	32.6	33.8	35.0	36.2	37.4	38.7	40.0	41.3
	Survival (%)	45	47	48	49	50	51	52	53	54	55
	VABS-3[2]	65	67	68	69	70	71	72	73	74	75
U-Shaped	Overall[1]	29.3	31.5	33.8	36.2	38.7	41.3	41.3	41.3	35.0	29.3
	Survival (%)	45	47	49	51	53	55	55	55	50	45
	VABS-3[2]	65	67	69	71	73	75	75	75	70	65
Harmful	Overall[1]	29.3	28.2	27.3	26.5	25.6	24.8	24.00	23.2	22.4	21.6
	Survival (%)	45	44	43	42	41	40	39	38	37	36
	VABS-3[2]	65	64	63.5	63	62.5	62	61.5	61	60.5	60

[0] Controlled Normothermia [1]VABS-3 Mortality Composite Score VABS-3 among survivors

For each of the scenarios described in TABLE 9.7A, we simulated 10,000 virtual trials and tracked the behavior of each trial, including the final outcome, the observed sample size, and selected duration of cooling that achieves 95% of the maximum treatment effect (ED95). In TABLE 9.7B, the results are summarized across all 10,000 simulated trials for each scenario. We define power as the proportion of trials that identify a positive effect of cooling based on the duration response curve, regardless of the selected target duration. Success on Aim 2 is clinically defined by selecting an ED95 that is within 1 or 2 durations of the true ED95. Early stopping for efficacy occurs when there is overwhelming evidence that the 96-hour cooling duration provides the best clinical effect. Late efficacy is defined when the trial does not stop early and the final analysis concludes that there is evidence increasing durations of cooling are associated with better outcomes.

Table 9.7.B: Operating characteristics of tested scenarios for the P-ICECAP trial

Scenario	Expected Sample Size	Aim 1 Power			Futility	Aim 2 Power - Proportion of Trials	
		Overall	Early Efficacy	Late Efficacy		Correctly Choose ED95 ±1 Duration	Correctly Choose ED95 ±2 Duration
Null	848	4.6	0.5	4.1	24.6	95.7	96.4
Plateau at 48 hours	898	89.7	0.5	89.2	0.0	42.2	77.0
Plateau at 72 hours[1]	**889**	**92.3**	**3.8**	**88.5**	**0.0**	**76.1**	**85.4**
Plateau at 72 hours (larger effect)	889	99.2	3.3	95.9	0.0	91.5	98.9
Plateau at 72 hours (higher baseline survival)	894	97.3	2.1	95.1	0.0	76.7	88.3
Constant Upslope	875	90.9	9.1	81.8	0.0	50.5	79.2
U-Shaped	897	66.5	0.0	66.5	0.7	37.6	56.5
Harmful	640	0.0	0.0	0.0	84.7	100.0	100

[1] Hypothesized scenario for power calculations

In the null scenario where there is no difference in mortality nor in VABS-3 among the survivors across any duration of cooling, we control our Type I error rate at 5% as evidenced by the 4.6% shown in the “Power” column. We are able to (correctly) declare early futility in 24.6% of the trials in the null scenario. The controlled normothermia arm is the ED95 for the null case; 95.7% of trials correctly chose either controlled normothermia or the 12-hour duration as the ED95.

In our hypothesized effect size scenario used for the primary power calculations (bolded in the table above), where cooling benefit plateaus at 72 hours ("Plateau at 72 hours"), efficacy (a cooling duration is found to be associated with better outcomes on the VABS-3 Mortality Composite Score compared to the controlled normothermia arm, based on either the early stopping for success or final evaluation criteria as detailed above) is demonstrated in 92.3% of trials. We note that in this scenario, a small percentage of simulations (3.8%) stop early due to overwhelming evidence (at least a 95% probability) that the 96-hour duration was the cooling duration with maximum effect. This finding would usually be considered a "clinically acceptable" efficacy determination, as the 96-hour dose in fact has an effect equal to the 72-hour dose. In this scenario, we have excellent power to detect duration response, and we are not frequently choosing the 96-hour duration mid-trial when the 72-hour duration performs similarly. In this scenario, we correctly identify the ED95 window (i.e. 60 hours, 72 hours, 84 hours) 76.1% of the time. Considering a "within two durations" window (i.e., 48 hours through 96 hours), we identified an acceptable ED95 in 85.4% of the trials in our primary scenario.

We maintain approximately 90% power or more in all presented scenarios assuming efficacy of longer cooling durations under different true models, except when the duration of cooling has a U-shaped response for the VABS-3 Mortality Composite Score. In this (unexpected) scenario where better outcomes are associated with mid-range durations of cooling , but then drops at the longest durations, power is limited to 66.5% to declare that any duration of cooling is associated with better outcomes than controlled normothermia, and ability to correctly choose ED95 is also limited.

9.8 Intention to treat and missing data

The primary analyses will be based on the intent-to-treat ITT population. The ITT population will include all participants randomized, where participants will be included in the treatment arm to which they were randomized, regardless of the duration of cooling applied. Operational procedures are optimized to minimize losing participants to follow up and to prevent missingness of data. Previous experience in the THAPCA Trials by the investigative team demonstrated very low rates of missing data. Any participants that are missing or withdraw from the study and have an unknown 12-month outcome will be included in the analyses of the primary endpoint with multiple imputation according to the longitudinal model previously described.

9.9 Subgroup Analyses

Further details of the pre-planned secondary analyses will be available in the full SAP. Analyses for important subgroups (gender, age strata, ethnicity/race, baseline PCPC, mechanism of injury, witnessed arrest, duration of chest compressions) will be conducted for the primary endpoint and secondary endpoints identified in the SAP.

9.11 Safety Monitoring

Further details of the safety monitoring will be available in the full SAP.

9.12 Staged Approval and Interim Analyses For Safety

The study was approved by the US FDA as a staged study. Initial approval was limited to 40 US institutions and 50 participants. For the first 40 participants, the investigators will submit interim safety reports to the DSMB and FDA every 10 participants. Prompt reporting is important. Therefore, we expect the 10th patient will have all SAEs through 7 days from enrollment entered by day 14 - therefore the first report will be prepared 14 days after the 10th enrollment. The report will include hourly temperature plots at the participant level. Serious adverse events, 30-day mortality, and primary outcome will be summarized by allocation and listed at the participant level. The report will include a listing of all serious adverse events by allocation and listed at the participant level. The report will be sent to the DSMB and FDA concurrently. Memos or detailed minutes prepared by the DSMB in their review will be promptly forwarded to FDA. Similar reports will be sent after the 20th, 30th, and 40th participants. Each of these reports will include the most up-to-date information, and data on participants from prior reports will be updated in subsequent reports. The comprehensive interim report inclusive of the first 40 participants will be accompanied by a request to expand enrollment. Additional details are included in the Data and Safety Monitoring Plan.

10. DATA MANAGEMENT

10.1 Data Management Overview

Data management will be handled by the DCC, which is housed in the Data Coordination Unit, of the Department of Public Health Sciences, College of Medicine, Medical University of South Carolina (MUSC). All activities will be conducted in coordination with the study PIs, the sites, and the CCC. The data validation procedure will be implemented in two stages. First, the automated data checks will flag items that fail a rule, and the rule violation message will appear on the data entry screen at the time of data entry. The Study Coordinator at a site will see these rule violations and will be requested to address it. His/her choices are to: (1) correct the entry immediately; (2) correct the entry at a later time; or (3) if the entered data are confirmed to be correct, dismiss the rule by checking that option provided by the WebDCU™ system. Any changes made to the data will have a full audit trail. Secondly, for some checks that are more complicated, additional consistency checks will be run periodically after data entry occurs at the site. All data items that fail the programmed consistency checks will be queried via the data clarification request (DCR) process initiated by the DCC data managers.

In addition to the study database, the DCC will provide the site staff password protected access to a standard set of web-enabled tools, including participant visit calendar, participant accrual status, case report form completion status, and outstanding DCR status pertaining to their respective sites.

10.2 Data Acquisition and Central Study Database

The entire study will be conducted using an electronic data acquisition method where all clinical data on enrolled participants will be data entered (single-keyed) by the site personnel into a web-based data management system, WebDCU™. In order to provide user-friendly and easy-to-navigate interfaces, the WebDCU™ data capture screens are designed based upon individual CRFs. Prior to study start, the system is validated to ensure the data entry screens mirror the CRFs and that the pre-programmed data rules appropriately detect incorrect data. The data will be managed after data entry via data queries from the DCC.

The latest version of each CRF will be available as a PDF file in the P-ICECAP database for use as worksheets and source documents by study personnel. This process facilitates version control of these study related documents, particularly since documents may evolve over the course of the study. This user-friendly web-based database system, developed by the DCC, will be used for participant randomization, data entry, data validation, project progress monitoring, participant tracking, user customizable report generation and secure data transfer.

10.3 Core Trial Database

The DCC programmers will maintain the core clinical database. The relational database is based on the study CRFs using Microsoft SQL Server. The study database is programmed with extensive consistency checks (e.g., data type, range and logic checks) to flag potential data entry errors, including missing required data, data out of pre-specified range, and data conflicts and disparities within each CRF and across different CRFs. All validation parameters are outlined in the Data Management Plan maintained by the DCC.

10.4 Randomization Module

A web-based Randomization Module will be used to randomize eligible participants. A study team member will log onto the WebDCU™ P-ICECAP web-based system using a unique username and confidential password. When a participant is deemed eligible, WebDCU™ will generate a unique ID number. The study team member will then enter the required participant information, including inclusion/exclusion criteria. The computer program will check for accuracy and completion of this information prior to selecting the intervention assignment for that participant based on current randomization vectors. The participant is considered randomized at the time that WebDCU™ generates the study intervention assignment. An automatic email notification of randomization will be sent to the appropriate parties (e.g., the P-ICECAP study leadership, the NIH Program Officers, and the CCC and DCC staff). If, under rare circumstances, the web system is not available, call the emergency randomization hotline **1 (866) 450-2016** to obtain a randomization assignment.

10.5 Reporting Module

The WebDCU™ system also has a real-time reporting component that allows authorized users to view protocol specific reports as data listings and in a summary format, overall and by site, at any time during the study via the password protected system. The reports are presented in a manner that protects the integrity of the study (e.g., blinded assessment).

The DCC will provide authorized study personnel access to a standard set of web-enabled tools on the WebDCU™. These tools allow the authorized research personnel to receive regular updates on accrual status and CRF status of enrolled participants. Examples of available reports include participant enrollment logs, basic participant demographics, CRF completion rate and number of data queries outstanding and resolved. Like all reports generated on the system, data reported are in real time.

10.6 Security, Privacy, and Confidentiality

The DCU employs several layers of data protection to ensure data security.

The first part of security is physical protection of the hardware systems employed by the DCU. The facility housing the DCU hardware is protected 24/7 by multiple layers of security, including electronic building and facility access secured by magnetic locks, onsite-personnel, monitored and recorded closed-circuit television, person-traps, and mandatory identity logging of all outside visitors. By limiting access, ensuring only authorized personnel have access, and tracking all entry, we can ensure this risk is minimal.

The network and system security are ensured by implementing multiple layered firewalls and a network intrusion prevention system for identifying and blocking malicious network activity in real time. Vulnerability scans are also run daily to ensure server and network hardening, preventing known application and OS vulnerabilities. Antiviral, Trojan and worm protection is achieved by using Microsoft Forefront, updated on a daily basis. All communication with the web server and client is encrypted via SSL to make certain network traffic 'sniffing' poses no threat.

Audit Trail Function for WebDCU™: To maintain electronic records in the database as adequate and accurate, WebDCU™ system tracks all changes made to any study participant-related and dynamically managed electronic records. This audit-trail information is created with a computer-generated time-stamp and the user name in chronological order, when the original data is modified or deleted.

Data Redundancy: The Volume Shadow Copy Service is enabled for all DCU file servers and web servers used in the storage of clinical trial related documents and website files in order to provide a quick recovery solution of lost data. This allows for "point-in-time" copies of all edited files to be maintained in a hidden file space on the server. The copies or "snapshots" of edited files are taken 3 times daily.

Backup (Disaster Recovery): The databases housed in the WebDCU™ are backed up in two steps. The Microsoft® SQL server maintenance plans are set up to initiate the internal data integrity checkup procedures and to produce off-line backup copies of the database prior to IBM® Tivoli Storage Manager (TSM) backup. The TSM then delivers the full data backup to all DCU servers used in the storage of database at daily basis. The TSM completely backs up all system files (i.e., system registry, operating system, software, etc.) and user data files on the server. In the event of a weather related emergency or other situations where the university implements emergency procedures, the DCU also begins emergency full backup of all servers and other procedures in accordance with the DCU's Emergency Operation SOP.

10.7 Quality Assurance / Site Monitoring

Upon entry of CRFs into the study database, quality control procedures will be applied at each stage of data handling in order to ensure compliance with GCP guidelines, integrity of the study data and document processing system reliability. Both remote and site data and source document monitoring will be employed in a coordinated fashion. Coordination and reporting of monitoring findings, data queries, site visits, and other performance metrics are centrally consolidated within a monitoring module incorporated into WebDCU™. Sites are required to make study documents and pertinent records available for inspection by monitoring authorities.

All sites will undergo source document monitoring by the study site monitors from the CCC. Site monitors are distinct from the medical safety monitors referenced above. Site monitors will review source documents and case report form information, and perform multifaceted quality assurance and protocol compliance reviews.

Site Monitors will also be able to generate DCRs when discrepancies are found during source to database verification. The DCRs will be generated, communicated to the sites, and resolved on the secure study website.

The study monitoring plan will define a baseline rate of monitoring visits, and items such as informed consent documentation that will undergo 100% source document monitoring. Additional monitoring visits will be conducted using a data-driven risk-based sampling strategy. Site monitoring will include a combination of on-site and remote source document verification.

Monitoring findings are reported to the study leadership and will be used to identify and correct problems in data collection and protocol performance. Corrective action plans will be collaboratively formed and implemented with sites. Creation, implementation, tracking and closure of corrective action plans is also performed with the on-line monitoring module.

11. HUMAN SUBJECTS

The protection of human subjects is paramount in this trial and in everything SIREN does. Strict compliance with all applicable regulations is mandatory.

11.1 Institutional Review Board (IRB) Review and Informed Consent

A single Central Institutional Review Board (CIRB) will be used for P-ICECAP pursuant to NIH policy for multicenter clinical trials. For sites outside the United States, an appropriate independent ethics committee will review and approve the protocol. The SIREN Emergency Research CIRB will be the IRB of record for all US sites. IRB approval for this trial must be obtained and maintained for all participating enrollment sites. Documentation of current IRB approval and other required IRB communications will be maintained within the WebDCU™ clinical trial management system.

Eligible participants in this trial will not have the capacity to provide informed consent. An informed consent process including written documentation from a legally authorized representative (LAR) (usually a parent) will be required. The process may be augmented by multimedia informational tools and an e-consent platform created for the study. Any tools or materials must be approved by the CIRB. In the absence of brain death or particularly malignant prognostic findings, it is consistent with common clinical practice to await signs of neurological improvement in comatose survivors of cardiac arrest over a period of 120 hours of life support if that is consistent with the wishes of a participant's family or LAR. An important element of the informed consent process will be to identify and only include participants for whom the family or LAR initially intend to pursue at least 120 hours of life support.

11.2 Subject Confidentiality

Case report form data and other records that leave the site will be identified only by the Study Identification Number (SID) to maintain participant confidentiality. Any material records will be kept in a locked file cabinet. Electronic records will be appropriately secured using compliant safeguards. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIH, the OHRP, the sponsor, or the sponsor's designee.

Return of results of the study to participants, and other study updates and thanks will be facilitated by a separate central database of contact information for participants. Contacts may opt out of this database at the end of a participant's participation or anytime afterwards.

11.3 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the NIH, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

11.4 Sites outside the United States (OUS)

The provisions under 21 CFR 812.28 apply. Specifically, the following must be included for each OUS clinical investigation:

Statement that each investigation was conducted in accordance with GCP as described in 21 CFR 812.28(a)(1);

Supporting information specified under 21 CFR 812.28(b), as specified in 21 CFR 812.28(a)(2), or a cross-reference to another section of the application or submission where the information is located.

If the OUS clinical investigation did not conform to GCP, then in accordance with applicable regulations, the IDE or device marketing application or submission must include one of the following:

Waiver request in accordance with 21 CFR 812.28(c); or

Statement explaining the reason for not conducting the investigation in accordance with GCP and a description of steps taken to ensure that the data and results are credible and accurate and that the rights, safety, and well-being of participants have been adequately protected.

11.5 Sub-part D determination (US sites)

This clinical trial meets the requirements for additional protections for children involved as subjects in research. This research is subject to subpart D of 45 CFR 46 and is designated as research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

As per §46.405, the potential research risk is justified by the anticipated potential of direct benefit to children participating in the trial, and the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches. Guideline concordant usual care of pediatric patients resuscitated from cardiac arrest already involves targeted temperature management inclusive of both the 33°C and 36.8°C target temperatures potentially used in this trial (Duff, 2019). In this trial 33°C is provided for durations of 12 to 96 hours followed by a target temperature of 36.8°C through 120 hours. Participants assigned to controlled normothermia will have a target of 36.8°C for 120 hours. Within this range, there is practice variability of usual care. Estimates of how often differing strategies are currently used are imprecise, change over time, and do not offer insight regarding equipoise in the community. As described in more detail in the background section of the protocol, previous trials did not prove any difference in benefit or risk between target temperatures, but have observed point estimates of improved survival and outcome with cooling, suggesting at least a potential for direct benefit in excess of potential risk. The longer duration cooling arms studied in this trial can exceed durations used in usual care in patients with pediatric cardiac arrest, but are consistent with those used (or previously studied) in neonatal global cerebral ischemic injury. Pre-clinical and clinical data indicating the potential for direct benefit of longer durations are also presented in the background section. Furthermore, the use of response adaptive randomization to allocated duration of cooling increases the likelihood of allocation to better performing arms (if any) as the trial progresses, ensuring that individual participants' potential benefit to risk ratio improves with accumulation of data in the trial. Despite the substantial data presented indicating an appropriate potential of benefit versus risk, FDA has expressed some residual concerns related to practice variability prior to randomization. These include a theoretical risk related to the transition from a short period of non-standardized targeted temperature management to the protocol allocated standardized targeted temperature management strategy. This variability in transition was observed in the prior THAPCA trial and did not appear to affect the favorable ratio of potential benefit to risk. Despite these data, FDA is concerned that greater than anticipated variability of routine practice could impact risk or interpretability of the trial which could impact continued permissibility of the trial under Subpart D. To protect against these risks, the DSMB and FDA will conduct safety reviews every 10 participants for the first 40 participants. It is anticipated that these data will confirm that practice variability pre-randomization is not greater than anticipated, does not demonstrate an association with any safety signal, and does not affect qualification under Subpart D.

Finally as per §46.405, the trial provides adequate provisions for soliciting the permission of the parents or legally authorized representatives. Because eligible children are comatose at enrollment and during the entire period of the study intervention, they are not capable of providing assent, and assent will not be required for participation. Given constraints of time and availability in emergency and critical care settings, enrollment will be permitted with the permission of a single parent if necessary as allowed under §46.408. Children will not be enrolled without written documentation of consent from a parent or legally authorized representative.

11.6 Risk Analysis

The 2020 American Heart Association Guidelines For Cardiopulmonary Resuscitation and Emergency Cardiovascular Care provide guidelines for post-cardiac arrest care in children in Part 4: Pediatric Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. (Topjian, 2020, B) This guideline states the following:

"For infants and children between 24 h and 18 yr of age who remain comatose after OHCA or IHCA, it is reasonable to use either TTM of 32°C–34°C followed by TTM of 36°C–37.5°C or only TTM of 36°C–37.5°C."

Pediatric Life Support: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations provides the following review of the current state of the evidence for temperature management after cardiac arrest. (Maconochie, 2020) : "*We suggest that for infants and children who remain comatose following ROSC from OHCA and IHCA, TTM be used to maintain a central temperature of 37.5°C or less (weak recommendation, moderate-certainty evidence). On the basis of 2 randomized trials and 8 retrospective observational cohort studies that provided comparative data on favorable neurological outcome, survival, and in-hospital adverse events, there is inconclusive evidence to support or refute the use of TTM 32°C to 34°C compared with TTM 36°C to 37.5°C (or an alternative temperature) for children who achieve ROSC but remain comatose after OHCA or IHCA*."

The THAPCA Out of Hospital trial did not observe a meaningful difference in safety outcomes between participants randomized to controlled normothermia (36.8°C) versus 48 hours of therapeutic hypothermia (33°C). (Moler, 2015) Survival analysis (using log-rank methods stratified by age) demonstrated significantly longer survival over time with hypothermia 149±14 days vs. 119±14 days; P = 0.04. Visualization of the survival curve does not suggest any early mortality in the hypothermia group (Figure S1 in appendix of Moler, 2015); all-cause mortality was not worse at 28 days (57% hypothermia, 67% normothermia, p = 0.08). Given the critical illness of children following cardiac arrest and high expected mortality, meaningful harms would be expected to manifest themselves via either excess mortality or adverse neurological outcomes or both. No significant differences were noted on the pre-specified main safety outcomes (blood product use, serious arrhythmias, culture- proven infections, between the normothermia and hypothermia groups. (Table 3, Moler 2015). A Bayesian reanalysis of the THAPCA-OH data (Harhay, 2022) found a 6% posterior probability of harm (worse survival or neurobehavioral outcome) from hypothermia versus controlled normothermia. The probability of severe harm, defined as an absolute 5% lower observed proportion of patients with survival or good neurobehavioral outcome was 1% (survival) or less than 1% (neurobehavioral).

A trial of neonatal hypoxic ischemic encephalopathy (HIE) that evaluated cooling to 32.0 °C or 33.5 °C for either 72 or 120 hours did not find meaningful differences in arrhythmia requiring therapy or major bleeding across these groups (all less than 5% of cases during cooling intervention). (Shankaran, 2014) This study did not have a normothermic control, however a meta-analysis of neonatal HIE trials comparing hypothermia to

normothermia did not find any evidence of increased adverse events that were clinically meaningful. (Shah 2010). While HIE and cardiac arrest are different, patients share some common pathology, and the observation that adverse events for longer cooling durations employed in neonatal HIE are similar in magnitude to those observed in THAPCA provides additional indirect supportive evidence that longer durations of hypothermia are not inherently unsafe.

12. STUDY ORGANIZATION

Overall study organization including reporting relationships follow the established structures and standard operating procedures of SIREN.

Overview: The SIREN Clinical Coordinating Center (CCC) at the University of Michigan will provide overall project management for the trial under a UG3/UH3 award. In addition to the investigators, the SIREN core staff consist of the Project Manager/Site Manager, and two Site Monitors, supported by effort from a SIREN research assistant, the Human Subjects Protection Coordinator, the Education Coordinator, the Administrative Director, and administrative assistants. An outcomes core team from the Kennedy Krieger Institute (KKI)/Johns Hopkins University, which participated in the THAPCA trials, will be subcontracted by the P- ICECAP CCC grant.

The SIREN Data Coordinating Center (DCC) at the Medical University of South Carolina will provide all data management and statistical functions under a companion U24 award. A statistical core group from the University of Utah, which participated in the THAPCA trials, will be subcontracted by the SIREN DCC. The DCC will additionally have a contract with Berry Consultants for specialized adaptive study design consultation. In addition to the investigators, the core staff consist of the SIREN-dedicated operations (project) manager and P-ICECAP data manager, supported by additional statistical and programming personnel resources.

Participating P-ICECAP enrollment sites will be contracted directly through the University of Michigan, as was done in the THAPCA trials and the adult ICECAP trial. The scope of work done by sites, including follow-up of participants in P-ICECAP, will be very similar to the work done in the THAPCA trials and the adult ICECAP trial. Payment for site work will be based on verified study participant milestones completed. Approximately 65% of P- ICECAP sites participated in the THAPCA trials, and we anticipate little difficulty in the establishment of contracts in a timely manner. For this reason, we anticipate 50% of sites will be activated by the end of the UG3 period.

Leadership Coordination: Coordination of leadership between the CCC and DCC is based on strong principles of collaboration, open channels of communication, and a familiar and comfortable work scope division that has been built over many years of cooperation on numerous clinical trials. The P-ICECAP core trial leadership consists of the three PIs of the CCC trial grant, the PI of the DCC companion trial grant, and one or more NIH

Program Scientists. For issues relating to overall SIREN network management, principal investigators of the SIREN Network CCC and DCC grants are engaged in this project.

Committee Roles: The P-ICECAP committee structure will be very similar to the model used in the THAPCA trials which worked extremely efficiently and well for the execution of these trials. The **P-ICECAP Executive Committee (EC)** will provide overall direction for the trial, monitor the trial progress in a multi-disciplinary setting, and perform major decision-making including approval of study amendments and all submitted manuscripts for publication. Meeting summaries from the P-ICECAP Steering Committee and P-ICECAP Research Coordinator Committee described below will also be reported. It will meet at least monthly for 1 hour and more often or longer if needed. There are subgroups of the P-ICECAP EC that have focused roles. The day-to-day activities of P-ICECAP will be accomplished by a small subgroup of the EC leadership, entitled the **P-ICECAP Trial Operations Group**. It will be composed of the 3 CCC PIs, the P-ICECAP Project Manager/Site Manager, DCC PI, NHLBI program officer, and others as needed. It will meet at least weekly. Issues from this group are reported up as needed to the SIREN Operations Committee weekly meeting of which P-ICECAP will be a standing scheduled agenda item. Information about the P-ICECAP trial is reported to the monthly SIREN Steering and Executive Committees. The **P-ICECAP Protocol Review Committee** will be made up of a majority of the EC members. It will provide guidance and review ancillary study proposals and secondary studies for the P-ICECAP trial. In THAPCA over 20 secondary papers were facilitated using a similar committee structure. The **P-ICECAP Clinical Standardization Team** will be another subgroup of five members from the EC. It will set guidelines for post-resuscitation care including blood pressure management for the clinical sites. The **P-ICECAP Outcome Assessment Core** will consist of at least 2 members of the EC, who will report follow-up success as a standard agenda item at each monthly EC meeting. The P-ICECAP EC will work with the existing SIREN Human Subjects Protection-Working Group and an external group from the Collaborative Pediatric Critical Care Research Network (CPCCRN) Family Network Collaborative with which the THAPCA trials worked. To summarize, at each monthly P-ICECAP EC meeting (modeled after the THAPCA-OH trial) there will be reports from the Trial Operations Group, Protocol Review Committee, Clinical Standardization Team, and Outcome Assessment Core, in addition to the P-ICECAP Steering Committee and Research Coordinator Committee.

The **P-ICECAP Steering Committee** will be made up of a site PI from each study site, the P-ICECAP PIs, the Project Manager/Site Manager and others as needed. The P-ICECAP PI will set agendas for the monthly meeting and the Clinical Standardization Team will be actively involved. Topics such as site activation status, site screening and enrollment by month, site protocol performance, protocol amendments, and study lessons learned will be covered. Ad hoc meetings will occur as needed.

The **P-ICECAP Research Coordinator Committee** will be made up by at least one research coordinator from each site and will meet at least monthly. The Project Manager/Site Manager will lead these meetings and set the agendas for these meetings, along with input from the Study Monitors/Study coordinators and Data Managers. An annual 2-3-day training/retraining meeting will occur with mandatory attendance by both site investigators and coordinators, as well as PIs and co-Is from both the DCC and CCC.

Oversight: Site coordination and oversight is a primary responsibility of the SIREN CCC. Regulatory management is facilitated through the WebDCU™ clinical trial management system and fully digital web-based e-study binders. Additional key elements of site oversight include structured readiness/activation teleconferences and dedicated in-house on site monitoring. Oversight of data quality is a primary responsibility of the DCC and is also facilitated by smart electronic case report forms with real-time logic and range checks and by a strong program of ongoing central data monitoring.

Several working groups also contribute to oversight of specialized aspects of the trial and report to the **P-ICECAP EC** and **P-ICECAP Trial Operations Group**. The **P-ICECAP Clinical Standardization Team**, will work to train clinical personnel in the consensus standard treatment strategies based on the most up to date post resuscitation care guidelines of the American Heart Association (AHA). It will monitor and review transgression data for enrolled participants. The **P-ICECAP Outcome Assessment Core**, will direct training and standards and coordinate all technology related to the measurement of functional, family and/or patient-reported, neurobehavioral, and neurological assessments. The existing SIREN Human Subject's Protection-Working Group will review and advise the P-ICECAP EC on the informed consent processes in this potentially vulnerable population. We will also utilize the Collaborative Pediatric Critical Care Research Network (CPCCRN) Family Network Collaborative which was used in the THAPCA trials. This group has voluntarily provided advice for the P-ICECAP trial. The group was very familiar with the THAPCA trials, a study they viewed as extremely important research in children.

A **P-ICECAP Ancillary Protocol Review Committee**, will solicit, coordinate, and develop protocols and applications as appropriate to address additional meritorious aims within the framework of the overall trial. Any proposed ancillary study cannot interfere with the scientific purpose or successful completion of the parent trial. Proposed ancillary studies must be approved by P-ICECAP Executive Committee, SIREN CCC and DCC leadership, the DSMB, and the NHLBI. Work associated with ancillary studies will be funded separately from the parent trial.

Coordination with NHLBI: NIH Program Scientists (P-ICECAP NHLBI program officer and SIREN program scientists from NHLBI and NINDS) and staff will be well integrated into the trial and coordinate with P-ICECAP and SIREN investigators through participation opportunities at all committee levels. In the THAPCA trials, the NHLBI program officer was an active member of both the P-ICECAP Executive Committees and Protocol Review Committee, and ad hoc for the Steering Committee and Coordinators Committee meetings. This was optimal for all parties.

Stakeholder Groups: P-ICECAP investigators are committed to involvement and cooperation with patient stakeholder groups. Through established channels we have convened some early parent panel consultations associated with the CPCCRN Family Network Collaborative in the design phase and their input contributed to the design of the trial proposal. These will continue and be expanded upon as needed through the implementation, enrollment, and dissemination phases of the project.

Dispute resolution: The Principal Investigators of the P-ICECAP CCC and DCC will share responsibility for the scientific integrity of the study, overall study management, and interpretation and dissemination of the study findings. Any disagreements regarding study matters are expected to be resolved collaboratively among the PIs, but if necessary final decisions will be determined by majority vote of the four PIs plus one other senior co-investigator. Disputes between the P-ICECAP leadership and enrollment sites are also expected to be resolved collaboratively, but if necessary, such disputes will be resolved by the P-ICECAP Executive Committee, which includes NIH Program Representatives. Disputes between any investigators and the NIH will also be resolved collaboratively whenever possible, but if necessary, will be resolved in favor of the Institute. In the two THAPCA trials, there were no dispute resolutions necessary, other than minor discussions needed with a couple of sites that lost key site personnel and making sure that these sites had plans for completion of participant follow up and all query resolutions

13. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the standard operating procedures developed by the SIREN and trial leadership. All presentations, abstracts, and manuscripts will include attribution of funding to the NIH and will be made available for review by the sponsor and the NIH.

The P-ICECAP investigators and the SIREN Network are committed to active dissemination of study results and source data. The primary results of the clinical trial will be disseminated by publication in the peer reviewed medical literature as described above. In accordance with the NIH Public Access Policy, the investigators will submit an electronic version of their final, peer-reviewed manuscripts (directly or through the publisher) to the National Library of Medicine's PubMed Central, no later than 12 months after the official date of publication. Dissemination will also include promotion of the study results through Institutional communications and media relations departments, through scientific and public presentations, and other forms of medical and lay public outreach.

The P-ICECAP trial will be registered and reported in ClinicalTrials.gov on or ahead of all scheduled requirements.

- The clinical trial will be registered, and all required information submitted to ClinicalTrials.gov within 6 months of notice of grant award and prior to participant enrollment. Results of the trial will be reported there within a year of trial completion. All submissions to ClinicalTrials.gov will be performed consistent with the requirements for applicable clinical trials per FDAAA 801 requirements and NIH policy.

- The final P-ICECAP informed consent document will include a specific statement informing participants that information about the clinical trial is posted at ClinicalTrials.gov and that aggregate results will be posted there as well.

After completion of the study and dissemination of primary study results, a public use dataset will be made available through the NHLBI data repository managed by BioLINCC or elsewhere as arranged with the Institute. The dataset will be prepared in accordance with the NHLBI Policy for Data Sharing from Clinical Trials and Epidemiological Studies, and in accordance with the Guidelines for NHLBI Data Set Preparation. All manuscripts, abstracts and press releases using the study data must acknowledge P-ICECAP/SIREN investigators and the NHLBI as the study sponsor with the relevant grant numbers.

The timeline of submission of the public use dataset will comply with all relevant repository guidelines, but in general, SIREN will submit data to the repository approximately one year after the primary manuscript of the trial is accepted for publication. During that year, the trial investigators will have opportunities to digest the study results and generate further hypotheses, and submit manuscript proposals, if so desired. The rationale for the timelines is to ensure that there is sufficient time to properly prepare the data, to provide priority to the study investigators in manuscript development, but with incentives to do so in an efficient and rapid manner, and to release the data to external investigators early.

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PROTOCOL CHANGES

Version 1 to Version 2

	Version 1		Version 2	
Section	**Page**	**Previous text**	**Page**	**New text**
Title	Title page	**Clinicaltrials.gov**: NCT<pending>	Title	**Clinicaltrials.gov**: NCT NCT05376267
Brief Synopsis and 1.1	9 and 10	To characterize the duration response curve for hypothermia and determine: whether the duration-response demonstrates cooling efficacy versus no cooling	9 and 10	To characterize the duration response curve for hypothermia and determine: whether increasing durations of cooling are associated with better outcomes
2.1	11	zero additional cooling (normothermia)		Deleted (normothermia)
2.1	12	If the treatment effect of cooling is … better neurobehavioral and survivor outcomes than normothermia.		Deleted
2.2	19	" 1) whether therapeutic hypothermia is superior to controlled normothermia and 2)"		Deleted
2.2	19	duration of target temperature management		duration of cooling

3	20	Alternatively, … including zero hours of cooling (normothermia).	19	Alternatively, ...including no additional cooling.
3.3	22	Those performing outcome assessments will be queried about potential inadvertent unblinding at the time of assessment.		Deleted
3.3	22	Trial leadership	21	Trial clinical leadership
4.1	23	The efficacy of therapeutic hypothermia		The efficacy of different durations of therapeutic hypothermia
4.2	25	Known pregnancy	23	Pregnancy
4.2	26	Patients who are known to be pregnant are excluded…	25	Patients who are pregnant are excluded…
4.4	27	The specific risks of participating will be outlined. (sentence added)	26	The specific risks of participating will be outlined. The LAR will be informed that hypothermia has not been identified to be of greater benefit than normothermia.
4.4.2	27	While unlikely, if, during the cooling period,... …Written informed consent should be obtained from either the new guardian or the competent participant attaining legal adulthood.	26	If at any point during the trial, a change in guardianship occurs and/or a participant reaches the age of majority and regains competency for research decision-making , the new LAR and/or adult participant will be offered the opportunity to withdraw from the trial and the informed consent process will be repeated. The consent by the new LAR and/or “adult” participant will be obtained using the written informed consent form approved by the IRB and

				documented in accordance with 21 CFR 50.27(a).
4.4.2	28	The desire of an LAR or a participant to withdraw from the study will be honored and does not require the LAR or participant to sign any documentation. The desire of an LAR or participant to remain … not required to do so as a condition of continued participation.	27	The desire of an LAR or a participant to withdraw from the study will be honored and does not require the LAR or participant to sign any documentation.
4.4.4	28	…cooling duration …	27	…allocated intervention duration …
4.6	29	Patients with a known, pre-existing pregnancy are excluded from P-ICECAP. ..status as their own decision maker, and this will be addressed as noted in 4.4.2 above.	27	Participants of childbearing potential cannot be randomized until a pregnancy test is negative.
5.1	29	The intervention will be random allocation to duration of cooling after cardiac arrest.	28	The intervention will be random allocation to duration of cooling after cardiac arrest, inclusive of a duration of no additional cooling where the participant is set to a normothermic target after randomization.
5.1	29	… set to a target of 33°C.	28	… set to a target of 33°C (targets from 32- 34°C and maintained continuously prior to randomization also qualify as start of cooling.)
5.1	30	In P-ICECAP, after the allocated duration of cooling is completed, controlled rewarming will be	28	In P-ICECAP, after the allocated duration of cooling is completed, controlled rewarming will be performed. Slow

		performed. Participants assigned to no additional cooling will have their target adjusted to normothermia after randomization. Slow rewarming to a temperature of 36.8°C will occur over approximately 16 hours for those participants assigned to cooling durations greater than zero.		rewarming to a temperature of 36.8°C will occur over approximately 16 hours for those participants assigned to cooling durations greater than zero.
5.1	30	New sentence added after “those participants assigned to cooling durations greater than zero.”	29	After rewarming a normothermic target will be used until 120 hours from device being set to hypothermic target (see figure in section 4.3 above).
5.1	30	If the participant is randomized to a zero hour duration cooling arm, the intervention will be by a definitive temperature control method to a target temperature of 36.8°C. Duration will be 120 hours from the time the device is set at 36.8°C.	29	Participants assigned to no additional cooling will have their target set to normothermia after randomization. Duration will be 120 hours from the time the device is set to a normothermic target.
6.3	32	The PCPC and POPC will be collected based on review of medical record and caregiver interview within 24 hours of admission for baseline score, at hospital discharge or at day 30 (Topjian , 2020).	30	The PCPC and POPC will be collected based on review of medical record and caregiver interview within 24 hours of admission for baseline score, and at hospital discharge or at day 30, whichever is first (Topjian , 2020).
7.1	35	All non-serious AEs occurring through 120 hours from setting the temperature control device to 33	33	All non-serious AEs occurring through 120 hours from setting the temperature control device to the assigned target and

		and all serious adverse events (SAEs) occurring…		all serious adverse events (SAEs) occurring…
9	37	imply efficacy of cooling versus no cooling		imply a dose (duration) response effect.
9	38	Participants will be adaptively randomized to a cooling duration.	38	Participants will be adaptively randomized to a cooling duration, inclusive of a zero additional cooling arm.
9.2	38	The primary analysis is conducted on the intent to treat (ITT) population. The primary analysis will address two objectives: 1) to determine whether the efficacy of any duration is superior to any shorter duration of cooling (Objective A);	37	The primary analysis is conducted on the intent to treat (ITT) population. The primary analysis will address two objectives: 1) to determine whether increasing durations of cooling are associated with better outcomes (Objective A);
9.2	39	demonstrate that cooling is effective versus no cooling	39	demonstrate a dose (duration) response effect
9.3.1	39	For the lowest dose region near 6 hours ($d = 1$), the dose-response curve is modeled as (potentially) increasing.	38	For the lowest dose region near 0 hours ($d = 1$), the dose-response curve is modeled as (potentially) increasing.
9.7	43	In this scenario, we have excellent power to detect that some cooling duration is better than 0 hours (and thus demonstrate that prolonged cooling “works”)		In this scenario, we have excellent power to detect duration response
9.12	45	(new section added)	44	9.12 <u>Staged Approval and Interim Analyses For Safety</u>

10.4	47	…without storing any personal identifying information.	46	Text deleted
11.5	51	Guideline concordant usual care of pediatric patients resuscitated from cardiac arrest already involves targeted temperature management inclusive of both the 33 degree and 36.5 degree target temperatures used in this trial. In this trial 33 degrees is provided for durations of 0 to 96 hours followed by a target temperature of 36.5.	49	Guideline concordant usual care of pediatric patients resuscitated from cardiac arrest already involves targeted temperature management inclusive of both the 33 degree and 36.8 degree target temperatures potentially used in this trial (Duff, 2019). In this trial 33 degrees is provided for durations of 0 to 96 hours followed by a target temperature of 36.8.
11.5	51	Finally as per §46.405, the trial provides adequate provisions for soliciting the permission of the parents or guardians.	50	Finally as per §46.405, the trial provides adequate provisions for soliciting the permission of the parents or legally authorized representatives.
11.6	51-52	(New Section Added)	50-51	<u>11.6 Risk Analysis</u>
14	60-64	(References Added)	64 - 69	Maconochie, 2020; Shah, 2010; Shakaran, 2014; Topjian, 2020

Version 2 to Version 3

	Version 2		Version 3	
Section	**Page**	**Previous text**	**Page**	**New text**
Face page	1	New text added	1	ADVARRA protocol number Pro00061683
2.1	17	…suggestive of survival benefit. (text added after this)	17	A Bayesian reanalysis of THAPCA-OH data found “the probability of any benefit from hypothermia was 94% for both the neurobehavioral outcome and survival at 1 year.” (Harhay, 2022)
2.1	18	If the optimal duration of therapeutic hypothermia to improve survival and neurobehavioral outcome in children can be identified, such findings would conclusively change clinical practice across the entire care spectrum of pre-hospital, emergency department, intensive care and rehabilitation for pediatric OHCA patients. The high priority and urgency of the proposed P-ICECAP trial is strongly supported by the recent International Liaison Committee on Resuscitation…	18	The International Liaison Committee on Resuscitation…
2.1	18	regarding	18	have identified
2.1	18	pediatric resuscitation research	18	pediatric cardiac arrest resuscitation research

2.1	18	These include the need for further studies to determine the duration of cooling as high priority for pediatric CA resuscitation research. The P-ICECAP trial's innovative study design will answer this question and address one other THAPCA-OH limitation by including children with milder encephalopathy post-OHCA .	18	These priorities include the need for further studies to determine 1) whether therapeutic hypothermia is superior to controlled normothermia and 2)the duration of targeted temperature management. P-ICECAP will not include a discrete "controlled normothermia" control arm throughout its implementation. Therefore, while it may further inform the comparison of outcomes with controlled normothermia and therapeutic hypothermia, P-ICECAP will not specifically address the first priority of determining whether therapeutic hypothermia is superior to controlled normothermia.
3	19	…as safe as normothermia…	19	…as safe as controlled normothermia…
3	19	…including no additional cooling.	19	… including no additional cooling (controlled normothermia).
4.4	26	… that hypothermia has not been identified to be of greater benefit than normothermia.	26	… that therapeutic hypothermia has not been identified to be of greater benefit than controlled normothermia.
5.1	28	…no additional cooling will have …	28	…no additional cooling (controlled normothermia) will have …
5.1	28	…after randomization. Duration will…	28	…after randomization. Participants assigned to this arm will be rewarmed promptly per routine clinical practice, and will not be rewarmed using the 16 hour procedure for the arms that receive therapeutic hypothermia for 12 to 96 hours. Duration of controlled

				normothermia will…
9	37	…inclusive of a no additional cooling arm.	36	…inclusive of a no additional cooling arm (controlled normothermia).
9	37	Regardless of whether participants are ever allocated to the zero additional cooling arm (or have possible exposure to some pre-randomization cooling), an increasing treatment effect across some set of durations would imply a dose (duration) response effect.	36	Regardless of whether participants are ever allocated to the no additional cooling arm (or have possible exposure to some pre-randomization cooling), an increasing treatment effect across some set of durations may imply a dose (duration) response effect.
9.2	38	…then this would demonstrate a dose (duration) response effect…	37	…then this may demonstrate a dose (duration) response effect…
9.3.1	38	“zero additional cooling”	37	controlled normothermia
9.7	41	Table 9.7.A	40	Added footnote that 0 arm was controlled normothermia
9.7	42	of the positive effect of cooling at some duration greater than 0 hours (no additional cooling).	41	increasing durations of cooling are associated with better outcomes
9.7	42	0 hour cooling period	41	controlled normothermia arm
9.7	42	the 0 hour	41	controlled normothermia
9.7	43	a cooling duration more than 0 hours is found to superior on the VABS-3 Mortality Composite Score compared to the 0-hour arm,	42	a cooling duration is found to be associated with better outcomes on the VABS-3 Mortality Composite Score compared to the controlled normothermia arm,

9.7	43	In this (unexpected) scenario where a benefit of prolonged cooling versus 0 additional hours exists, but then drops at the longest durations, power is limited to 66.5% to declare that any duration of cooling is better than 0 hours, and ability to correctly choose ED95 is also limited.	42	In this (unexpected) scenario where better outcomes are associated with mid-range durations of cooling, then drops at the longest durations, power is limited to 66.5% to declare that any duration of cooling is associated with better outcomes than controlled normothermia, and ability to correctly choose ED95 is also limited.
11.5	50	…through 120 hours. Within this range,...	49	…through 120 hours. Participants assigned to controlled normothermia will have a target of 36.8°C for 120 hours. Within this range,...
	51	The THAPCA Out of Hospital trial did not observe a meaningful difference in safety outcomes between participants randomized to normothermia versus 48 hours of TTM at 33°C.	50	The THAPCA Out of Hospital trial did not observe a meaningful difference in safety outcomes between participants randomized to normothermia versus 48 hours of therapeutic hypothermia (33°C).
11.6	51	…hypothermia groups. (Table 3, Moler 2015). (text added after)	50	A Bayesian reanalysis of the THAPCA-OH data (Harhay, 2022) found a 6% posterior probability of harm (worse survival or neurobehavioral outcome) from hypothermia versus controlled normothermia. The probability of severe harm, defined as an absolute 5% lower observed proportion of patients with survival or good neurobehavioral outcome was 1% (survival) or less than 1% (neurobehavioral).

14	58	Additional reference added	57	Harhay, M.O., Blette, B.S., Granholm, A., Moler, F.W., Zampieri, F.G., Goligher, E.C., Gardner, M.M., Topjian, A.A. and Yehya, N., 2022. A Bayesian interpretation of a pediatric cardiac arrest trial (THAPCA-OH). NEJM Evid, 2022;2(1) https://doi.org/10.1056/EVIDoa2200196
Changes	64	Words added	63	Version 1 to Version 2