Clinical Trial Protocol

Title:	**Influence of Cooling duration on Efficacy in Cardiac Arrest Patients**
Short Title:	**ICECAP**
NCT:	**04217551**
Date:	**May 4, 2020**

ICECAP

NIH SIREN Emergency Trials Network

ICECAP

STUDY PROTOCOL

ICECAP: 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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William Meurer, IDE Number G160072

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NCT 04217551

Protocol Version 1

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.

14 APR 2020

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 subjects.

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)

Contact Information

For updated contact information, including the Emergency 24/7 Toll Free Contact Number, please refer to the 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
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
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ED	Emergency Department
EEG	Electroencephalogram
EMS	Emergency Medical Services
ET	Endotracheal
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
kg	Kilogram
LAR	Legally Authorized Representative
mg	Milligram
Min	Minute
mL	Milliliter
mm	Millimeter
MoP	Manual of Procedures
mRS	Modified Rankin Scale
MSM	Medical Safety Monitor
MUSC	Medical University of South Carolina
NIH	National Institutes of Health
O2	Oxygen
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

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BRIEF SYNOPSIS

Protocol Title	Influence of Cooling duration on Efficacy in Cardiac Arrest Patients
Acronym	ICECAP
Clinical Trial Phase	Phase II/III
Study Design	Randomized, response-adaptive, duration/dose finding, comparative effectiveness clinical trial with blinded outcome assessment
Sites / Period	About 50 hospitals / 4 years
Study Population	Comatose adult survivors of out of hospital cardiac arrest that have already been rapidly cooled using a definitive temperature control method. Those with and without initial shockable rhythms will be studied as distinct populations.
Primary Study Objectives	To characterize the duration response curve for hypothermia and determine in each of two populations: A. the shortest duration of cooling that provides the maximal treatment effect, and B. whether the duration-response implies efficacy versus no cooling
Secondary Study Objectives	i. to characterize safety of varying durations of cooling, ii. to characterize the effect on neuropsychological outcomes, iii. to characterize the effect on patient reported quality of life.
Sample Size	Maximum of 1800 subjects
Inclusion Criteria	Coma after resuscitation from out of hospital cardiac arrest, >18 years of age, <34 deg C within 240 minutes, definitive temperature control device applied, Informed consent from LAR including intent to maintain life support for 96 hours, enrollment within 6 hours of initiation of cooling
Exclusion Criteria	Hemodynamic instability, pre-existing condition confounding outcome determination, pre-existing terminal illness, unlikely to survive to outcome determination, planned early withdrawal of life support, presumed sepsis as etiology of arrest, prisoner
Study Intervention	The intervention will be random allocation to duration of cooling after cardiac arrest.
Primary Outcome	Modified Rankin scale (mRS) at 90 days after return of spontaneous circulation.
Statistical Analysis for Primary Outcome	Modeling of duration response using a mean weighted mRS incorporating both the proportion of subjects achieving a good neurological outcome and degree of impairment among those with good neurological outcomes. Identification of the shortest duration of cooling that provides the maximum treatment effect. Determination of superiority of any longer duration compared to any shorter duration.

SYNOPSIS

Influence of Cooling duration on Efficacy in Cardiac Arrest Patients (ICECAP)

A multicenter, randomized, adaptive allocation clinical trial to determine if increasing durations of induced hypothermia are associated with an increasing rate of good neurological outcomes and to identify the optimal duration of induced hypothermia for neuroprotection in comatose survivors of cardiac arrest.

Cardiac arrest is a common and devastating emergency of the heart and the brain. More than 380,000 patients suffer out of hospital cardiac arrest (OHCA) each year in the US. Improvements in cardiac resuscitation (the early links in the "chain of survival" for patients with OHCA) are tempered by our limited ability to resuscitate and protect the brain from global cerebral ischemia.

Neurological death and disability are common outcomes in survivors of cardiac arrest. Therapeutic cooling of comatose patients resuscitated from shockable rhythms markedly increases the rate of good neurological outcome, but poor outcomes still occur in as many as 50%, and the benefit of cooling in those resuscitated from asystole and pulseless electrical activity has not been shown in a randomized study.

<u>Objectives</u>

The overarching goal of this project is to identify clinical strategies that will increase the number of patients with good neurological recovery from cardiac arrest. We hypothesize that longer durations of cooling may improve either the proportion of patients that attain a good neurological recovery or may result in better recovery among the proportion already categorized as having a good outcome.

Primary Objectives:

A. To determine, in each of two populations of adult comatose survivors of cardiac arrest (those with initial shockable rhythms and those with PEA/asystole), the shortest duration of cooling that provides the maximum treatment effect as determined by a weighted 90 day modified Rankin score

B. To determine, in each of two populations of adult comatose survivors of cardiac arrest (those with initial shockable rhythms and those with PEA/asystole), whether increasing durations of cooling are associated with better outcomes or recovery implying efficacy of hypothermia to no cooling.

Secondary Objectives:

i. To characterize the overall safety and adverse events associated with duration of cooling
ii. To characterize the effect of duration of cooling on neuropsychological outcomes

iii. To characterize the effect of duration of cooling on patient reported quality of life

Design

This study is a randomized, response-adaptive, duration (dose) finding, comparative effectiveness clinical trial with blinded outcome assessment. The design is based on a statistical model of response as defined by the primary endpoint, a weighted 90-day mRS, across the treatment arms. The design will fit patient outcome data to a duration response model (separately for shockable and non-shockable rhythms), in which the potentially non-linear association between durations of cooling and the primary endpoint are estimated. All conclusions about the treatment arms are based on this model. The functional form of 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.

Subjects will initially be equally randomized between 12, 24, and 48 hours of cooling. After the first 200 subjects have been randomized, additional treatment arms between 12 and 48 hours will be opened and patients will be allocated, within each rhythm type, by response adaptive randomization. As the trial continues, shorter and longer duration arms may be opened. Specifically, a 6-hour duration arm will be opened if the emerging duration-response curve from 12 hours is flat. Similarly, a 60-hour or 72-hour duration arm will be opened if the emerging duration response curve shows an increasing treatment benefit through 48 hours.

This trial will have frequent interim analyses to stop the trial early for futility if it is highly likely that no treatment arm offers a greater benefit then the 6-hour duration arm.

Primary Outcome Measure

The primary outcome measure will be the modified Rankin scale at 90 days after return of spontaneous circulation. The mRS will be analyzed as a weighted score incorporating both the proportion of subjects achieving a good neurological outcome and degree of residual functional impairment among those with good neurological outcomes.

Study Population

Comatose adult survivors of out of hospital cardiac arrest that have already been rapidly cooled using a definitive temperature control method (endovascular or surface) will be enrolled in the emergency department or intensive care unit. Hub and spoke hospitals from the SIREN network will be enriched with high potential ancillary Hubs. Approximately 50 or more hospitals are anticipated to each enroll an average of 9 subjects per year.

Inclusion

- Coma after resuscitation from out of hospital cardiac arrest
- Cooled to <34 deg C within 240 minutes of cardiac arrest
- Definitive temperature control device initiated
- Enrollment within 6 hours of initiation of cooling
- Age ≥ 18 years
- Informed consent from LAR including intent to maintain life support for 96 hours

Exclusion

- Hemodynamic instability
- Pre-existing neurological disability or condition that confounds outcome determination
- Pre-existing terminal illness, unlikely to survive to outcome determination
- Planned early withdrawal of life support
- Presumed sepsis as etiology of arrest
- Prisoner

Randomization

Central computerized randomization by web-based interface will be used. Subjects will be potentially randomized over the course of the trial to the following possible durations of cooling (in hours): 6, 12, 18, 24, 30, 36, 42, 48, 60, and 72. The first 200 patients will be randomized 1:1:1 to the 12, 24, and 48-hour durations only. After this initial "burn in" period, response adaptive randomization will be used to allocate subjects to durations inclusive of 12 to 48 hours initially, and then subsequently to the 6, 60 or 72 hour durations if specified conditions are met and the emerging duration-response curve suggests that the maximum treatment benefit might be on those durations. The response adaptive randomization probabilities for each arm will be determined separately for the two rhythm type populations. Randomization probabilities will be updated approximately every 50 enrollments, or approximately every month based on the expected accrual rate.

Consent

Eligible patients for this trial will not have the capacity to provide informed consent. Written informed consent from a legally authorized representative will be required.

Intervention

The intervention will be random allocation to duration of cooling after cardiac arrest. Cooling in the study will be by a definitive temperature control method to a target temperature of 33 deg C. Any endovascular or surface cooling system with closed loop feedback will be allowed. Duration of cooling will be measured from the time that cooling with a definitive device is

initiated in the hospital (see 5.1.2). As part of routine medical care, cooling may be initiated by EMS or in the emergency department. Eligibility will require that a temperature of <34 degrees C be obtained by 240 minutes after cardiac arrest. After the allocated duration of cooling is completed, controlled rewarming will be performed. Rewarming to a temperature of 36.5 deg C will occur over the shorter of 24 hours or a rewarming period equal to the allocated duration of cooling. Definitive cooling devices may be used for maintenance of normothermia after rewarming is complete. A clinical standardization guideline will be followed to reduce the effects of practice variability. Key physiologic and practice variables will be tracked and compliance with clinical standardization and deviation from physiologic targets reported back to study teams.

Statistical Analysis for the Primary Outcome Measure

We will model the mean weighted mRS at 90 days across the treatment arms. The weighted mRS incorporates both the proportion of subjects achieving a good neurological outcome and degree of impairment among those with good neurological outcomes. The primary analysis is conducted separately for each rhythm type, allowing for a different treatment effect by rhythm type, and has two components. First, we identify the most likely target duration, where the target duration is the shortest duration that achieves the maximum treatment effect (Objective A). Second, we calculate whether the efficacy of any duration is superior to any shorter duration of cooling indicating a positive duration response (Objective B). Establishing a positive duration response implies confirmation that cooling is effective in improving outcome or recovery versus normothermia, when a normothermia control arm is not clinically acceptable.

A maximal sample size of 1800 subjects enrolled over 4 years (estimated accrual rate of 37.5 subjects/month) is anticipated.

Investigational Device Exemption

This trial is conducted under an IDE from the Food and Drug Administration.

1. STUDY OBJECTIVES

1.1 Primary Objectives

A. To determine, in each of two populations of adult comatose survivors of cardiac arrest (those with initial shockable rhythms and those with PEA/asystole), the shortest duration of cooling that provides the maximum treatment effect as determined by a weighted 90 day modified Rankin score

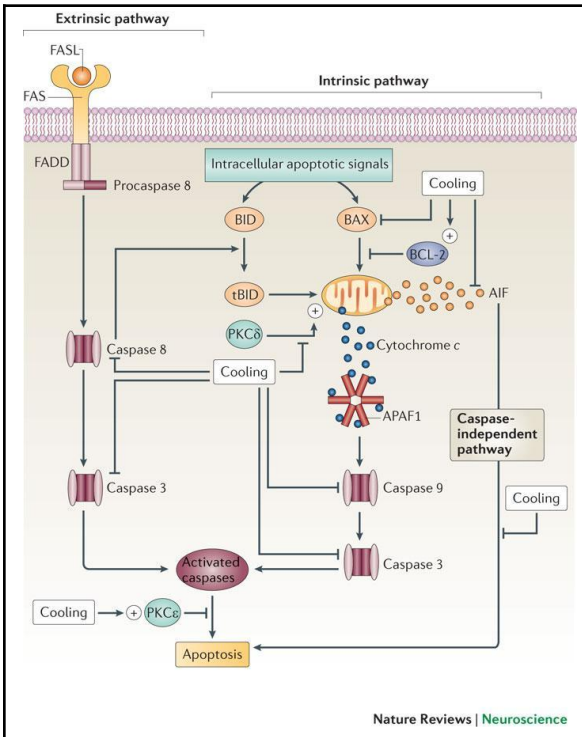
B. To determine, in each of two populations of adult comatose survivors of cardiac arrest (those with initial shockable rhythms and those with PEA/asystole), whether increasing durations of cooling are associated with better outcomes or recovery implying efficacy of hypothermia to no cooling.

1.2 Secondary Objectives

The secondary objectives of this project are

i. to characterize the overall safety and adverse events associated with duration of cooling,
ii. to characterize the effect of duration of cooling on neuropsychological outcomes,
iii. to characterize the effect of duration of cooling on patient 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 signalling 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 cooling of 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 induced hypothermia has not been investigated. ICECAP is a randomized adaptive clinical trial to characterize the duration-response curve of induced hypothermia in comatose survivors of cardiac arrest and to determine the optimal duration of cooling. There are a total of 10 possible treatment arms exploring 6 through 72 hours of cooling duration. Subjects will initially be randomized to 12, 24, or 48 hours of cooling. After the first 200 subjects have been enrolled, response adaptive randomization will allocate subjects to additional durations from 12 through 48 hours. A shorter duration (6 hours) treatment arm will be opened for enrollment if there is not an increase in the treatment effect across the durations. Alternatively, longer durations (60 or 72 hours) will be opened for enrollment if the treatment effects are increasing (rather than plateauing or decreasing) through 48 hours. Comatose adult survivors of cardiac arrest that have already been rapidly cooled using a definitive temperature control method (endovascular or surface) will be enrolled. The primary

outcome will be a modified Rankin score at 90 days analyzed as a weighted score incorporating both the proportion of subjects achieving a good neurological outcome and degree of residual functional impairment among those with good neurological outcomes.

The overarching goal of this project is to identify clinical strategies that will improve the neurological outcomes of patients with cardiac arrest. We hypothesize that longer durations of cooling may improve either the proportion of patients that attain a good neurological recovery or may result in better recovery among the proportion already categorized as having a good outcome. If the treatment effect of cooling is increasing across duration, for at least some set of durations, then this provides evidence of the efficacy of cooling itself versus normothermia, even in the absence of a normothermia control arm, confirming previous RCTs for survivors of shockable rhythms and to provide first prospective controlled evidence of efficacy in those without initial shockable rhythms.

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, 1431). The 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.

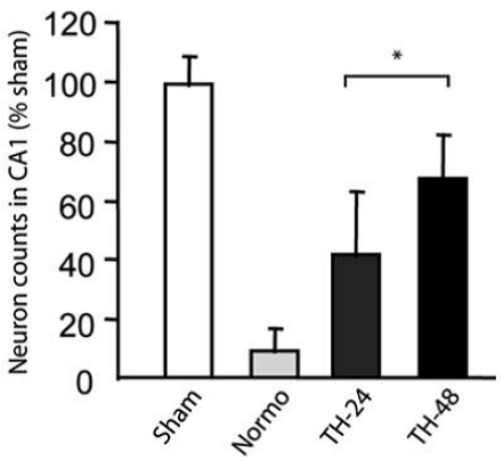
In preclinical models of both global and focal ischemia, hypothermia is consistently one of the most effective treatments to reduce neuronal damage. In seminal work on this subject, rats were subjected to intra-ischemic brain temperatures of 36, 33, and 30 deg C.(Busto, 1989, 904) Release of glutamate 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, 467)

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, 467) 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

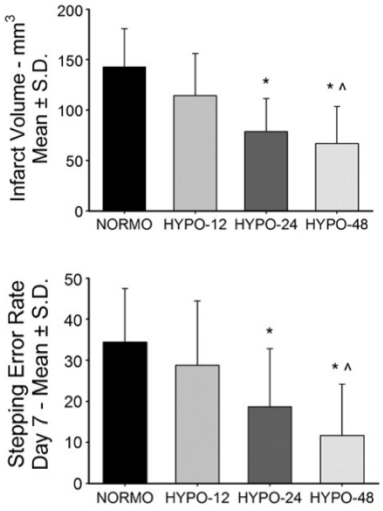
deprivation in cell culture). Hypothermia had the highest STAIR score of any neuroprotective strategy reflecting the reproducibility of efficacy across models, species, outcome metrics, and severity of injury. Preclinical investigations of hypothermia in cerebral ischemia have continued at a high rate 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, 265). 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, 7250). 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, 1423). 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.



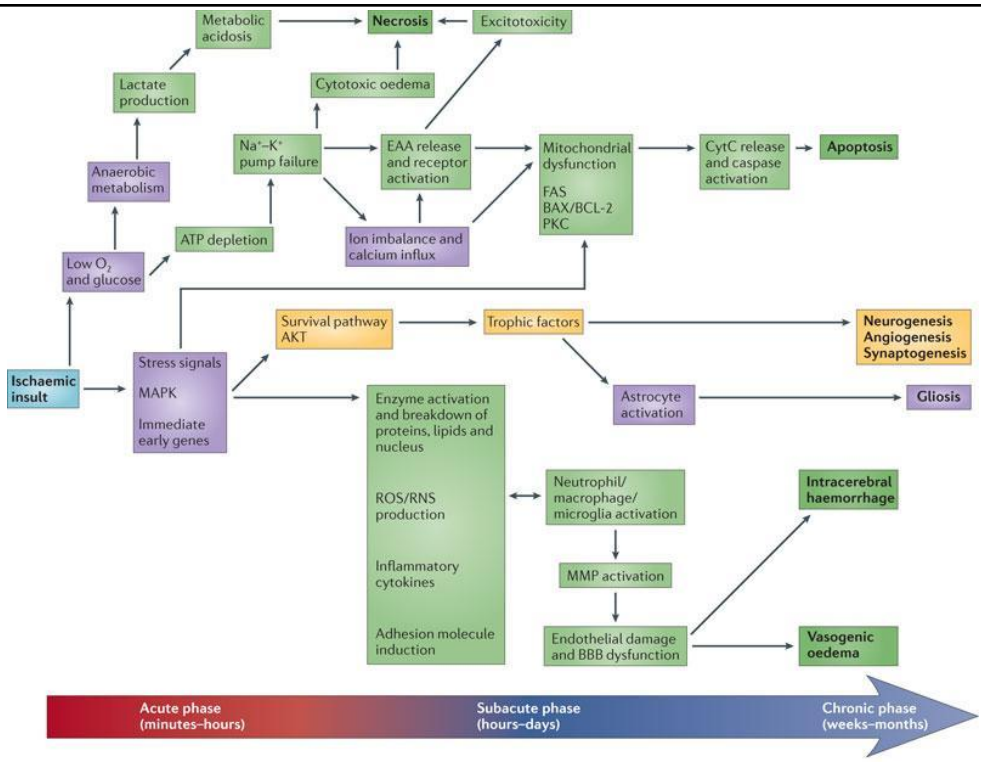
Che – Cardiac Arrest Global Ischemia



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, 123) 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, 332). 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, 386;Clark, 2009, 391). 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, 122). 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, 1725). 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, 625). 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, 1632). 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

Four moderate to large RCTs 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.(Group, 2002, 549) HACA demonstrated improved neurological outcomes (55% versus 39% - statistically significant) in the group receiving 33 °C of hypothermia 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 subjects 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, 557).

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, 2197). The target of 36 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 degrees 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 degrees 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 has reinforced the importance of

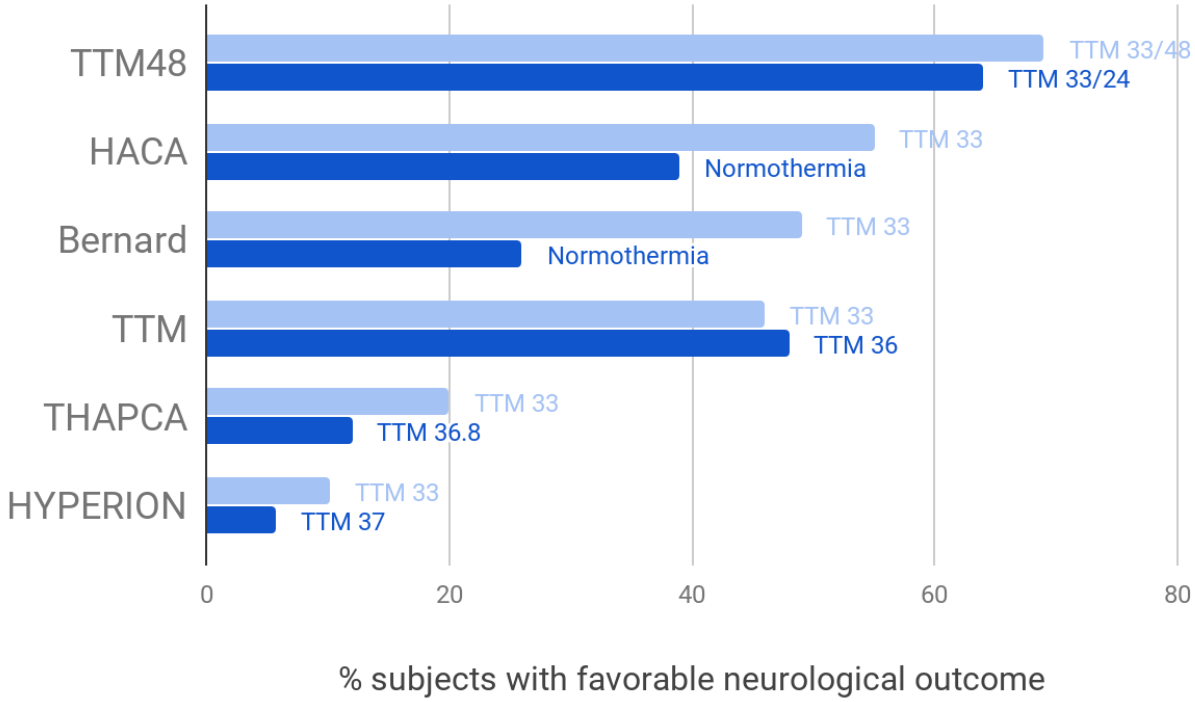
having another study like ICECAP to more robustly confirm efficacy of cooling or to restore sufficient uncertainty in the larger clinical community to permit a future trial with a normothermic control arm.

Recently, (subsequent to the funding of ICECAP) the HYPERION trial enrolled 584 comatose survivors of cardiac arrest from non-shockable rhythms and randomized to treatment with 24 hours of targeted temperature management at 33 degrees versus 37 degrees in 25 French ICU's. 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 These findings buttress the inclusion of patients with non-shockable rhythms cooled as part of standard care in the ICECAP trial, and reinforce the need to confirm the efficacy finding, and seek dose optimization in this patient cohort in the current trial (Lascarrou et al. 2019).

Additional Context

Prior clinical trials have created a sometimes confusing, sometimes nihilistic context relevant to ICECAP. The HACA and Bernard trials published in 2002 compared 33 degrees to normothermia and showed marked efficacy of cooling, but had methodological flaws.(Bernard et al. 2002; Hypothermia after Cardiac Arrest Study Group 2002) The European TTM trial published in 2015 compared 33 to 36 degrees and found that 36 was neither more or less effective.(Nielsen et al. 2013) Outcomes in both arms were similar to the cooling arms in the prior trials. TTM also showed that 36 was neither safer nor easier than 33 degrees. Nevertheless, TTM resulted in some clinicians rejecting the 33 degree target, but changes in practice using higher target temperatures have sometimes been problematic and associated with worse outcomes in observational studies.(Bray et al. 2017) The impact of HYPERION is not clear as this was just published. Two other related trials have also affected understanding. Into this milieu, THAPCA, a pediatric OHCA study comparing 33 to 36.5 was also published in 2015.(Moler et al. 2015) THAPCA was a neutral study despite observing point estimates with 8% absolute (66% relative) higher rates of survival with good neurological outcomes. Then the TTM48 trial was published in 2017, comparing 33 degrees for 24 hours to 48 hours.(Kirkegaard et al. 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 degree 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 to be as good or better than their control arms, such that it remains a promising standard target to be used in ICECAP. Despite a pending 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.



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. Because of this uncertainty, the trial design explores a broad range of durations. The design of this trial is based on a statistical model of the primary endpoint, a weighted 90-day mRS, 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 patients across the (up to) 10 treatment arms. The adaptive randomization algorithm effectively searches for the durations that provide the maximum treatment effect while also allocating patients to learn overall about the shape of the duration response curve.

Efficacy of therapeutic hypothermia was reported in only two randomized controlled trials, and these used different durations of cooling. Cooling was maintained for 12 hours in one trial and for 24 hours in the other, and as a result both 12 and 24 durations of cooling are used routinely in clinical practice. Therefore, to be conservative, the study design initially allocates subjects to only these two standard durations and one longer duration, 48 hours. As the trial continues, if the data suggest increasing efficacy with increasing duration, then the study design incrementally opens longer durations of cooling (up to 72 hours) to randomization. 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, and can open up a 6 hour duration arm. This design minimizes the possibility of subjects 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 6-hour duration arm.

3.1 Clinical Sites

Hub and spoke hospitals from the SIREN network will be enriched with high-potential ancillary Hubs, including some former Resuscitation Outcomes Consortium sites. Approximately 50 hospitals are anticipated to each enroll an average of 9 subjects per year. The enrollment period is anticipated to be 4 years (estimated accrual rate of 38 subjects per month).

3.2 Randomization and allocation

Central computerized randomization by web-based interface will be used. Subjects will

potentially be randomized over the course of the trial to the following possible durations of cooling (in hours): 6, 12, 18, 24, 30, 36, 42, 48, 60, and 72. For the first 200 patients, only the 12, 24, and 48-hour arms will be open to enrollment. These first 200 patients will be randomized 1:1:1 to the 12, 24, or 48-hour arms. After this initial randomization period, subjects will be randomized to treatment arms from 12 through 48 hours in duration (i.e. only the 6, 60, and 72 hour arms will remain closed to enrollment) based on a pre-specified response adaptive randomization algorithm. Randomization probabilities will be updated about every 50 enrollments, or approximately every month based on the expected accrual rate. The 6, 60 or 72-hour arms may be opened for enrollment if the emerging duration-response curve suggests a treatment benefit for those arms. If the shape of the duration response curve from 12 hours is flat or decreasing, the 6 hour arm will be opened for enrollment. If the shape of the duration response curve is increasing to 48 hours, the longer durations will be opened incrementally. Separate randomization probabilities will be developed for the two populations defined by initial rhythm, allowing that the treatment effect across the arms and the optimal duration of cooling may vary between them.

3.3 Blinding / masking

The primary outcome assessment in this trial will always be performed by a study team member blinded to treatment. Subjects themselves will be comatose during the intervention period. It is not practicable to blind the clinical care team or the subject's family to the duration of cooling. Study procedures to prevent inadvertent unblinding include minimized contact between study team members involved in the study intervention and those performing follow up at 3 months through the use of centralized outcomes assessment. Subjects 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.

4. SELECTION AND ENROLLMENT OF SUBJECTS

Comatose adult survivors of out of hospital cardiac arrest that have already been rapidly cooled using a definitive temperature control method (endovascular or surface) will be enrolled in the emergency department or intensive care unit.

4.1 Inclusion Criteria and Rationale

Criteria

- Coma after resuscitation from out of hospital cardiac arrest
- Cooled to <34 °C within 240 minutes of cardiac arrest
- Definitive temperature control device applied
- Age ≥ 18 years
- Informed consent from LAR including intent to maintain life support for 96 hours
- Enrollment (randomization) within 6 hours of initiation of cooling

Rationale

Coma after resuscitation from out of hospital cardiac arrest

Although potentially neuroprotective in other forms of global or focal cerebral ischemia, in human adults therapeutic hypothermia has thus far only been demonstrated to improve outcomes in comatose survivors of out-of-hospital cardiac arrest. The purpose of this study is to attempt to optimize (and confirm) this previously demonstrated effect, and thus is restricted to this population. Patients with in-hospital cardiac arrest have varying degrees of underlying comorbidity for which they were initially hospitalized resulting in unknown and unpredictable variability potentially confounding the study results and are therefore not included.

Cooled to <34 °C within 240 minutes of cardiac arrest

The importance and effect of rapidity of cooling in therapeutic hypothermia is unknown. Furthermore, some data indicate there may be an interaction between rapidity of cooling and duration of cooling that impacts efficacy. Because time to target temperature cannot be prescribed or randomized, and is dependent on myriad factors including system performance and investigator behavior, this study design attempts to minimize this condition as a source of variability by restricting entrance to those with relatively early and consistent induction of cooling performed as part of their routine patient care. The target selected represents a stringent but pragmatic goal that can reasonably be achieved in many patients by either surface or endovascular cooling methods.

Definitive temperature control device applied

Inclusion requires that a definitive temperature control system be applied to ensure that subjects are maintained at the target temperature for the allocated duration. Without such systems temperature lability is common. Inability to maintain the target would result in unplanned crossovers that add unnecessary variability and may dilute treatment effect. See 5.1.2 for the definition of definitive device.

Age ≥ 18 years

The efficacy of therapeutic hypothermia in pediatric patients surviving cardiac arrest is unknown and is currently being studied in an alternative randomized clinical trial. Brain recovery and outcome from cardiac arrest in young children is markedly different from adults and likely represents a distinct medical condition. Furthermore outcome markers used in this study are not validated or readily interpretable in young children.

Informed consent from a legally authorized representative (LAR) including intent to maintain life support for 96 hours

Patients 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 subjects. Therefore, consent must be obtained from an LAR to enroll a patient in the study. LAR 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. The timing of withdrawal of life support is 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 withdrawal of life-sustaining care for patients on the ICECAP protocol are intended to allow each subject a similar exposure to the intervention, and a similar duration of intensive care and opportunity to awaken. Implementation of these principles are detailed in the trial's clinical standardization guidelines.

Only those patients whose LAR intend to maintain life support for 96 hours are enrolled.

Enrollment within 6 hours of initiation of cooling

All subjects will be enrolled within 6 hours of the initiation of cooling because that is the shortest duration of cooling that could be assigned by the study algorithm. Enrollment is defined as the time of randomization.

4.2 Exclusion Criteria and Rationale

Criteria

- Hemodynamic instability (systolic BP < 80 mm Hg despite aggressive management)
- Pre-existing neurological disability or condition that confounds outcome determination
- Pre-existing terminal illness, unlikely to survive to outcome determination
- Planned early withdrawal of life support
- Presumed sepsis as etiology of arrest
- Prisoner

Hemodynamic instability

Patients with hemodynamic instability (systolic blood pressure < 80 mm Hg despite fluid loading/vasopressor use and/or inotropic medication and/or mechanical assist device) are excluded from participation because both their neurological recovery (the study primary outcome) and their ability to undergo the intervention (varying durations of hypothermia) will be confounded by high rates of very early cardiovascular death. Hemodynamic instability usually also systematically precludes the ability to reliably meet the physiological targets established in the clinical standardization plan. Hemodynamic instability is fully defined in the MoP but is generally meant to preclude those with persistent recurrent cardiac arrest, vasopressor refractory hypotension, or profound cardiogenic shock refractory to medical or mechanical support.

Pre-existing neurological disability or condition that confounds outcome determination

Patients whose condition prior to their cardiac arrest would interfere with and preclude subsequent measurement of their neurological recovery using the mRS are unable to inform the primary outcome. Guidance is provided in the MoP, and advice can be obtained from the study hotline investigator, but this is fundamentally a clinical judgment made by a site physician investigator.

Pre-existing terminal illness, unlikely to survive to outcome determination

Patients who already had a diagnosis of a terminal condition prior to their cardiac arrest and who were already thought to be unlikely to survive to 3 months even before having a cardiac arrest cannot inform the primary outcome and are excluded.

Planned early withdrawal of life support

This exclusion criterion is simply the inverse of the sixth inclusion criteria. It is an intentionally redundant criterion listed to reinforce the importance of only enrolling subjects that are likely to

have the opportunity to complete the allocated study intervention.

Presumed sepsis as etiology of arrest

Patients whose index cardiac arrest is presumed to have been caused by advanced septic shock are excluded because of speculation that longer durations of hypothermia may make it harder to successfully treat the underlying sepsis, possibly posing unacceptable safety risks.

Prisoner

Prisoners are excluded because they represent a potentially highly vulnerable population, and because research including this population requires additional regulatory burden.

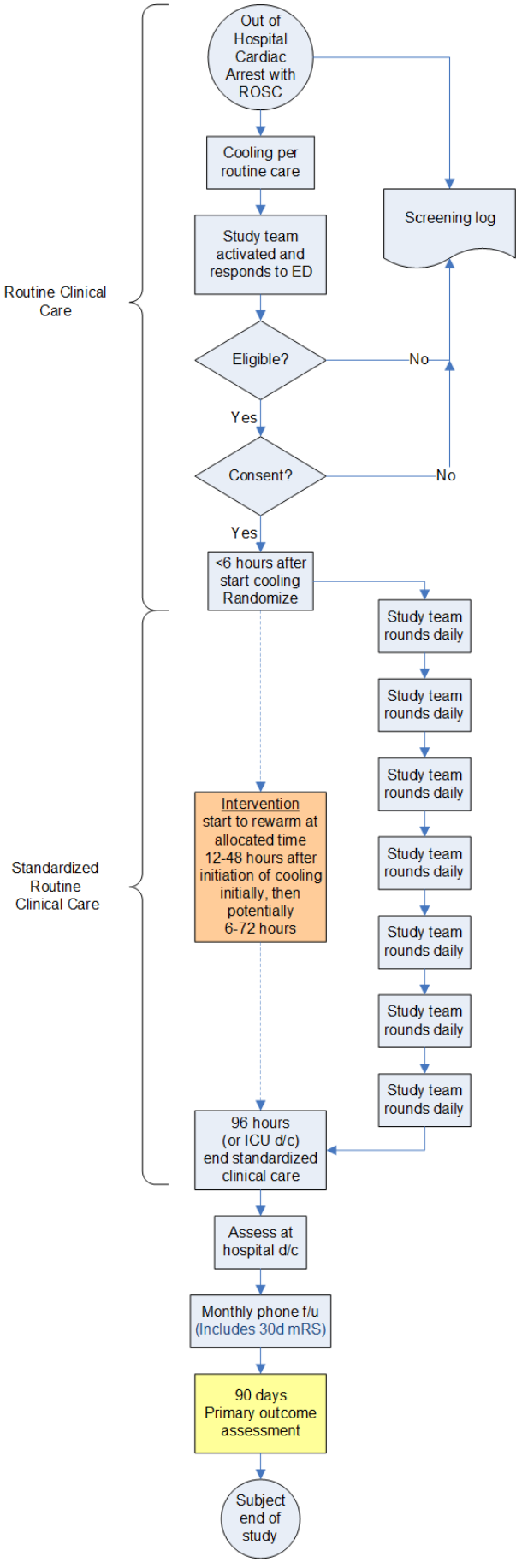
4.3 Study Enrollment Procedures

The on-call study team will respond to the emergency department to screen survivors of cardiac arrest for eligibility, engage eligible patients' legally authorized representatives in an informed consent process, coordinate with the clinical care team, and randomize enrolled subjects. EMS and enrollment case report forms will be completed in the emergency department. In particular, study teams will determine and identify the source for the times of arrest and of initiation of cooling. Temperature and physiologic data collection may be augmented by a study data logger. The study team will follow each subject daily until subject end of study or day 7 for data collection and shepherding of clinical standardization. There will be additional data collection at discharge, and follow up assessment on day 90. Telephone contact between discharge and day 90 will protect against loss to follow up. Computerized adaptive testing will be used at follow up to assess patient reported outcomes and neuropsychological performance at 90 days.

A screen failure log will be completed at all sites that includes all patients with an emergency department diagnosis consistent with cardiac arrest (ICD-10 code of I-46, I-49.01, I47.2, R96, R98, R99, or equivalent codes in another diagnostic system) that are treated in the ED but not enrolled.

4.4 Consent Process

Informed consent to participate in the study will be obtained by study personnel. Because eligible patients for this study will be comatose and unable to participate, the informed consent process will be conducted with the patient's legally authorized representative (LAR) as defined by prevailing local law or regulation. During this process the LAR will receive a verbal explanation (in a language with which they have sufficient fluency) 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 required. The specific risks of participating will be outlined. The LAR will be informed that the optimal duration of hypothermia has not yet been determined, and that participation is completely voluntary and that declining to participate will not adversely affect their loved one's care. The verbal consent process will be supported by review of the informed consent document. All patient questions and concerns will be answered and addressed. Those choosing to enroll their loved one will sign a written informed consent document (paper or e-consent), and copies will be placed in the patient's chart and the site's paper or electronic study binder.

The LAR is also the surrogate decision maker in clinical practice regarding choices related to the timing of withdrawal of life support in the days following resuscitation. The timing of withdrawal of life support is 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, typically as part of the consent process. Consistent study defined criteria for brain death and early termination are provided, but for other scenarios, only those patients whose LAR has indicated, as part of the informed consent process, intent to maintain life support for 96 hours are enrolled.

4.5 Randomization Process

The objective of subject randomization is to prevent possible selection bias by providing random treatment assignment to each subject, and to prevent accidental treatment imbalances for the known prognostic variables.

Randomization will be conducted through the WebDCU web interface. 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.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The intervention will be random allocation to duration of cooling after cardiac arrest. Cooling in the study will be by a definitive temperature control method to a target temperature of 33 °C. Any endovascular or surface cooling system with closed loop feedback will be allowed. Duration of cooling will be measured from the time that definitive cooling is initiated in the hospital, as indicated by placement and activation of a definitive cooling device (see 5.2 for definition). Cooling by other means may be initiated by EMS or in the emergency department as per local protocols for standard care. Eligibility will require that a temperature of <34 degrees be obtained by 240 minutes after cardiac arrest. After the allocated duration of cooling is completed, controlled rewarming will be performed. Rewarming to a temperature of 36.5 °C will occur over the shorter of 24 hours or a rewarming period equal to the allocated duration of cooling. Definitive cooling devices may be used for maintenance of normothermia after rewarming is complete.

5.2 Definition of Definitive Device

Definitive device is defined as a closed loop feedback endovascular or surface cooling device that can be used to both induce and maintain therapeutic hypothermia.

5.3 Temporary Cessation of Cooling

In certain instances it may be necessary to disconnect the subject from the definitive cooling device such as during patient transport to and from diagnostic or therapeutic procedures. Interruptions in active temperature management should be minimized but brief periods of less than 1 hour are allowed as required. For longer periods of potential interruption, the definitive cooling device should accompany the patient and be re-instituted during the procedure to avoid temperature excursions. Core temperatures should be documented every 30 minutes during interruptions in cooling.

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: avoiding hypotension, avoiding hypoxia, controlling rebound hyperthermia, treatment of seizures, treatment of shivering, management of sedation and paralysis, prognostic testing, and defining and treating infections. Clinical standardization guidelines define that neurologic prognostication leading to withdrawal of life support is only allowed after 96 hours. Details

related to neurological prognostication are provided in the clinical standardization guidelines.

6. OUTCOMES

6.1 Primary Efficacy Outcome

The primary outcome measure will be the modified Rankin scale at 90 days after return of spontaneous circulation. The mRS will be analyzed as a weighted score incorporating both the proportion of subjects achieving a good neurological outcome and degree of residual functional impairment among those with good neurological outcomes. The mRS will be determined primarily by a central assessor at the CCC by telephone or telepresence, and secondarily by a site investigator or research staff certified by the CCC in the performance of the scale. In addition, this individual must be blinded to the treatment group assignment for the subject.

6.2 Safety Outcomes

The primary safety outcome is all cause mortality at 90 days. All cause mortality is selected because it incorporates 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 reflect any permanent morbidity and are therefore secondary.

Secondary safety outcomes include active monitoring for severe adverse events (SAEs) throughout the trial. Specific SAEs are anticipated to be related to therapeutic hypothermia. These selected SAEs include pneumonia, other infections (including urinary tract infections and bacteremic sepsis), malignant cardiac arrhythmia (cardiac arrest, ventricular fibrillation, ventricular tachycardia, atrial arrhythmias with hemodynamic compromise), seizures, neurological worsening, electrolyte abnormalities, venous thrombotic disease, and coagulopathies. The occurrences of these safety outcomes by treatment arm will be reported in the periodic safety reports to the DSMB. We will also report counts and proportions of mortality for each treatment arm (by rhythm), along with the number of SAEs that are probably or definitely related to intervention.

6.3 Secondary Efficacy Measures - Patient Reported Outcomes

Neuro-QOL is a set of self-report measures that assesses the health-related quality of life (HRQOL) of adults and children with neurological disorders.

Neuro-QOL is comprised of item banks and scales that evaluate symptoms, concerns, and issues that are relevant across disorders - along with measures that assess areas most relevant for specific patient populations.

The Neuro-QOL tool includes carefully developed and rigorously calibrated comprehensive item banks of patient-reported outcomes that are relevant to people with neurological disorders. The item banks include: Physical Health (e.g., Mobility; Fine Motor/ADL; Fatigue; Sleep

Disturbance), Social Health (Ability to Participate in Social Roles & Activities; Satisfaction with Social Roles & Activities), Emotional Health (e.g., Depression, Anxiety, Stigma, Positive Affect & Well-Being; Emotional-Behavioral Dyscontrol), Cognitive Health (ie, Cognitive Function; Communication).

Item pools for the Neuro-QOL measurement system were developed through a process of engaging patients and other stakeholders (e.g., medical providers) to identify possible domains and items of interest/importance through focus groups, individual interviews and survey research. Existing items were identified, evaluated, and revised from existing items from the published literature. New items were written to fill identified construct gaps. Items were classified into domain-specific bins for conceptual and organizational purposes. Items were reviewed and revised using patient perspectives (e.g., cognitive interviews) and stakeholder judgment (expert item review) to assure understanding, relevance, and clarity. The process also included comprehensive cultural/linguistic review of items to ensure ease of translatability, universality of concepts and clarity of phrasing, and multi-step comprehensive translation of items into Spanish language.

6.4 Secondary Measures - Neuropsychological Outcomes

Neuropsychological (NP) testing provides an opportunity to examine, with great sensitivity, potentially subtle but meaningful differences in outcomes between treatment groups.

The measures chosen include focused traditional measures that have proven reliability and validity for use in trials of patients with cardiac arrest(Becker, 2011, 2158). In addition, we have selected measures that comprise the cognitive domain of the NIH Toolbox(Gershon, 2013, S2). This particular combination of tests is designed to capitalize on both the advantages of using traditional paper and pencil tests as well as those advantages unique to the NIH Toolbox tests; including computerized administration (which allows precise and reliable timing), the availability of characterized composite scores, and the anticipation that the Toolbox cognitive battery will be commonly utilized in future neurological trials allowing for cross trial comparisons and aggregation of trial results.

Furthermore, this particular combination of tests has been carefully designed to be comprehensive, with special emphasis on measures of domains that have been found to be most significantly impacted in previous studies of cardiac arrest, namely learning, memory, attention and executive functioning.(Lilja, 2015, 1340;Nichol, 2015, 74) Select traditional paper and pencil tests have been chosen to both supplement and complement the standard NIH Toolbox measures. Specifically, the standard NIH Toolbox includes measures of episodic memory, executive functioning (specifically flexibility and inhibition), vocabulary comprehension, reading, processing speed and working memory. The traditional paper and pencil measures including Trail Making Test (attention and executive functioning, flexibility), and

Stroop Test (executive functioning, inhibition) were chosen to complement the newer NIH Toolbox tests in domains of particular interest. Likewise, traditional tests including the Rey Auditory Verbal Learning Test (verbal memory) and the Controlled Oral Word Association Test (verbal fluency) were chosen because these particular domains are not tested via the NIH Toolbox.

Domain	Measure	Admin.Time (mins)
NIH Toolbox Tests		
Executive – Flexibility	Dimensional Change Card Sort Test	4
Executive – Inhibition	Flanker Inhibitory Control and Attention	3
Memory – Episodic	Picture Sequence Memory Test	7
Processing Speed	Pattern Comparison Processing Speed	3
Working Memory	List Sorting Working Memory Test	7
Language - Reading Decoding	Oral Reading Recognition Test	3
Language - Vocabulary Comprehension	Picture Vocabulary Test	4
Processing Speed - Working Memory	Oral symbol digit test (uses Toolbox App)	3
Traditional Neuropsychological Tests		
Memory – Verbal	Rey Auditory Verbal Learning Test	10
Attention (A). Executive – Flexibility (B)	Trail Making Test A and B	7
Executive – Inhibition	Stroop Test	5
Language – Verbal Fluency	Controlled Oral Word Association Test	4

The NIH Toolbox tests can be subdivided into crystallized (i.e., general knowledge base) and fluid (i.e., thinking and reasoning) measures, providing information about both patients' premorbid and current functioning. A fluid composite score will be obtained for fluid measures (i.e., those expected to change with injury). A stability composite score will be calculated for crystallized measures (i.e., those not expected to change with injury). The use of two distinct composite scores rather than combining all into a single composite measure will result in both greater sensitivity of the fluid composite as well as provide us with a separate estimate of premorbid functioning.

Neuropsychological testing has been limited to 1 hour to enhance patient compliance and

minimize patient fatigue. Patients who cannot tolerate the complete battery of tests and interviews in one session may be scheduled for a second session.Study participants will be evaluated 90 days following randomization. Study team members responsible for neuropsychological outcome assessment will be trained and certified per study procedures.

6.5 Schedule of Assessments

Form #	CRF	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Hospital Discharge	Day 30 +/- 15 days	Day 90 +/- 15 days	End of Study
N/A	Subject Enrollment	XM											
F101	Eligibility	XM											
F102	Randomization	XM											
F296	Demographics	XM											
F502	EMS Code Review	XM											
F506	ED Code Review and Treatment	XM											
F106	Medical History	X											
F117	Vital Signs	X											
F105	Laboratory Tests	X											
F509	Brain Imaging	ORM	ORM	ORM	ORM	ORM	ORM	ORM	ORM	ORM			
F175	Full Outline of Unresponsiveness Score (FOUR)		XRM	XRM	XRM	XRM	XRM	XRM	XRM				
F501	Daily Temperature Log		XM	XM	XM	XM	XM	XM	XM				
F505	Daily Seizure Monitoring		XM	XM	XM	XM	XM	XM	XM				
F507	Daily Electrolye Log		XM	XM	XM	XM	XM	XM	XM				
F510	Daily Selected Medications		XM	XM	XM	XM	XM	XM	XM				
F508	Daily Glucose Transgressions		XM	XM	XM	XM	XM	XM	XM				
F503	Daily Physiological Assessments		XM	XM	XM	XM	XM	XM	XM				
F504	Neuro Prognostication/Brain Death			OR	OR	OR	XRM	OR	OR	OR			
F123	Hospital Discharge									XM			
F144	Modified Rankin Scale										X	X	
F136	Controlled Oral Word Association Test											XM	
F152	Stroop Color and Word Test											XM	
F298	Rey Auditory Verbal Learning Test											XM	
F154	Trail Making											XM	
F511	NIH Tool Box Central Data Entry											X^	
F104	Adverse Event		ORM	ORM	ORM	ORM	ORM	ORM	ORM	ORM	ORM	ORM	
F127	Med Watch		OR^{C1}	OR^{C1}	OR^{C1}	OR^{C1}	OR^{C1}	OR^{C1}	OR^{C1}	OR^{C1}	OR^{C1}	OR^{C1}	
F126	End of Study												XM

X = Required
O = Optional
R = Repeatable
M= Monitor verfication required
C1 = MedWatch is required per SM review
^ = Completed centrally

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 AEs occurring through the fourth study day and all serious adverse events (SAEs) occurring until participation in study has ended are recorded on the online AE case report form (CRF) through the WebDCU™. The Hub 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. Non-serious AEs are collected through the fourth study day. All non-serious AEs occurring through the fourth study day 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 site PI is responsible for the monitoring and follow-up of AEs until resolution (or end of study for that subject) and appropriate documentation in the subject 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 subject, premature withdrawal from the study by the subject, or subject'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 subject'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 subject must be entered to allow for timely review by the medical safety monitors (MSMs). Medical safety monitoring will be conducted as detailed in the 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 are likely and anticipated and will be closely tracked consistent with previous guidance regarding AE reporting.

- Pneumonia 40-60%
- Other infections (including UTI and bacteremia) 17-40%
- Malignant cardiac arrhythmia 46-65%
- Seizures 20-40%
- Neurological worsening 30-50%
- Electrolyte abnormalities 70-80%
- Venous thrombotic Disease 10-20%
- Coagulopathies 10-20%

8. TRAINING

The SIREN network utilizes multiple methods to optimize education and training of site personnel including 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 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. 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 meetings will occur periodically. In addition, ICECAP includes the following specific training programs:

Hypothermia administration: To ensure the safe and effective cooling of subjects, successful previous use in a sufficient number of non-study patients will be required to ensure competency in the technical aspects of the definitive device placement, cooling protocol, control of shivering, rewarming protocol, and equipment use. The CCC will evaluate the existing protocols of study sites already using hypothermia as part of site initiation. For study sites that are newly incorporating therapeutic hypothermia or targeted temperature management into standard care, we will also request (in addition to their existing protocol) four redacted hospital charts of patients who have been treated with temperature control devices.

Clinical standardization: A training program will teach the consensus standardization guidelines created for ICECAP to clinical care teams at participating sites to reduce variability in standard practice.

Outcomes assessment training: To address the need for certification in the patient reported outcome tools and the neuropsychological outcome metrics. Training will involve didactic and hands-on training with the computer testing equipment.

Periodic investigator meetings: To address any impediments to subject enrollment, discrepancies in treatment between centers, and protocol violations of concern. 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 1800 patients. The primary endpoint is a weighted modified Rankin Score (mRS) measured at 90 days after the return of spontaneous circulation. The design of this trial is based on a statistical model of the mean weighted 90-day mRS, i.e. the duration response curve. This trial will enroll patients with and without initially shockable rhythms. All subjects will have already been rapidly cooled 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 6, 12, 18, 24, 30, 36, 42, 48, 60, or 72-hours of cooling.

Within each of the two rhythm type populations, patients will be adaptively randomized to a cooling duration. The trial will determine in each of two populations the shortest durations of cooling that provide the maximal treatment effect and whether increasing durations of cooling are associated with better neurological outcomes. In the absence of a normothermia control arm, an increasing treatment effect across some set of durations would imply efficacy of cooling versus no cooling. In this section we provide a detailed overview of the statistical design and operating characteristics. Further details are provided in the Study Design and Simulation Report in Appendix iii.

9.1 Primary Endpoint

The primary endpoint is the 90-day mRS. The primary analysis weights the 7 possible 90-day mRS values. Let M90 be the 90-day mRS. The weight for each possible mRS value is

$$W(M_{90}) = \begin{cases} 10 & M_{90} = 0 \\ 9 & M_{90} = 1 \\ 8 & M_{90} = 2 \\ 6 & M_{90} = 3 \\ 0 & M_{90} = 4,5,6 \end{cases}$$

For each treatment arm, we model the mean weighted outcome.

9.2 Primary Analysis

The primary analysis of the trial will model the mean weighted mRS for each treatment arm. The primary analysis is conducted on the intent to treat (ITT) population and is conducted separately for each rhythm type. The primary analysis will answer two questions. We will identify the most likely target duration, where the target duration is the shortest duration that achieves the maximum treatment effect (Objective A). We will also determine whether the efficacy of any duration is superior to any shorter duration of cooling (Objective B). In the

absence of a normothermia control arm, if increasing durations of cooling are associated with an increasing treatment benefit in at least one part of the duration-response curve, then this would imply that cooling is effective versus no cooling in improving neurological outcomes.

1. Objective A: The most likely target duration for rhythm type r is h*, where h* is the treatment arm for which the posterior probability that h is the target duration is maximized.
2. Objective B: The conclusion that cooling duration *h** is effective in rhythm type *r* is made if the posterior probability that the mean weighted 90-day mRS for arm *h** is greater than the mean weighted 90-day mRS for a duration shorter than *h**, is greater than 0.975.

9.3 Statistical Models

9.3.1 Duration-Response Curve Model

We model the mean weighted 90-day mRS 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. For each rhythm type a separate and identical instance of the model is used; therefore we present the details for a single instance. Let θ represent the mean weighted mRS and h represent the treatment arm.

The duration-response model is:

$$\theta_h = \begin{cases} \beta_0 + \beta_1 h^{\beta_3} & h \le \gamma_1 \\ \beta_0 + \beta_1 \gamma_1^{\beta_3} & \gamma_1 < h \le \gamma_2 \\ \beta_0 + \beta_1 \gamma_1^{\beta_3} - \beta_2 (h - \gamma_2)^{\beta_4} & \gamma_2 < h \end{cases}.$$

We refer to the parameters γ_1 and γ_2 as the change-points. The parameter γ_1 represents the change point between the increasing phase and the plateau phase. The duration response curve is "flat" between γ_1 and the second change point γ_2. γ_2 represents the change point between this plateau phase and the decreasing phase, so the duration response curve is then decreasing after γ_2. An important aspect of the model is that the change-points can be smaller than the minimum cooling duration, *h*=1 (6 hours), or greater than the maximum cooling duration, *h*=10 (72- hours), thus allowing the curve to be increasing, decreasing, or flat over the entire range of cooling. The model has the following constraints: $\gamma_1 < \gamma_2$ and $\beta_1, \beta_2, \beta_3, \beta_4 > 0$. The γ_1 parameter is interpreted as the theoretical optimal duration of cooling, the shortest

duration that achieves the maximum treatment effect. We define the *target duration* based on γ_1 and γ_2. The target duration is the shortest duration greater than γ_1, if γ_1 is less than 72-hours, or the longest duration if γ_1 is greater than 72-hours.

9.3.2 Longitudinal Model of 90-day mRS

At each interim analysis there will be subjects who have not yet reached 90-days and will therefore not have a final mRS outcome. We use the 30-day mRS value as possibly predictive of the 90-day mRS, allowing subjects with this earlier measurement to be included in the analyses of the 90-day measurement. This modeling is referred to as the longitudinal model. The longitudinal model allows for learning the relationship between the 30-day and 90-day mRS values as the accruing empirical data is used to determine the strength of the association between the two values for each treatment arm and rhythm type. Analyses of the 90-day mRS values are performed with multiple imputation from the longitudinal model for patients with an unknown 90-day mRS value.

The longitudinal model maps the 7 possible 30-day mRS values to the 7 possible 90-day mRS values. We use a Markovian structure for the "transitions" from the 30-day mRS state to the 90-day mRS state. The probability vectors have separate posterior distributions by treatment arm and rhythm type. The observed transitions for the same treatment arm *h* and rhythm type *r* contribute fully to that particular posterior distribution, while the transitions from other treatment arms and for other rhythm types contribute 1/4 of their full weight to the posterior distribution. Thus, there is borrowing of partial information from other treatment durations and the alternate rhythm type.

9.4 Adaptive Randomization

The first 200 patients will be equally randomized to the 12, 24, and 48 hour arms. After this initial randomization period, adaptive randomization will begin. During the response adaptive randomization stage, separate allocation schemes are created for each rhythm type. Randomization probabilities to each treatment arm are weighted according to the posterior probability that each treatment arm is the target duration and randomization probabilities will be updated about monthly. The goal of the adaptive randomization is to allocate subjects to the arms most likely to be the target duration, but also to learn effectively about the duration-response curve.

The probability that a treatment arm is the most likely target duration for a rhythm type is

$$\Pr_{h,r}$$.

The randomization probabilities for each treatment arm within each rhythm type is proportional to $\Pr_{h,r}$.

$$q_{h,r} = \frac{\Pr_{h,r}\delta_{h,r}}{\sum_{l=1}^{10}\Pr_{l,r}\delta_{l,r}} \text{ for } h = 1,2,\ldots,10$$

The treatment arms for 6-hours (h=1), 60 hours (h=9), and 72 hours (h=10) will initially be closed, but may be later opened. If a treatment arm is open we set $\delta_{h,r}$ = 1, and if a treatment arm is closed we set $\delta_{h,r}$ = 0. Therefore, the adaptive allocation scheme favors the arms most likely to be the target duration, but also favors arms with a greater variability (uncertainty) around the primary endpoint or a smaller sample size.

The 6-hour duration treatment arm will be opened for a rhythm type *r* if there are more than 100 subjects enrolled across all arms in that rhythm type and there is at least a 0.33 probability that 6 hours is the target duration for that rhythm type. The 60 and 72- hour duration treatment arms will be opened incrementally. These arms open on either rhythm type if there is at least a 0.33 probability that the target duration for that rhythm type is at or above that next shorter duration.

9.5 Interim Monitoring for Futility

Interim analyses begin after 200 patients have been enrolled and will occur about monthly. At each interim analysis, the trial may stop for futility if no cooling duration greater than 6 hours is found to be more effective than the 6-hour duration. Futility will be assessed separately for each rhythm type. Therefore, the trial could be declared futile for one rhythm type, and yet continue to enroll subjects of the opposite rhythm type. If both rhythm types are not stopped for futility, the trial will continue to enroll to the maximum sample size of 1800 patients. Specifically, a rhythm type will stop for futility if

1. At least 50 patients have been randomized to the 6- hour duration arm for that rhythm
2. There is at least a 50% probability that the 6- hour duration is the target duration.

9.6 Sample Size

This trial will enroll a maximum of 1800 patients. We expect patients will be accrued at the rate of 450 patients per year. Therefore, we expect this trial will be completed within 5 years. Interim analyses for futility will begin when about 200 subjects have been enrolled and will be conducted about monthly or about every 50 subjects. If the trial is not stopped early for futility,

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 1800 patients. Sensitivity of operating characteristics to a range of sample sizes was also simulated.

9.7 Power

There are two components of the primary analysis and we define power for each. The following procedure is used to define power as related to the selection of the target duration (objective A). For each simulated scenario, we define up to three durations as clinically accurate selections. These include duration set in the scenario input as the shortest duration that achieves the maximum treatment effect and up to two more durations that are clinically very similar. To be considered sufficiently similar these durations must be within 12 hours of the set optimal duration and must achieve at least 70% of the maximum treatment effect. We define power for this component of the primary analysis as the probability any one of these three clinically acceptable durations is selected as the target duration. The following procedure is used to determine if the efficacy of cooling versus no cooling is implied (objective B). For each simulated scenario we test whether the treatment effect for any duration is greater than for a shorter duration. In certain situations, the design may have convincing evidence of duration response, but may not be able to definitively choose a duration (e.g. a gently upsloping with plateau scenario.) Conversely, the design may be able to choose a target duration, but may not be able to definitively demonstrate duration response (example: true target duration 12 hours, but end trial results are insufficient to declare 12 hours is superior to 6 hours). We define power for this objective as the probability of concluding that there is a positive duration response curve in the simulated scenarios in which the scenario input includes any increase in treatment effect with increasing duration, regardless of the target duration and whether it is correctly selected.

Our reference scenario assumes a modest benefit of cooling at 18 hours, followed by a plateau in the treatment effect through 72 hours. This reference scenario is based upon conservative interpretation of the two randomized controlled trials that provide the basis for current therapeutic recommendations. These trials used 12 and 24 hours durations of cooling respectively to achieve absolute increases of 16-23% in the proportion of patients with a good neurological outcome after cardiac arrest with an initial shockable rhythms compared to controls without cooling. In the reference scenario we assume an approximately 16% treatment effect for both shockable and non-shockable rhythms. The assumed treatment effects for the reference scenario are detailed in the trial design and simulation report in the appendix. In this scenario, the target duration is 18 hours, but 24 and 30 hours would also be considered clinically acceptable. They are each within 12 hours of the target duration arm and offer the same treatment effect. With a maximum of 1800 patients, assuming 50% are in each rhythm

type, this trial will select one of the three clinically acceptable target durations with 70% probability and will determine that the duration-response curve is positive with 31% probability. This trial will open enrollment to the 6 hour duration arm with 58% probability and will stop for futility with only 3% probability.

Sample size selection is also detailed in the Study Design and Simulation Report. Sensitivity of the power to changes in maximum sample size was determined by simulation of the reference scenario and four additional variations of the reference, altering target duration and rhythm type balance, for maximum sample sizes ranging from 1500-2300. In the reference scenario, the power for selection of duration at a maximal sample size is 80%, and the power for determination of a positive duration response is 77%. Variation in the operating characteristics with sample size was modest, and 1800 was selected as the most practicable maximum sample size that achieved approximately 80% or better power.

9.8 Type I error control

We define Type I error as the probability, across all doses, that cooling is considered effective when the duration response curve is actually flat or negative. The final analysis of a 97.5% cut-off for the posterior probability will be used and was selected as an appropriately judged threshold for success. The design of this trial does not increase type I error. There is no early stopping for success in the trial, nor is there selection of patient subgroups. The question of type I error control is then whether the method for the primary analysis maintains control of type I error. Under the null hypothesis, that all durations have the same treatment effect, the simulated type I error may depend on the relative probabilities of the mRS outcomes, the accrual rates, the longitudinal pattern of 30-day mRS to 90-day mRS, and the proportion of subjects in each rhythm type. We simulated a range of Type I error scenarios (13 null cases detailed in the Study Design and Simulation Report) and the simulated type I error is typically smaller than 0.025 (a one-sided type I error). However, we will also create a plan to determine the type I error operating characteristic for the trial based on the parameters actually observed in the trial. At the conclusion of the trial, the design will be re-simulated using the actual subject data. Within each rhythm type all subjects will be placed in a list with their treatment arm identifier removed. Subjects will be randomly sampled or “bootstrapped” from this list and sham durations will be assigned. This creates a setting where, theoretically, all durations have the same treatment effect as all subjects are drawn from the same pool. The post-trial simulation type I error will be reported as the type I error for the trial. The 97.5% threshold will be used for primary success, regardless.

9.9 Intention to treat and missing data

The primary analyses will be based on the intent-to-treat ITT population. The ITT patient population will include all patients randomized, where patients 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 subjects to follow up and to prevent missingness of data. Previous experience in the network has demonstrated very low rates of missing data. Any subjects that are missing or withdraw from the study and have an unknown 90-day mRS will be included in the analyses of the primary endpoint with multiple imputation according to the longitudinal model previously described.

9.10 Pre-planned secondary analyses

Further details of the pre-planned secondary analyses will be available in the full statistical analysis plan. Analyses for important subgroups (gender, age strata, pre-existing comorbidities including diabetes, malignancy, prior neurological disease) will be conducted within each rhythm stratum for the primary endpoint and secondary endpoints identified in the statistical analysis 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 subject visit calendar, subject 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 subjects 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 on the ICECAP website 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 subject randomization, data entry, data validation, project progress monitoring, subject tracking, 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 patients. A study team member will log onto the WebDCU™ ICECAP web-based system using a unique username and confidential password. When a subject is deemed eligible, WebDCU™ will generate a unique subject ID without storing any personal identifying information. The study team member will then enter the required subject information, including presenting rhythm and inclusion/exclusion criteria. The computer program will check for accuracy and completion of this information prior to selecting the intervention assignment for that subject based on current randomization vectors. The subject 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 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 DCCwill 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 subjects. Examples of available reports include subject enrollment logs, basic subject 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 is 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 patient-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 check up 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 ups 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 Institutional Review Board (IRB) will be used for ICECAP pursuant to NIH policy. The SIREN Emergency Research CIRB will be the IRB of record for all 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 subjects in this trial will not have the capacity to provide informed consent. An informed consent process including written documentation from a legally authorized representative will be required. The process may be augmented by multimedia informational tools and an e-consent platform created for the study. 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 96 hours of life support if that is consistent with the wishes of a patient's family or LAR. An important element of the informed consent process will be to identify and only include patients for whom the family or LAR initially intend to pursue at least 96 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 subject 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 subject, 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 subject'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 subjects are protected.

12. STUDY ORGANIZATION

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

The SIREN Clinical Coordinating Center at the University of Michigan will provide overall project management for the trial. Participating sites will be involved through an amendment to the ongoing master agreement between the SIREN CCC and SIREN Hubs. Hubs are responsible for subcontracting with and organizing clinical spoke sites. The SIREN Data Coordinating Center will provide all data management and analytic functions under their own bundled award.

Daily management of the trial will be facilitated by weekly meetings of an operations working group and as a standing scheduled agenda item in weekly meetings of the SIREN operations committee. Strategic decision-making will take place in an executive committee incorporating all participants in the trial leadership.

The ICECAP clinical standardization team will work to refine and train clinical personnel in the consensus standard treatment strategies, and will review transgression data.

The SIREN human subjects protection working group will review and advise on the informed consent processes in this potentially vulnerable population.

A publications committee will coordinate and support communications about the trial in the published medical literature.

An ICECAP ancillary trials working group 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 studies cannot interfere with the scientific purpose or successful completion of the parent trial. Proposed ancillary studies must be approved by the trial and SIREN leadership, the DSMB, and the NIH.

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.

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LINK TO PROTOCOL APPENDICES

PROTOCOL CHANGES

	Post-DSMB approval version D December 30, 2019		Version 1 April 30, 2020	
Section	**Page**	**Previous text**	**Page**	**New text**
	1		1	Study design and planning supported by U01NS073476 from The NIH OD and the FDA
	1	Post-DSMB approval Version d (December 30, 2019) Month Day, Year	1	Protocol Version 1
Synopsis	8	Approximately 50 hospitals	8	Approximately 50 or more hospitals
Synopsis	9	Randomization probabilities will be updated monthly, or approximately every 38 patients based on the expected accrual rate.	9	Randomization probabilities will be updated approximately every 50 enrollments, or approximately every month based on the expected accrual rate.
Synopsis	10	This trial is expected to require an IDE from the Food and Drug Administration.	10	This trial is conducted under an IDE from the Food and Drug Administration.
3.2	21	...will be updated monthly, or approximately every 38 patients...	21	...will be updated about every 50 enrollments, or approximately every month...
3.3	21	Those performing outcome assessments will be queried about potential inadvertent unblinding at the time of assessment.	21	
4.1	23	The following principles will guide withdrawal of care for patients on the ICECAP protocol: No withdrawal for poor neurological prognosis is allowed within 96 hours. Withdrawal of life support for non-neurological reasons is allowed. Between 72 and 96 hours, withdrawal of life support is permissible for patients meeting institutional brain death criteria. After three days, withdrawal of life support is permissible for patients whose exam shows GCS motor of 1 or 2, have no corneal reflexes, and no pupillary response, with findings sustained for 24 hours, without any	23	The principles guiding withdrawal of life-sustaining care for patients on the ICECAP protocol are intended to allow each subject a similar exposure to the intervention, and a similar duration of intensive care and opportunity to awaken. Implementation of these principles are detailed in the trial's clinical standardization guidelines.

		sedation or paralytics (intact train of 4). Exams must be performed by a qualified neurological examiner (those qualified to perform brain death exams at that institution).		
4.3	26	...day 9...	26	...day 7...
4.3	26	...at least monthly...	26	
4.3	26		26	figure updated, “t=0” deleted
4.5	27	...needed perform...	27	...needed to perform...
4.5	27	...statistical programmer….	27	...statistical team...
5.4	28	...will include defined parameters for malignant prognostic findings. Early withdrawal of life support will only be clinically recommended when these parameters have been met after 96 hours: After three days, withdrawal of life support is permissible for patients whose exam shows GCS motor of =<4, have no corneal reflexes, and no pupillary response, with findings sustained for 24 hours, without any sedation or paralytics (intact train of 4). Exams must be performed by a qualified neurological examiner (those qualified to perform brain death exams at that institution).	28	...define that neurologic prognostication leading to withdrawal of life support is only allowed after 96 hours. Details related to neurological prognostication are provided in the clinical standardization guidelines.
6.2	30	...related to mortality.	30	...related to intervention.
6.3	31	...insure easy of translatability...	31	...ensure ease of translatability...
6.4	32	...Stroop Test (executive functioning, inhibition) and Digit Symbol (attention and working memory) were chosen...	32	… and Stroop Test (executive functioning, inhibition) were chosen...
6.4	32	table - traditional - Digit Symbol Coding	32	table - NIH toolbox - Oral Symbol Digit
6.5	34		34	updated table with specific CRF’s
7.1	35	...AE’s occurring within 24 hours of treatment...	35	...AE’s occurring through the fourth study day...
7.1	35	All non-serious AEs occurring within 24 hours of treatment must...	35	Non-serious AEs are collected through the fourth study day. All non-serious AEs occurring through the fourth study day must...

9.3.2	40	...contribute 1/3 of their full weight...	40	...contribute 1/4 of their full weight...
9.4	40	...updated monthly...	40	...updated about monthly...
9.4	40	Let the number of subjects enrolled on treatment duration arm h for rhythm type r be nh,r. The posterior variance of the mean weighted 90-day mRS for each treatment arm and rhythm type is V(θh,r). The probability that a treatment arm is the most likely target duration for a rhythm type is [formula]. A variance component, Vh,r , is constructed for each treatment duration arm within each rhythm type. The variance component is [formula] for h=1,2,…,10 and r = 1,2.	40	The probability that a treatment arm is the most likely target duration for a rhythm type is [formula].
9.4	41		41	updated formulas
9.4	41	...if there are at least 300 subjects enrolled across all arms...	41	...if there are more than 100 subjects enrolled across all arms...
9.4	41	These arms open to both rhythm types simultaneously if there are at least 10 subjects on the next shorter duration across both rhythm types and, for at least one of the rhythm types, there is at least a 0.33 probability that the target duration for that rhythm type is at or above that next shorter duration.	41	These arms open on either rhythm type if there is at least a 0.33 probability that the target duration for that rhythm type is at or above that next shorter duration.
9.5	41	...occur monthly…	41	...occur about monthly...
9.6	42	...when 250 patients...	42	...when about 200 subjects...
9.10	44	...and secondary endpoints.	44	...and the secondary endpoints identified in the statistical analysis plan.
10	47-8	...SDMC...	47-8	...DCC...
10.4	46	...study coordinator...	46	...study team member...
10.4	46	...presenting rhythm, age, and...	46	...presenting rhythm, and ...
10.5	46	The Reporting Module is developed based on input from the EC and includes reports on enrollment, SAEs, CRF processing, and subject progress.	46	
10.5	46	...will provide the EC and authorized...	46	...will provide authorized...
11.1	49	IRB approval for this trial must be	49	IRB approval for this trial must be

		approved and maintained...		obtained and maintained...
14.	53		53	Lascarrou, Jean-Baptiste, Hamid Merdji, Amélie Le Gouge, Gwenhael Colin, Guillaume Grillet, Patrick Girardie, Elisabeth Coupez, et al. (2019). "Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm." N Engl J Med 381(24):2327-2337
Protocol Changes			55	This table added