OHSU SIREN NETWORK NEWS

Issue: April 2021

CALENDAR

4/6 1-2pm ET Study Coordinator Meeting – Web Link

4/8 3-4pm ET Finance Committee Call – Web Link

4/28 12-1:30pm ET Steering Committee Meeting – Zoom Link

4/21 1pm ET Journal Club Link TBD

5/4 1-2pm ET Study Coordinator Meeting – Web Link

Contact us: Jenny Cook, Coordinator, 503.494.1230
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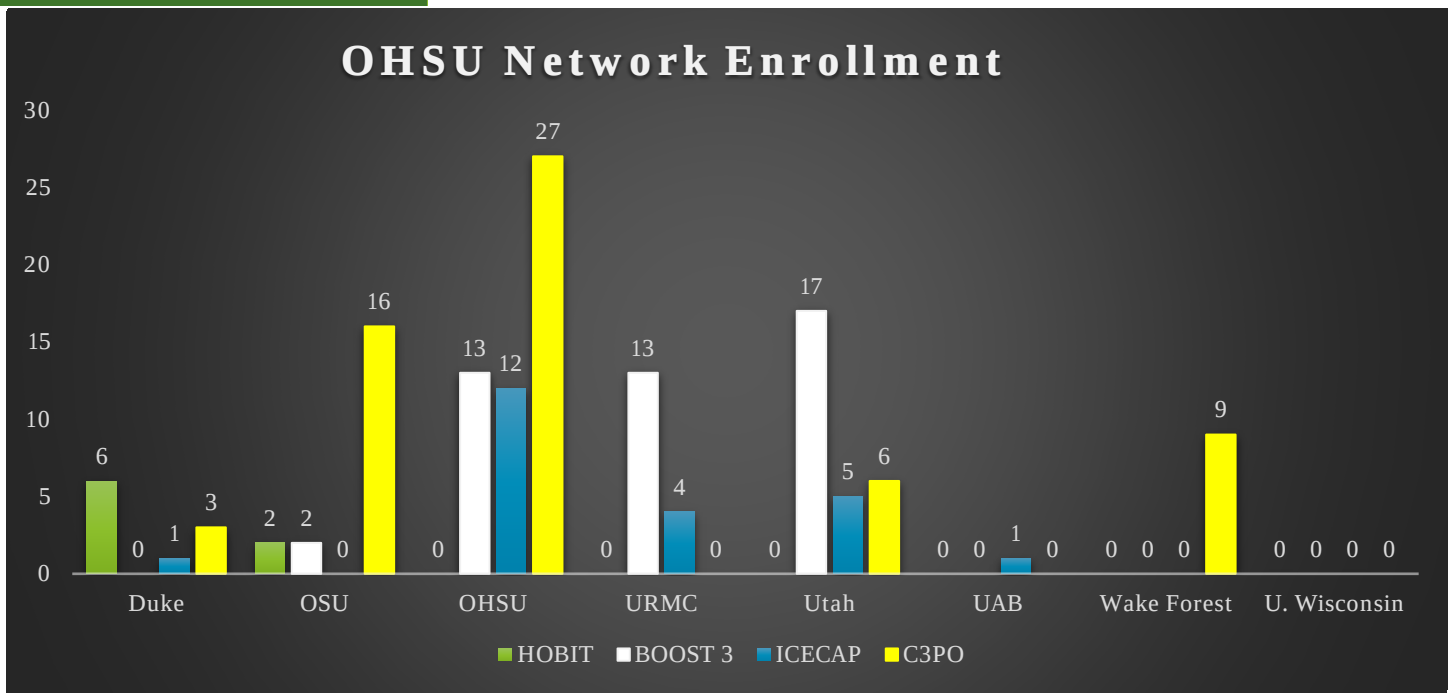
Newsletter at a Glance

OHSU NETWORK PERFORMANCE AT A GLANCE

The OHSU network continues to be the top performing network in SIREN. We are the highest enrolling network in BOOST3, and 2nd in both HOBIT and ICECAP. Thank you to all sites for submitting your annual reports for our NIH grant reporting. As a group, we have successfully enrolled in each of the ongoing trials despite the research challenges related to the pandemic.



SIREN FELLOWSHIP ANNOUNCEMENT

The SIREN Network has a new Fellowship program – an opportunity to provide mentorship to emerging researchers who will be the future leaders of emergency research in neurologic, heart, lung and blood conditions.

Expectations:

We anticipate the fellows would be embedded into the leadership teams of ongoing SIREN trials. The trial and Network PIs would work with the fellows to determine the roles and responsibilities. Each fellow would be placed on a trajectory to generate at least one peer-reviewed manuscript related to the experience. We anticipate the fellows will attend approximately 3-4 hours of weekly operational and planning calls and be involved in additional projects focused on planning, operations, and interpretation of the trials. Fellows would have additional expectations (present at SIREN journal club, and other opportunities tailored to individual goals) during the experience. Additionally, the fellows would be involved in the planning of new trials being considered by the Network. Fellows will be accepted on a rolling basis for approximately one-year terms, but multi-year experiences may be possible.

Eligibility:

Candidates for the fellowship could be residents with protected time for research, fellows (in ACGME and non-ACGME programs), and early-career faculty with an interest in patient oriented emergency care research. Knowing that there are a variety of career pathways, there is not a specific time limit from completion of training in order to be eligible.

Application Process:

Interested candidates should submit a biosketch with a personal statement indicating motivations and interest. Please be sure to cover what you hope to gain from this experience up front in your personal statement. SIREN leadership and the Education, Training and Collaboration Working Group will review applications and request additional information, including potential letters of support from departmental leadership / supervisor of the fellow.

SIREN Fellowship Application Link

Additional Information: SIREN Fellowship webpage and email questions to Dr. Will Meurer.

C3PO NEWS & UPDATES

- Final Enrollment Total: **511 (61 subjects enrolled from our network)**
- Have an idea for a secondary research paper? Submit your C3PO ideas here: https://siren.network/clinical-trials/c3po/research_ideas
- ***Study Data should be complete at this time.*** *(Biospecimen shipping for some sites may not be completed yet – if your site is still pending that is OK)*
- Vitalant, BARDA and the FDA are working on instructions for what to do with leftover C3PO plasma that is in your blood bank. Do not use it! It probably will either go to support another trial or be released to your blood bank for local use (this will need an official letter either way).
- On Wed, April 7, Noon ET, we plan a webinar with all investigators to share the final data. This will be your chance to see the results as they are submitted for publication. To avoid "public presentations" that

may jeopardize publication in some very competitive journals, we will probably make this a password / invite webinar: look for details. Also, answer the survey about "who are co-investigators at your site". This information is for the manuscript.

- Dr. Kea (OHSU C3PO Site PI), Dr. Korley (C3PO MPI), and Dr. Durkalski-Maudlin (DCC PI), submitted a Long COVID grant for funding consideration, titled **"R2D2**: **R**ecovering from SARS-CoV-**2**: Risk Factors Contributing to the **D**evelopment of Post-Acute Sequelae of SARS-CoV-**2** in Persons with Mild to Moderate COVID-19 Illness" A summary of the proposal is at the end of this newsletter.

BOOST 3 NEWS & UPDATES

- BOOST 3 enrollments: 153 (Target enrollment 1094)
- **OHSU Network Enrollment: 45 (29% of total enrolled subjects)**
- Attention BOOST 3 site coordinators – we'd like to find a time for our BOOST network study coordinators to meet and discuss best practices, challenges, creative solutions, etc. Please e-mail Jenny Cook (cookjen@ohsu.edu) and let me know whom from your site should be invited to this call.

HOBIT NEWS & UPDATES

- Enrollment: 57 (Goal:200)
- **OHSU Network enrollment: 8 (15% of total enrolled subjects)**
- A new updated version of the HOBIT Safety Pause (Revision 2) is now available in the http://www.hobittrial.org toolbox, under Chamber Resources.

ICECAP NEWS & UPDATES

- Enrollment: 171 (Goal: 1800)
- **OHSU Network Enrollment: 23 (13% of total enrolled subjects)**
- The Zoll Education Booklet that was discussed during the March Steering Committee Meeting is posted to the Toolbox under Clinical Team Resources. It discusses the ICECAP Protocol and provides a Practice Overview for sites using intravascular cooling. Booklet is attached to this newsletter

GLOSSARY OF FREQUENTLY USED ABBREVIATIONS

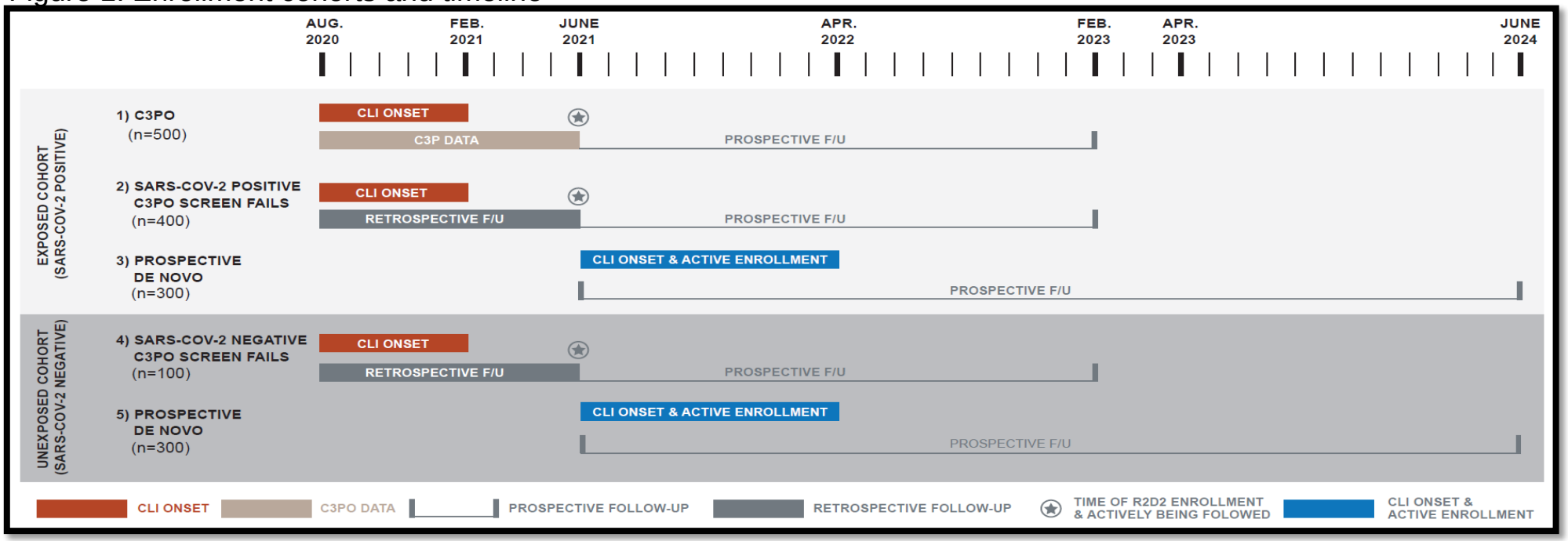
CCC = Central Coordinating Center (i.e. University of Michigan)
EFIC= Exception from informed consent
CC = Community Consultation
PD = Public Disclosure
cIRB = Central IRB (in this case Advarra)

R2D2 Project Overview

Title: **R2D2**: **R**ecovering from SARS-CoV-**2**: Risk Factors Contributing to the **D**evelopment of Post-Acute Sequelae of SARS-CoV-**2** in Persons with Mild to Moderate COVID-19 Illness

Abstract: Little is known regarding the long-term consequences of those infected with SARS-CoV-2, including the natural history and the seemingly heterogeneous population suffering from post-acute sequelae of SARS-CoV-2 infection (PASC). In order to close the knowledge gap and identify early interventions to PASC, we leverage the C3PO trial infrastructure, a randomized controlled-trial of convalescent plasma for those mild/moderate COVID-19 symptoms in 47 emergency departments. One study reported up to 30% of ambulatory patients had ongoing symptoms at 6 months. This population is still growing in number as the pandemic continues, and understanding why symptoms linger despite initial illness severity is critical. The etiology of PASC is likely multifactorial and may be influenced by pre-morbid host factors, acute illness severity, host biological response to acute illness, environment, and treatment factors. However, the importance of these potential risk factors has not been well-studied prospectively. By recruiting diverse patients from our C3PO trial and newly infected patients (1200 SARS-CoV-2 positive patients), and appropriate controls (400 individuals with COVID-like symptoms but COVID negative), we will establish a heterogeneous longitudinal cohort linking clinical data, functional assessments, and biospecimens over a two-year period to determine the incidence and natural history of PASC. We will also develop algorithms for predicting the risk of PASC and mechanisms that could be targets of early interventions to prevent PASC.

Figure 1. Enrollment cohorts and timeline



ICECAP

ICECAP:
PROTOCOL AND PRACTICE OVERVIEW

ICECAP: INFLUENCE OF COOLING DURATION ON EFFICACY IN CARDIAC ARREST PATIENTS

ICECAP is a multicenter, randomized, adaptive allocation clinical trial to identify the optimal duration of induced hypothermia for neuroprotection in comatose survivors of cardiac arrest. This trial is funded by NIH and under FDA IDE G160072. The trial plans to enroll a maximum of 1,800 subjects over four years.

Study Population

Comatose adult survivors of out-of-hospital cardiac arrest (OHCA) 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 (Strategies to Innovate Emergency Care Clinical Trials) network will be enriched with high-potential ancillary Hubs.

Primary Efficacy Outcome

The primary outcome measure will be the modified Rankin scale (mRS) at 90 days after return of spontaneous circulation (ROSC). 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.

Primary Safety Outcomes

The primary safety outcome is all cause mortality at 90 days.

Second Safety Outcomes

Severe adverse events (SAEs) are monitored throughout the trial. They are anticipated to be related to therapeutic hypothermia and may include pneumonia, other infections (including urinary tract infections and bacteremia 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.

Inclusion

1. Coma after resuscitation from out-of-hospital cardiac arrest
2. **Cooled to < 34°C within 240 minutes of cardiac arrest (from 911 call)**
3. Definitive temperature control device initiated (must have closed-loop feedback)
4. Enrollment within 6 hours of initiation of cooling
5. Age ≥ 18 years
6. 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.

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. **The trial design anticipates needing at least 50 sites. ICECAP requires sites that can enroll an average of 9 subjects per year.**

Study Intervention

The intervention for this trial is random allocation to **duration of cooling** after cardiac arrest (not target temperature or method of cooling).

Clinical Standardization

A team of national committee experts in neurocritical care, medical critical care, cardiology, and emergency medicine developed the ICECAP clinical standardization guidelines in accordance with the published guidelines of the AHA. The clinical standardization guidelines will be followed by investigation sites to reduce the effects of practice variability.

Temperature Management

Temperature Monitoring

Core temperature must be monitored continuously throughout cooling, rewarming, and controlled normothermia period.

Esophageal, bladder, or blood (e.g., pulmonary artery catheter) are the preferred sites for measuring core temperature. 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.

Use of two measurement sites/sources is preferred (e.g., esophageal and bladder temperature sensors).

Target Temperature
The target temperature during hypothermia is **33°C**. Deviations from the target temperature should not exceed 1°C.

Rewarming
The target temperature at the end of rewarming is **36.5°C**.

Rewarming will be done in a controlled manner using the temperature management device at a rate of about **0.15°C/hr** (for those in groups 24 hours or more), or a rewarming period equal to the assigned arm if the assigned arm is shorter than 24 hours (6,12, or 18 hours).

Duration of Cooling
Duration of cooling each subject will be obtained from randomization. Duration of cooling will be measured from the time that cooling with a definitive device is initiated in the hospital.

Cooling or Warming Methods
Hypothermia may be initiated with any combination of modality or device. A definitive device is defined as a closed-loop feedback endovascular or surface cooling device used to maintain therapeutic hypothermia and rewarming.

Why Consider Core Cooling Technology?
Data indicates there may be an interaction between quickness of cooling and duration of cooling that impacts efficacy. This study design attempts to minimize variability or limit the condition from time to target by restricting patients enrolled to those with relatively early and consistent induction of cooling.

Studies have shown that core cooling is a rapid and precise method compared to surface cooling.[1] In a recent study,[2] 100% of patients achieved target temperature of < 34°C within 3 hours compared to a surface cooling trial,[3] in which only 50–71% of patients cooled below 34°C within 4 hours, despite additional cooling methods (i.e., ice packs) used and restricting patients weight for enrollment (> 250 lb excluded). Core cooling has no limitation or restriction on patients weights or heights since it cools from inside.

In addition, some populations (i.e., diabetics; peripheral vascular disease patients; those with poor nutritional status, steroid use, or high dose vasopressor therapy) are at higher risk of skin injury with a surface cooling device.[4]

Temperature Management After Rewarming (Normothermia or Fever Prevention)
Controlled normothermia (36.5°C to 37.5°C) by active means is encouraged for 48 hours following rewarming in all subjects. Longer periods of controlled normothermia may be undertaken based on local practice. Whenever possible the definitive servo-control device (closed-loop feedback) should be continued to maintain normothermia.

Shivering Management
Shivering is a normal physiologic response to changes in temperature (cooling and rewarming). It may slow cooling or make it more difficult to accurately maintain the target temperature. In some cases, shivering may be difficult to distinguish from seizures. In those cases, EEG is necessary to diagnose seizures. Shivering should be assessed hourly using the Bedside Shivering Assessment Scale (BSAS).

Bedside Shivering Assessment Scale[5]

0	None: no shivering noted on palpation of the masseter, neck, or chest wall
1	Mild: shivering localized to the neck and/or thorax only
2	Moderate: shivering involves gross movements of the upper extremities (in addition to neck and thorax)
3	Severe: shivering involves gross movements of the trunk and upper and lower extremities

Interventions should be used as needed to maintain a BSAS <1, or to prevent or respond to slow cooling or difficulty maintaining target temperature.

Shivering is often most intense during initial induction of hypothermia. Initial induction of hypothermia in this trial takes place prior to enrollment and randomization, so control of shivering during induction is therefore typically beyond the scope of the clinical standardization plan. During maintenance and rewarming, shivering should be addressed using a locally defined protocol (a suggested shivering management protocol follows).

If only assessing the presence or absence of shivering, especially with surface cooling, sites should record a BSAS=0 for no shivering and BSAS=2 for any shivering.

Targeted Temperature Management (TTM) for Cardiac Arrest Shivering, Sedation, and Neuromuscular Blockade Pathway per ICECAP Study Protocol Guidance			
Stage of Cooling	Sedation for Shivering	Neuromuscular Blockade (NMB)	Other Shivering Therapy
INDUCTION	Fentanyl: 25–50 mcg/hr and Propofol:20–40 mcg/kg/min Monitor BSAS hourly Titrate sedation to BSAS of <1	Vecuronium 0.1mg/kg Never use NMB in lieu of adequate sedation (i.e., BIS < 50) If BSAS ≥1 titrate to lack of shivering	
MAINTENANCE	Monitor BSAS hourly Titrate sedation to BSAS of <1 If BSAS=0 then titrate to RASS target	Continue only as needed for BSAS >1 despite titration of sedation cEEG monitoring indicated during extended NMB	Acetaminophen 1g IV q6 (adjust dose or avoid for liver dysfunction) Counter-warming: warm air blanket to neck, torso, and extremities
REWARMING	Fentanyl: 50–200 mcg/hr Decrease Propofol prn Consider adding dexmedetomidine Once rewarmed, rapidly wean sedation to allow evaluation	Discontinue all NMB	Acetaminophen Counter-warming Replace magnesium to ≥4
BSAS = Bedside Shivering Assessment Scale **cEEG =** Continuous Electroencephalography		**BIS =** Bispectral Index Monitor **RASS =** Richmond Agitation Sedation Scale	

Physiological Goals and Management

Blood Pressure

Arterial blood pressure may be obtained noninvasively or by arterial line.

Mean arterial pressure should be maintained to at least 65 mmHg.

Interventions for a MAP below this boundary may be addressed based on clinical situation. Fluids, vasopressor, inotrope, or mechanical augmentation may be chosen alone or in combination based on the clinical situation.

Oxygenation

Pulse oximetry should be measured continuously. Arterial blood gas (ABG) should be measured only as needed.

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 used if oxygen saturation is ≥98%.

Always reduce supplemental oxygen (FiO_2 > 0.21) to lowest level that maintains the hemoglobin oxygen saturation target (AHA Class I, LOE C).

Interventions for oxygenation below target includes increasing FiO_2 and optimizing ventilatory mode, rate, volume, or PEEP.

Ventilation

Normocapnia/normocarbia is preferred, unless there is an underlying lung pathology.
$PETCO_2$ should be maintained at 35–40 mmHg (given variability in accuracy and calibration of this parameter, this will not be tracked as a transgression). Titrate tidal volume (initially 4–8 mL/kg) and ventilatory rate to maintain target $Pa/ETCO_2$ (AHA Class IIb, LOE C).

Euglycemia

Treatment of hypoglycemia or hyperglycemia will be dependent on local practice and the preferred target of serum glucose is between 80 to 180 mg/dL.

Withdrawal From Active Intensive Care and Life Support

Patients are ineligible for this study if there is early withdrawal of life support **(within 5 days).** All participants in the trial are expected to receive life support and active intensive care as needed for **at least 96 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 on hospital day 5 for participants not regaining consciousness, which will inform subsequent withdrawal of life support decisions.

Seizure Management

An EEG for the diagnosis of seizure should be performed with prompt interpretation as soon as possible, but at least within the first 24 hours after ROSC. Continuous EEG (cEEG) is preferred, initiated as soon as possible and continued through rewarming. If cEEG is not available, then a repeat EEG during the second 24 hours after ROSC should be performed (AHA Class IIb, LOE C).

Treatment is mandated only for unequivocal, overt clinical or electrographic seizures (which in this population is status epilepticus by definition). Electrographic seizures should be treated as aggressively as the patient's clinical status may safely tolerate. Other epileptiform activity is treated per local standards. Treatment should be as aggressive as possible to safely control seizures. Use of other antiepileptic medications is at the discretion of the attending physician.

Infectious Complications

Monitoring / Diagnosis

Daily chest X-ray and daily CBC, if desired by the treating team, are appropriate and may be used to screen for infection, especially during the period of intubation and cooling. Cultures should not be performed for monitoring or surveillance in the absence of clinical indications.

Cultures of blood, urine or sputum, and urinalysis should be performed based on specific indications.

Treatment

Prophylactic antibiotics to avoid ventilator-associated pneumonia are permitted but not required. When there is sufficient suspicion of infection, use and choice of antibiotics should be given consistent with institutional or clinical team preferences and local antibiotic susceptibilities.

Thrombotic Venous Complications

Prevention: **DVT prophylaxis** via SCDs, intermittent subcutaneous heparin, low molecular weight heparin, or other recommended prophylaxis pharmacological agents shall be instituted **within 24 hours of ROSC**, unless a contraindication exists.

No routine surveillance is suggested.

Treat with unfractionated or low molecular weight heparin with transition to oral anticoagulation as appropriate.

Management of Cardiac Interventions

PCI — This will be performed at the discretion of the local care team in accordance with AHA guidelines for early treatment of post-cardiac arrest patients, based on clinical suspicion, EKG findings, and cardiac biomarkers.

AICD — Placement of AICD will also be at the discretion of local clinical team.

IVTM DEVICE INSTRUCTIONS FOR USE

Equipment Needed:

1. Thermogard XP®
2. IVTM™ Catheter Insertion Kit
3. IVTM Start-Up Kit
4. 500 cc bag of sterile NS (NOT 1000 cc)
5. Patient temperature probe (see temperature monitoring recommendation)

How to Select Cooling Catheter:

- Quattro®: Fastest cooling rate (3.1°C/hr),[6] preferred option, femoral placement, 45-cm length
- Icy®: Rapid cooling (2.1°C/hr),[6] alternative option for femoral placement, 38-cm length
- Solex 7®: Fast cooling rate (1.8°C/hr) via internal jugular or subclavian vein placement; only select this if femoral approach is contraindicated

Patient Weights and Heights	Catheter Consideration
>120 lbs or >5'1"	Quattro catheter
<120 lbs or < 5'1"	Icy catheter

General Practice

Initiation Phase

- All cooling catheters should be placed under Seldinger technique over a guidewire.
- Set the console for pre-cool and Max Power at the earliest opportunity.

Induction Phase

- Set the console in "Run" mode to start.
- Check to see if the pinwheel is spinning. If it is not spinning, check the following:
    - Air bubble may be in the flow indicator; flick the flow indicator to clear the bubble.
    - Catheter may be kinked; slightly reposition the catheter.
    - Tubing in the roller pump may have been loaded backwards; correct placement.
- Monitor patient; if there is shivering, treat per protocol.
- If the heater from a ventilator or continuous renal replacement therapy (CRRT) device interferes with cooling, turn off heater.

Maintenance Phase

- Monitor blood glucose, insulin level, polyuria, and electrolytes.
- Dressing should be changed if it becomes soiled, wet, or loose following hospital CVC protocol.
- Medication administration should be considered via IV or one of the infusion ports of cooling catheter (has triple lumen CVC function). Oral, nasogastric, or subcutaneous administration may be affected during cooling based on the degree of hepatic metabolism, first pass effect, and absorption impairment.

Rewarming Phase

- Anticipate hyperkalemia, hypercalcemia, hypoglycemia, hypotension, hypovolemia, and decreased SVR.
- Paralysis and sedation should be weaned
- Cooling catheter can be discontinued after rewarming if used to maximum indwell period.
- Maintain normothermia or fever avoidance by either ZOLL® STx™ surface cooling or exchange to another cooling catheter (also with CVC function).
- Cooling catheter is removed and disposed per hospital guidelines for CVC. Ensure that the catheter inflow and outflow lumens (orange color) are open prior to removing the catheter in order to allow residual saline to be expelled from the catheter balloons.

THERAPEUTIC HYPOTHERMIA
CLINICAL EXPERIENCE AND TIPS SHARED

1. Are trauma patients considered a contraindication for cooling? (University of Michigan protocol)

- There are very few post traumatic contraindications for TH except for significant active bleeding that cannot be controlled; if identified and controlled, TTM can be considered.
- Rib fractures are not a contraindication to cooling.

2. Are there considerations regarding temperature monitoring?

- When two temperature sources are used from different locations, patient temperature readings may vary. Prolonged discrepancies of greater than 1°C should be investigated.
- If patient has a history of renal disease with an hourly urinary output less than 30 mL/hr, consider using a rectal or esophageal probe.

3. What are early signs of shivering?

- Drop in oxygen saturation
- Increased respiratory rate
- Facial tensing
- Palpitation of muscle fasciculation of the face or chest

4. Is a chest X-ray needed to confirm the placement of cooling catheter?

- Per University of Chicago clinical experience, an X-ray may not be needed for femoral lines placement unless the patient is exceptionally short. It is not a reason to delay cooling initiation.

5. Does cooling need to be stopped if patients show bradycardia or are hypotensive during the cooling phase?

- Normal sinus bradycardia should be anticipated during hypothermia. Occasionally, a first-degree block may be seen, as well as prolonged QT intervals and Osbourne waves. These are all temporary and will disappear upon rewarming. No need to stop cooling. (Harborview protocol)
- If hypotensive, consider assessing fluid responsiveness as cooling can cause diuresis. (Harborview protocol)

6. Can an intra-aortic balloon pump (IABP) be used at the same time as a cooling catheter?

- Yes. The IABP is in the femoral artery and the cooling catheter is in the femoral vein. It is better to use the opposite leg of the patient due to the size of both catheters.

7. If a patient's temperature is below 33°C at hospital arrival, what target temperature should be used?

- Below is a list of suggested approaches per Harborview Medical Center protocol. It is not a recommendation from the company. It may or may not fit your hospital situation. Please follow your own hospital protocol if applicable.

<30°C (rare)	Therapy to **30°C** using Max Power • Select Pre-warm • Set TGXP target temperature to 30°C • Select Max Power mode of treatment • Set TGXP "Hi" temperature alarm limit to 30°C
30–33°C and hemodynamically unstable (rare)	Therapy to **33°C** using Max Power • Select Pre-warm • Set TGXP target temperature to 33°C • Select Max Power mode of treatment
30–33°C and hemodynamically stable (rare)	Therapy to **33°C** using Controlled Rate • Select Pre-warm • Set TGXP target temperature to 33°C • Select Controlled Rate mode of treatment and rewarm patient at a rate of 0.15°C/hr

8. Can the patient be placed on continuous renal replacement therapy (CRRT) during hypothermia therapy?

- Yes. Follow hospital protocol for CRRT. If the institution's CRRT equipment doesn't have a heater as part of its system, it may cause a slower rewarming rate. If this occurs, place warm blankets or an air warming blanket over the patient; turn the heater on the ventilator to 37°C.

References:

Information regarding the ICECAP Trial can be found here: https://siren.network/clinical-trials/icecap

[1]Bartlett E, et al. Systematic review and meta-analysis of intravascular temperature management vs. surface cooling in comatose patients resuscitated from cardiac arrest. *Resuscitation*. 2019;124:82–85.
[2]Maekawa T, et al. Precision and safety of an intravascular temperature management system for postcardiac arrest syndrome patients: a multicenter clinical trial (COOL-ARREST JP). *Therapeutic Hypothermia and Temperature Management*. 2020;10(3): 179–185.
[3]Heard K, et al. A randomized controlled trial comparing the Arctic Sun to standard cooling for induction of hypothermia after cardiac arrest. *Resuscitation*. 2010;81:9–14.
[4]Safety Communication from *U.S. Food and Drug Administration website*, 2020, https://www.fda.gov/medical-devices/safety-communications/fda-reminds-users-about-importance-following-instructions-cold-therapy-mode-water-circulating. Accessed 11 Jan. 2021.
[5]Badjatia N, et al. Metabolic impact of shivering during therapeutic temperature modulation. The bedside shivering assessment scale. *Stroke AHA*. 2008:39:12:3242–3247.
[6]Sonder P, et al. Efficacy of different cooling technologies for therapeutic temperature management: A prospective intervention study. *Resuscitation*. 2018;124:14–20.

MCN TP 2010 0280
104454-001, Rev. 02