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

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

Clinical Standardization Guidelines

Version 1

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TABLE OF CONTENTS

APPENDICES **22**

Table of Abbreviations

AE	Adverse Event
AHA	American Heart Association
BP	Blood Pressure
CARES	Cardiac Arrest Registry to Enhance Survival
CCC	Clinical Coordinating Center
CRF	Case Report Form
DBBE	Department of Biostatistics, Bioinformatics and Epidemiology
DCR	Data Clarification Request
DCU	Data Coordination Unit
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EEG	Electroencephalogram
EMS	Emergency Medical Services
ET	End Tidal or Endotracheal
ICU	Intensive Care Unit
LAR	Legally Authorized Representative
MAP	Mean Arterial Pressure
O2	Oxygen
OHCA	Out of hospital Cardiac Arrest
PI	Principal Investigator
ROC	Return of Circulation
ROSC	Return of Spontaneous Circulation
SAE	Serious Adverse Event
SDMC	Statistical & Data Management Center
SOP	Standard Operating Procedures
TTM	Targeted Temperature Management

Purpose of this Document

This document summarizes key elements in the clinical care of patients with post-cardiac arrest syndrome who are participants in the P-ICECAP multicenter clinical trial. These guidelines are not intended to dictate clinical practice for patients that are not enrolled in P-ICECAP, although there is no prohibition from using them more broadly. The purpose of these guidelines is to minimize treatment variability of participants when possible in the P-ICECAP trial in order to optimally discern the effect of the study intervention. In patients that are participants in P-ICECAP, provision of care in accordance with these guidelines is critical to the scientific goal of the study and the success of this trial.

These guidelines reflect a process of consensus among a multidisciplinary clinical standardization team and vetting with feedback and revision among participating sites. For most elements of care addressed in this guideline there are insufficient data to prove the optimal treatment choice, however national guidelines were utilized for some elements. This guideline should therefore not be interpreted as best practice per se, but as representing practice that can be accepted and consistently performed at all sites. Given patient heterogeneity, some practice variability is unavoidable, and these guidelines should never override specific unique clinical needs that may arise for individual patients.

Whenever possible the guidelines promote a goal-oriented strategy that maintains some flexibility in approach as long as a consistent target parameter is attained. It is expected that each participating site will identify and adapt their local procedures and order sets necessary to accurately implement these guidelines within its own institutions.

Clinical Standardization Team

The P-ICECAP clinical standardization team, a national committee of experts in pediatric neurocritical care, critical care, and neurology, developed the P-ICECAP clinical standardization guidelines in accordance with the published guidelines of the AHA and clinical standards.

The members of the clinical standardization team are:

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Definitions

Time of cardiac arrest is most often not known in pediatric cardiac arrests. Time of arrest will be estimated as the time when the arrest started when possible. The duration of chest compressions and number of epinephrine doses received provides useful information about the OHCA in children. **Time of initiation of TTM** is operationally defined as the time that the button on the definitive closed loop cooling device that initiates temperature control is pressed.

Time of initiation of cooling (start of the intervention to TTM 33°C) is operationally defined as the time the button is pressed on the definitive closed loop surface cooling device that initiates cooling to 33°C . This should be done within 15 minutes of randomization, unless cooling to <34°C was initiated prior to randomization. **If cooling to <34°C was initiated prior to randomization**, then time of initiation of cooling will be the time point TTM was set to a temperature < 34°C.

Time of enrollment in the trial is operationally defined as the time of randomization. The time of randomization is required to be 6 hours or less from the time of ROSC.

ROSC is operationally defined as the restoration of a palpable pulse or a measurable blood pressure. If cardiac monitoring is available, ROSC requires an organized cardiac rhythm. We are using ROSC and not ROC because ECMO prior to randomization is an exclusion criteria.

Sustained ROSC is when the patient has achieved ROSC with signs of circulation persisting for at least 20 consecutive minutes.

Temperature Management

Temperature Monitoring

Core temperature must be monitored continuously throughout cooling induction and maintenance, rewarming and the controlled normothermia period. Core body temperature will be measured at two sites for safety (eg. esophageal, bladder, or rectal). In rare circumstances only one temperature probe may be feasible. Esophageal and bladder are the preferred sites for measuring core temperature but not required. Rectal measurement of core temperature is less preferred, but is an acceptable alternative if other sites are not available. Bladder temperature sensors may be less reliable in anuric patients and may not be available for the smallest patients.

The **primary probe** is the temperature probe that is connected the servo-regulated surface cooling device

The **secondary probe** is the temperature probe that is connected to the bedside monitor.

Note: The esophageal probe is the preferred primary probe which will be connected to the surface cooling unit. However, in the event that an esophageal probe is not judged to be feasible, the Foley catheter or rectal probe may be used as the primary probe and the remaining probe will be the secondary probe which will be connected to the bedside monitor. **For patient safety, the lowest value will be assumed correct if there is a discrepancy in measurements. If there is a discrepancy of greater than 2 ˚C between the two measurements, the temperature probes should be inspected for proper positioning and function.**

NOTE: Temperature sensing foley catheters, esophageal and rectal probes contain metal and may need to be removed prior to an MRI.

Cooling/Warming Modality

Hypothermia will be induced using a servo-regulated surface cooling device (eg. Blanketrol, Arctic Sun). No internal cooling procedures or devices will be used (e.g., gastric lavage, intravascular cooling catheter). In the rare event a patient is supported with ECMO following randomization, the ECMO circuit temperature will be used to regulate TTM.

Acetaminophen can be administered in addition to the servo-regulated surface cooling device.

Cooling Guidance

Randomized to 33C for 12-96 hours

If the participant is randomized to 33C for any of the durations of 12-96 hours, the servo-regulated surface cooling device is set to 33C after randomization regardless of the pre-randomization device set temperature. The participant will be maintained at a set temp of 33C for the total randomized duration of cooling.

If the servo-regulated surface cooling device was set to a temperature continuously between 32 and 34C prior to randomization that time point will be the initiation of the randomized cooling duration. The device should still be set to 33C after randomization (see above)

If the servo-regulated surface cooling device was set to a temperature above 34C prior to randomization the time the button is set to 33C after randomization will be the beginning of the randomized duration of cooling.

Rewarming

Rewarming begins at the end of the randomized duration of cooling when the device and thus the patient's temperature is raised back to a set temperature of 36.8C. This should be done slowly over a period of approximately 16 hours. Different devices have different means of cooling, but the general target is to rewarm approximately 1 degree every 4 hours. On some devices this can be done by increased the set temperature by 1 degree hourly resulting in the goal of 36.8C

Normothermia through 120 hours

Following rewarming, participants will be maintained at 36.8 on the device through 120 hours.

Randomized 36.8C (0 hours of cooling/no additional cooling)

The device will be set to 36.8C for a total of 120 hours from the time at the time of randomization to 0 hour cooling duration (no additional cooling). Based on the patient temperature at time of randomization the servo-regulated surface cooling device will be titrated with a goal set temp of 36.8C.

If the patients pre-randomization temperature is < 35C, the patient should be rewarmed by 1 degree C per hour to reach 36.8C

Extubation Prior to 120 hours

If the participant is rewarmed and extubated prior to the completion of the 120 hours the participant should be have their temperature monitored to prevent fever and in some circumstances could be treated with a cooling device for high fever.

Managing Effects of Cooling

Side effects of therapeutic hypothermia induction, maintenance and rewarming are common and should be monitored and addressed as appropriate. The below table highlights side effects, anticipated phase, proposed mechanisms and interventions to consider. (For phase: I = induction, M= maintenance, R = rewarming)

Side Effect	Phase	Mechanism	Intervention
Bradycardia	I/M	• Decreased metabolic rate	Usually does not require intervention
Vasoconstriction and possible hypertension	I/M	• Increased SVR	None needed

			Place venous and arterial access as early as possible to minimize challenges
Mildly prolonged PR, wide QRS, increased QT	I/M	• Direct effect of repolarization	Does not require intervention
Cold diuresis and associated hypotension	I, M	• Increased venous return • Increased ANP/Decreased ADH	Fluid repletion
Hyperglycemia	I/M	• Insulin resistance • Diuresis	Monitoring See Euglycemia below
Hypokalemia, Hypophosphatemia, Hypomagnesemia	I, M	• Intracellular shift due to hypothermia and exacerbated by insulin • Tubular dysfunction	Monitoring Repletion to normal ranges Mg > 1 K> 2 Phos > 2.5
Shivering	I/R	• Cutaneous response to increase body temperature to hypothalamic target • Often resolves when < 34°C • Often recurs when rewarming	See Shivering Management below
Mild coagulopathy Decreased platelet function Decreased platelet count	I/M		Monitoring Intervention per clinical need (bleeding)
Drug clearance	I/M/R	• Metabolism may be slower depending on medication	Monitor impact of medications Monitor drug levels when appropriate to do so

Increase in heart rate	R	• Increased metabolic demand	Does not require intervention Monitor fluid status
Vasodilation	R	• Decreased SVR	Fluid repletion Vasopressors
Hyperkalemia	R	• Extracellular shift • Exogeneous repletion (occurs during induction)	Remove potassium from fluids Monitor closely Treat hyperkalemia

Vascular Access

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

An arterial line is also required for continuous monitoring of blood pressure post cardiac arrest and during targeted temperature management. This should be done as early as possible as cooling peripherally vasoconstricts and makes it challenging to place peripheral arterial and venous access.

Sedation and Analgesia

<u>Sedation and Analgesia Targets</u>

Sedation and analgesia use will be at the discretion of the primary clinical team caring for the patient with the goal of achieving a clinical response of “sluggish or no response to noxious stimulus.” (e.g. SBS -2, RASS -4). Institutions should use their standard sedation scores and target the above response. In this document we refer to clinical targets that can be aligned with site specific sedation protocols. This is the goal when the patient is not paralyzed.

Sedation and analgesia by continuous infusion, used simultaneously, with intermittent dosing should be initiated and titrated during targeted temperature management and rewarming for all cooling durations to treat/prevent agitation and shivering. Sedation and analgesia should be titrated based on objective scales.

After rewarming, clinical response goals can be dictated by the clinical team.

Sedation and analgesia may have been started prior to the initiation of cooling, therefore, investigators should incorporate the below guidance as long as sedation and analgesia goals are achieved.

Sedation

Goal: clinical response of "sluggish or no response to noxious stimulus" (e.g. SBS -2, RASS -4)

Midazolam or dexmedetomidine are common primary sedative agents, but not required, for use in this study. Clinicians should use loading doses and a continuous infusion to achieve sedation goals. If required, additional doses of sedation may be given. The infusion rate can then be increased or decreased as needed to achieve a clinical response of "sluggish or no response to noxious stimulus."

If after the first 4 hours of the intervention the patient has no clinical response to noxious stimulus (and is not on paralytics), the sedating infusion may be weaned to target a clinical response of "sluggish response to noxious stimulus." Sedating infusions may be weaned off after the first 24 hours if there is no clinical response to noxious stimulus.

Other sedating agents may be used at the site's discretion.

Analgesia

Goal: clinical response of "sluggish or no response to noxious stimulus

Fentanyl is the analgesic agent recommended, but not required. Other narcotics (e.g., morphine, hydromorphone) may be used as an alternative to fentanyl at the clinical site's discretion. Clinicians should use loading doses and a continuous infusion to achieve sedation goals. If required, additional doses of analgesics may be given. The infusion rate can then be increased or decreased as needed to achieve a clinical response of "sluggish or no response to noxious stimulus." The infusion rate can then be increased as needed to achieve a clinical response of "sluggish or no response to noxious stimulus."

If after the first 4 hours of the intervention the patient has no clinical response to noxious stimulus (and is not on paralytics), the analgesic infusion may be weaned to target a clinical response of "sluggish response to noxious stimulus." The analgesic infusion may be weaned off after the first 24 hours if there is no clinical response to noxious stimulus.

Shivering Management

Shivering is a normal physiologic response to changes in temperature (cooling and rewarming), but may be more problematic when inducing hypothermia for therapeutic purposes. Shivering will slow cooling to a goal temperature. It will also make it more difficult to maintain target temperature, may be uncomfortable for patients, and will adversely affect the patient's metabolic needs. Clinical monitoring for shivering is required in all participants. In some cases, shivering may be difficult to distinguish from myoclonus or seizures and EEG may be needed to distinguish. Shivering may be subclinical and respond to sedation and neuromuscular blockade.

Sedation and analgesia can be used to treat shivering. Dexmedetomidine can prevent shivering and neuromuscular blockade can stop shivering as well.

During TTM, including cooling and rewarming, shivering should be addressed using a local practice which may include but are not limited to sedation, analgesia, surface counterwaming and neuromuscular blockade.

Use of Neuromuscular Blockade

Any non-depolarizing neuromuscular blockade agents may be used (eg. vecuronium, cis-atracurium, rocuronium.) A paralytic loading dose will be administered to patients to facilitate cooling. Repeated doses will be administered as needed to maintain paralysis until the patient is cooled to the therapeutic range.

Once target temperature is achieved, neuromuscular blockade is usually not required, except as needed to control shivering resistant to sedative/analgesic agents and rewarming without clinical shivering. If a cooled patient that you do not want to rewarm begins to rewarm above 34.5℃ in spite of the absence of clinical shivering, neuromuscular blockade can be administered to facilitate keeping the patient in goal range. Neuromuscular blockade may also be used for other aspects of care at the discretion of the primary care team (such as ventilator asynchrony).

During the rewarming period, neuromuscular blockade often is needed to be used to prevent rapid rewarming or labile temperature fluctuations, and shivering.

Physiological Goals and Management

Blood Pressure

Blood pressure will be monitored by an arterial line. The optimal post-arrest blood pressure target is unknown, but mean arterial pressure (MAP) should definitely be greater than the 5th percentile for age (Appendix). (AHA Class 1, LOE C-LD) This is intended to be a minimum boundary rather

than a target MAP; **We recommend targeting a goal-directed blood pressure higher than at least the 25th percentile in order to avoid hypotension < 5th percentile.**

Hypotension is common after cardiac arrest and interventions to maintain MAP above this minimal boundary are needed. Clinicians should anticipate, prevent, and be prepared to rapidly respond with fluids, vasopressors and inotropes and may choose to use these alone or in combination based on the clinical situation. The sequential use or combination of agents will be at the discretion of managing clinicians. The purpose of targeting a > 25th percentile MAP in this study is to avoid severe hypotension (MAP < 5th percentile), associated with worse survival and neurologic outcome.

Oxygenation

Pulse oximetry should be measured continuously.

For patients with expected baseline SpO2 >94%, oxygen saturation should be maintained greater than or equal to 94% with supplemental oxygen or other means as needed, but supplemental oxygen should not be increased if oxygen saturation is ≥98%. (AHA Class 2b, LOE C-LD)

For patients with baseline lower saturations due to an underlying condition (e.g cyanotic heart disease), clinicians should target saturations appropriate to the patient's underlying condition, equivalent to their baseline expected oxygen saturation.

Interventions for oxygenation below target include increasing FiO2, and optimizing ventilatory mode, rate, volume, or peak end expiratory pressure (PEEP) and are at the discretion of the clinical team.

Ventilation

For patients with expected pre-arrest baseline PaCO2 35-45, clinicians should attempt to target normocapnia (ie, normal for the child), (eg.PaCO2 35–45 mm Hg), limiting exposure to severe hypercapnia and hypocapnia. (AHA Class 2b, LOE C-LD) while accounting for appropriate pH.

For patients with pre-arrest higher PCO2 due to an underlying condition (eg. Chronic lung disease) clinicians should target pCO2 appropriate to the patient's underlying condition and baseline PCO2, limiting exposure to relative hypercapnia and hypocapnia, while accounting for appropriate pH.

Interventions to optimize ventilation and pH are at the discretion of the clinical team.

Euglycemia

Treatment of hypoglycemia or hyperglycemia will be dependent on local practice and the recommended target of serum glucose is between 80 to 200 mg/dL. This can be achieved by administering glucose containing fluids and titrating insulin or removing dextrose from fluids. Clinicians should closely monitor serum glucose during insulin use to prevent hypoglycemia (<80 mg/dL). On rewarming, insulin resistance lessens and hypoglycemia may develop rapidly. This requires careful glucose monitoring and anticipation of early discontinuation of insulin.

Insulin can cause hypokalemia which can be exacerbated during induction of therapeutic hypothermia. Close monitoring is essential and repletion of potassium during induction may be necessary. Likewise, removal of potassium from IVs and potassium supplements if needed during the rewarming period should be considered in patients who have been receiving insulin.

Seizure Management

Seizures are common after cardiac arrest. When resources are available, continuous electroencephalography (EEG) monitoring is recommended for the detection of seizures and evaluation of treatment efficacy (AHA 1, LOE C-LD) If continuous EEG is not available, intermittent screening EEG can be used. Clinicians should be aware that when neuromuscular blockade is being administered cEEG is the only way to detect seizures. Duration of monitoring is at the discretion of the clinical team.

Treatment is recommended for clinical and electrographic seizures (AHA 1 , LOE C-LD). Treatment of electrographic status epilepticus should optimally occur in conjunction with neurologists (AHA 2a, LOE C-EO). Selection of anti-seizure medication(s) is at the discretion of the attending physician(s). Side effects of antiseizure medication should be considered.

Laboratory Testing

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

Electrolytes (sodium, potassium, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, chloride, magnesium, and calcium (total) will be monitored at the following timepoints for safety indications:

- During active cooling induction and rewarming: electrolytes will be completed at least every 6 hours. If electrolytes are drawn more frequently than once every 6 hours, all values will be recorded
- During maintenance hypothermia and normothermia periods: electrolytes will be completed at least every 12 hours.

<u>Other blood monitoring</u>

All values obtained during the intervention period (through 120 hours) will be recorded.

- Daily complete blood count (CBC),
- Daily liver function tests (LFTs), specifically alanine aminotransferase (ALT),aspartate aminotransferase (AST), bilirubin (BILI), albumin
- Daily coagulation profile: prothrombin time (PT) and International Normalized Ratio (INR), partial thromboplastin time (PTT),

<u>Arterial blood gas (ABG) including ionized calcium and lactate</u>

- At least, daily for the first 72 hours.
- Labs will run blood gasses at current patient temperature or corrected to normal temperature. Blood gases should be reported based on normal temperature

<u>Screening Cultures</u>

Blood cultures

- Around the time of randomization (day 0) and on days 2 and 4.

Additional cultures may be obtained if infection is suspected clinically.

Respiratory Cultures

- Baseline.

Imaging

Chest x-rays

- Daily during the intervention period to confirm esophageal temperature probe position in lower ⅓ of esophagus and the endotracheal tube position.
- If multiple radiographic examinations are obtained during any study day, the examination closest to 8:00 A.M. will be recorded.

Withdrawal from active intensive care and life support

Patients are ineligible for this study if an early withdrawal of life support (prior to 120 hours) is consistent with the goals of care as determined from the patient's parent or legally authorized representative (see exclusion criteria). Except as noted below, all participants in the trial are expected to receive life support and active intensive care as needed for at least 120 hours after cardiac arrest (i.e. after rewarming from the longest possible duration of cooling to which participants may be allocated in the trial). An evaluation of neurologic prognosis will be performed after 120 hours from randomization for participants, which will inform subsequent withdrawal of life support decisions.

Withdrawal of life sustaining therapies prior to 120 hours after randomization

On any day after participants have completed their allocated cooling and rewarming and an appropriate waiting time for clearance of sedatives and analgesics, participants without evidence of neurologic recovery may undergo an evaluation for brain death per institutional standards and removal of organ support if appropriate. Other reasons for withdrawal prior to 120 hours are also listed below. (see below).

Brain Death Diagnosis: Participants in the trial may undergo brain death testing and diagnosis as defined by institutional standards (or as defined by guidelines by the American Academy of Pediatrics/Child Neurology Society/Society of Critical Medicine pediatric guidelines).Participants need to be rewarmed, and sedation and paralytics should be stopped for at least 24 hours prior to a brain death exam. *In individuals who have undergone cooling for more than 24 hours the risks of accumulated sedatives may be greater, and a longer time interval prior to initiation of a brain death evaluation should be considered.*

Neurologic Futility: Although withdrawal of care prior to 120 hours after randomization is discouraged, there may be cases where this is warranted, based on neurological prognosis (eg. herniation on neuroimaging, or prolonged (>24h) fixed non-reactive pupillary responses, coupled with absent motor responses to painful stimuli in the absence of paralytics or sedation). Consultation with neurology and documentation of criteria upon which the decision to withdraw life-sustaining therapies should be considered in this setting.

Non-neurological Prognosis: Life support may be withdrawn prior to 120 hours from randomization because of futility or otherwise poor prognosis based on non-neurological

problems (e.g. previously unknown disseminated end-stage cancer or multisystem organ failure, refractory shock, or repeated recurrent arrest).

Changes in Goals of Care: Changes in goals of care are not to be pursued with the parent or LAR prior to 120 hour from randomization. Withdrawal of life support is permitted at any time for unsolicited changes in goals of care by the participant's decision makers.

Withdrawal of life sustaining therapies after 120 hours from randomization

On and after 120 hours from randomization participants should undergo a complete, competent, and objective evaluation of neurologic prognosis. After this evaluation, in consultation with the participant's parent or LAR if available, the clinical treatment team may limit intensive care support or withdraw technologic support if appropriate.

Determination of neurologic prognosis: If the clinical team feels that the neurologic prognosis is most consistent with irreversible injury such that a favorable outcome is no longer possible, they may undertake testing for neurologic prognostication. Neurologic prognostication of unfavorable outcome is a common basis for withdrawal of life sustaining therapies that invariably leads to death.

The 2015 American Heart Association Post Cardiac Arrest Management (Callaway et al 2015) guidelines recommend that the earliest time for neurological prognostication using clinical examination in patients treated with TTM, where sedation or paralysis could be a confounder, may be 72 hours after return to normothermia (Class IIb, LOE C-EO). However, this recommendation did not include children nor did it anticipate the extended periods to which participants may be allocated in this trial (ie. rewarming completed at 120 hours post arrest). Cessation of sedation and paralytics must be undertaken for sufficient time that will not confound testing, and, in general will be at least 24 hours after cessation of sedation and paralytics.

Withdrawal of life sustaining therapies should never be based on neurologic exams that are impaired by pharmacological or reversible metabolic effects or confounded by hypothermia

All prognostication and criteria for decisions on life sustaining treatment will be documented in the medical record.

Approach to surgical procedures or imaging

At times patients may require procedures or imaging during the cooling intervention. Brief imaging (eg. head CT) may be accomplished by closely monitoring temperature during transport while

being aware that temperature may drop further below the intended range. More prolonged imaging such as MRI is unlikely to be performed as neuroprognostication will not occur until after 120 hours.

In the case of procedures or surgeries that are deemed clinically necessary during the cooling intervention, clinicians and proceduralists should consider the impact of cooling (eg. bleeding risk) on the participant and determine if rewarming is necessary based on what is best for the patient.

Tracking and Reporting of Clinical Guideline Variations and Excursions

The SIREN culture and philosophy is that just promulgating clinical standardization for trials is insufficient. Adherence with the guidelines must also be tracked and reported. Tracking and reporting compliance with the guidelines has two purposes.

The first purpose is to administratively support and motivate continuous quality improvement processes during the trial. Variance from the guidelines on an individual subject and cumulative basis is reported back to the site trial leadership on a daily basis. Site performance is reported in ranked comparison with the other sites to leverage innate competitiveness as a motivator for those with worse than the average number of variances from the guidelines.

The second purpose is to scientifically characterize, at the end of the trial, the extent of standardization achieved on the most important elements of the guidelines. Data describing the clinical care of study participants allows insight that can help with interpretation of the primary results of the trial. This observational data can also be used to preliminarily explore other questions, and to improve subsequent trials.

We use the following nomenclature to describe compliance with clinical standardization within SIREN. The term “excursion” is used to describe any individual variance from the targets set in the clinical standardization guidelines in a unit of time pertaining to ranges for lab or physiological parameters. The term is used to distinguish these excursions related to the clinical standardization guidelines from the term “deviations” which is used only to describe deviations from the study protocol describing the actual investigation itself. The unit of time may vary by parameter and by specific study, but for P-ICECAP is usually one calendar day. A variation is departure from a process, such as the frequency of laboratory monitoring.

Variations and excursions are based on selected parameters described in the standardization guidelines that are thought to represent those in which clinical variation is potentially common and in which it is most likely that variations may manifest as differences in outcome for the

subject. The study team rounds on each subject daily while the subject is in the intensive care unit and at fixed intervals thereafter during acute hospitalizations. A daily case report form is used and data entered each day to identify which (if any) excursions occurred on the previous calendar day. Variation parameters on daily CRF's are source documents monitored at site visits. Periodic reports describe the cumulative and recent rates of excursions. Variations, such as monitoring electrolytes less frequently than outlined in this guideline, will be identified in site visits. Hubs and spokes may be ranked by these metrics in the periodic report.

APPENDICES

Goal Blood pressures for 25% (Rosner American Journal of Epidemiology 2008)

Patient Age Group	5th percentile MAP	25th percentile MAP
birth to 6 months	45	50
>6 months - 6 years	50	60
> 6 years	55	65

*Data adapted from Roberts et al, PCCM, 2020