NIH SIREN Emergency Trials Network

MANUAL OF PROCEDURES

Patterns **O**f **S**urvivors' Recovery **T**rajectories in the **ICECAP** trial (**POST-ICECAP**)

POST-ICECAP is an ancillary study to the NINDS/NHLBI funded, 'Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients trial, conducted within the NIH Strategies to Innovate Emergency Care Clinical Trials Network. POST-ICECAP will describe the extent of improvement or deterioration in functional, cognitive, and health-related quality of life outcomes within 12 months after an out-of-hospital cardiac arrest (OHCA). It will estimate the prospective associations of clinical interventions, rehabilitation, and social determinants with those dimensions of recovery in a large, well-characterized, racially/ethnically diverse, US-representative cohort of OHCA patients.

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Clinicaltrials.gov: This is an observational study, not an applicable clinical trial under FDAAA. Reporting in ClinicalTrials.gov is allowed but is not required by US law. There is no requirement by the NIH per the issued notice of award.

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1 Study Operations

Patients will be enrolled in the Intensive Care Units (ICU), inpatient floors or discharged from hospitals that are either in or are affiliated with the **S**trategies to **I**nnovate Eme**R**g**EN**cy Care Clinical Trials Network (SIREN) - Network. The SIREN Clinical Coordinating Center at the University of Michigan will serve as the Clinical Coordinating Center (CCC) for the POST-ICECAP study. The SIREN Data Coordinating Center (DCC) at the Medical University of South Carolina will serve as the Data Coordinating Center for the POST-ICECAP study.

More than 50 clinical sites are expected to participate in POST-ICECAP. It is expected that each participating site will enroll on average 5 subjects per year, allowing the enrollment to be completed within 4 years.

1.1 SIREN Organization

The NIH created the SIREN network to enable the conduct of high-quality, multi-site clinical trials and studies to improve outcomes for patients with neurologic, cardiac, respiratory, hematologic, and trauma emergency events.

The SIREN network consists of a DCC, a CCC, and 13 Award Hub Communities, each with up to several Hubs. Hubs, in turn, have Spokes. NIH collaborates actively in the SIREN network via the NIH SIREN Scientific and Administrative Program Directors.

1.2 SIREN Clinical Coordinating Center (CCC)

The SIREN CCC principal investigator chairs the SIREN Steering Committee and works closely on all SIREN activities in conjunction with co-investigators. The CCC PI is responsible for the integration of all elements of the network and all regulatory compliance. The CCC PI directs all budgetary activities and contracts within the network. The CCC Administrative Director and all administrative staff report to the CCC principal investigators. The SIREN CCC PIs serve as the primary advocates and representatives of the network promoting its mission within the specialties of Neurology and Emergency Medicine and at the NIH. The SIREN CCC co-PI assists the PI in directing the network and supporting its leadership and administrative needs. The SIREN CCC PI and co-PI are the primary liaisons for the NINDS Scientific Program Director and the Administrative Program Director. The CCC is responsible for communication with sites, training, and certification of Hubs, assurance of Hub regulatory compliance, monitoring of Hub performance, and the provision of feedback to ensure improvement of performance. The site manager, study monitors, and training coordinators perform these tasks. The CCC is also

responsible for study management including solicitation and internal network scientific evaluation and review of protocols and publications. Finally, the CCC is responsible for the management of all central study operations including the development of Manuals of Procedures, and operations of the Human Subjects Protection Unit.

1.3 SIREN Data Coordinating Center (DCC)

The DCC is responsible for the overall management of all SIREN statistical and data management activities. The DCC leadership provides extensive statistical and clinical studies expertise and serves as voting members of the SIREN Steering and Executive Committees. The POST-ICECAP DCC PI is responsible for the execution and oversight of the data management aspects of the study. The DCC will create and maintain the WebDCU clinical trial management system.

1.4 Contact Information and Whom to Call

For all issues related to eligibility, questionnaires, or instruments, email is the preferred option POST-ICECAP-contact@umich.edu

Education (training, website access, material development, technical support): Courtney Miller coraymon@med.umich.edu

WebDCU Support (user account requests, technical support, CRF completion): Sara Meyer (843) 792-1599 butlers@musc.edu

Site Management: Natalie Fisher brownnat@med.umich.edu

Finances: Deneil Harney dkolk@med.umich.edu , Valerie Stevenson vwillis@umich.edu

2 POST-ICECAP Protocol and other pertinent documents

Direct link to the study protocol.

Direct link to the study brief synopsis

2.1 Direct link for POST-ICECAP in a nut-shell

The study protocol for POST-ICECAP is also publicly available. It can be viewed by anyone with the URL address, and the public can find the link from the SIREN and ICECAP websites.

Clarifications, interpretations, and elaborations of the protocol are found throughout this Manual of Procedures. Refer questions and comments about the protocol to the Clinical Coordinating Center at POST-ICECAP-contact@umich.edu

3 Enrollment Procedures

3.1 Eligibility Criteria

Eligibility criteria for the POST-ICECAP study, and their underlying rationale, are defined in section 4 of the study protocol. Resources such as the study flyer (IRB-approved version) and templates for pocket cards listing eligibility criteria will be posted on the study website.

Additional information including clarifications of the criteria and specific examples of how the eligibility criteria are applied will be added to the FAQ section of the study website.

Directions on how to complete the eligibility Case Report Form (CRF) are provided in the CRF completion guidelines.

3.2 Operational Definitions Related to Enrollment

Coma after resuscitation from cardiac arrest is a patient who is endotracheally intubated and not following commands.

Sometimes the initial examination may be confounded by drugs or treatments delivered during resuscitation or in the emergency department. For example, patients who wake up within a few hours after sedatives are stopped on the first day may not have been comatose. Please reach out to discuss any cases with indeterminate coma - POST-ICECAP-contact@umich.edu.

Out-of-hospital cardiac arrest includes any cardiac arrest prior to arrival in the emergency department. It includes arrests witnessed by EMS on the scene or en route. It excludes cardiac arrests that occur in the Emergency Department or the inpatient setting.

Other Potential Scenarios:

- Patient came to another hospital emergency department with an unrelated condition and experienced a cardiac arrest in the ED or en route, while being transferred to your center for further care, they are no longer an OHCA.

- If they had a cardiac arrest in a doctor's office or urgent care we would still call it an OHCA. Essentially, a freestanding ED with CT scan and other resources, we would NOT call an OHCA.

- However, if it were an employee or a visitor and were not seeking care for an acute condition, we would consider those patients to be an OHCA.

3.3 Targeted Temperature Management in POST-ICECAP

- ★ **Any definitive temperature control device, e.g., surface or intravascular cooling, ECMO, or cooling blankets, either initiated or ordered within 24 hours of cardiac arrest.** All target temperatures, including fever control and durations, are acceptable (for example, an order during the first 24 hours to turn on a cooling device if temperature > 37.5℃ would be "active fever control" even if turning on the device was never required.)
- ★ **Protocol-driven fever prevention (even without a device), either initiated or ordered within 24 hours of cardiac arrest.** Qualification is based on intent and a structured plan. For example-
    - Documented nursing or institutional protocol or order set with Temperature target (e.g., <37.5°C or normothermia) and predefined escalation steps to intensify temperature-control measures if the target is not achieved or maintained.
    - Escalation may include increasing pharmacologic intensity (e.g., PRN → scheduled antipyretics), addition of non-invasive cooling measures (e.g., cooling blanket), or transition to device-based temperature management.

  Situations that do NOT qualify:

    - PRN antipyretics alone (e.g., "acetaminophen if fever")
    - One-time or ad hoc medication orders
    - Passive or ad hoc measures (e.g., ice packs, fans) without a structured protocol
    - No defined temperature target or escalation plan

  Please reach out to us for any clarifications at POST-ICECAP-contact@umich.edu

3.4 Severe mental illness requiring urgent psychiatric care

A patient with diagnoses like Schizophrenia or Bipolar disorder that are well managed with medication and therapy is eligible. The word "urgent" means untreated and out-of-balance disorders at the time of ED visit, and need to be addressed immediately in the days/weeks

following a patient's OHCA.

3.5 Participant ID Assignment.

Participant identification numbers are assigned in WebDCU™ for participants at the time that study data is first entered into the study database after enrollment. This number is the only means of participant identification used by the DCC. The date of enrollment is the time of the first-month visit regardless of the successful completion of the visit and gets captured in WebDCU™. The date of consent will be captured on the Subject Enrollment form.

4 Informed Consent

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

4.1 Informed Consent Process

Eligible participants may provide informed consent at any time prior to the first POST-ICECAP evaluation. The study aims to obtain consent within 30 days of OHCA, with the day of OHCA designated as Day 0. In special circumstances, the consent window may be extended to a maximum of 45 days, consistent with the timing of the first assessment.

Of note, 30-day assessment windows may receive extensions up to 60 days following discussion with the outcomes team; however, the consent window will remain capped at 45 days.

A member of the investigator team should approach an eligible patient to explain the study and its requirements. Leveraging our prior experience of recruiting cardiac arrest survivors in a longitudinal study, we have prepared a general guide for site coordinators to use for recruitment and retention purposes, as well as share their own experiences and best practices for collaborative learning.

Direct link to recruitment guide

To minimize the burden on families, it is reasonable to separate consent for ICECAP and consent for POST-ICECAP. Many ICECAP-eligible patients will not survive to hospital discharge and discussing POST-ICECAP would pose a burden without benefit to these families. Likewise, a family who declines randomization in ICECAP (screen failure) may not want to immediately discuss another study. That same family may be receptive to POST-ICECAP when it is clear that the patient is recovering and/or survives the hospitalization. Of note, waiting to ask for consent until it is probable that a patient will survive to hospital discharge does not threaten the data collection for POST-ICECAP. A patient, who is approaching discharge from the ICU, with a plan to go to a destination other than hospice, is likely to be eligible for POST-ICECAP.

A patient from whom consent for POST-ICECAP is obtained but who dies before discharge or is discharged to hospice from the acute care hospital will be considered not enrolled.

Initial Status	**Outcome at 1-month mark**	**Terminology**
Screened	Could not approach for consent, or declined participation	Screen Failure
Consented	Became ineligible before 1-month assessments (e.g., withdraws consent, went to hospice or died)	Not Enrolled
Consented	Could not complete 1 month or later assessments but not known to be dead (e.g. declined participation in the visit, unable to reach, or lost to follow-up)	Enrolled
Consented	Completes 1-month assessment	Enrolled

Eligibility of a person to serve as a subject's legally authorized representative (LAR) is determined in accordance with local law at the study site. It is important to remember that informed consent is a process rather than a piece of paper. Study coordinators and investigators should be familiar with the protocol and the content of the consent document. The study team should focus on helping the LAR understand the key elements of consent and should be sensitive to the information needs and emotions of the LAR.

The informed consent process should also be briefly documented in a study enrollment note (template) recorded in the participant's medical record or elsewhere as needed.

Special Considerations:

1. **Patients with Disorders of Consciousness**: For the majority of patients eligible to participate in the POST-ICECAP study, informed consent will be obtained from the participants. However certain patients with severe brain injury will be unable to follow commands at the time of consent. In those cases, the consent will be acquired from the LAR of the patient. We will seek to identify a court-appointed LAR/guardian or appropriately executed healthcare proxy. We will endeavor to document the authority of

the individual to serve as the LAR designated to provide surrogate consent by requiring the individual to present legal documents attesting to the fact. In the absence of a court-appointed legally authorized representative/guardian or appropriately executed health care proxy or a legal document, we will seek proxy consent from the following individuals or next of kin, as dictated by your local laws for order of proxies (Also included in the parent trial ICECAP informed consent policy): proxies may include the spouse (if not legally separated from the patient) or the domestic partner, a son or daughter eighteen (18) years of age or older, a parent, a brother or sister eighteen (18) years of age or older, or a close friend (meaning a person eighteen (18) years of age or older who has maintained such regular contact with the patient as to be familiar with the patient's activities, health, and beliefs).

In cases where the participant's representative gives consent, the participant will be informed about the study to the extent possible if the participant regains consciousness or capacity. During the course of the study, if the participant regains the capacity to consent, the participant will be told about their participation and offered the ability to leave the study if desired.

2. Pregnant women are not excluded from the ICECAP trial, and therefore potentially included in POST-ICECAP. Maternal OHCA is an important population to study and is included in POST-ICECAP.

4.2 Informed Consent Document

The informed consent document is a tool to help perform and document the informed consent process. A properly completed, legally effective, informed consent document is required prior to every enrollment.

The consent document can be found on the POST-ICECAP website (under final review). To promote equity, the same consent form will be used for this study at all sites. The IRB will insert the names and contact information for each site on each site's version of the locked-down form.

Preference of e-consent over paper consent forms: The consent form should typically be reviewed and signed on the e-consent platform. The e-consent platform accommodates those who need an enlarged font size, reduces the risk of accidentally using an outdated version of the consent form, and reduces the likelihood of a mistaken date or time of signature. The e-consent platform improves accountability and allows remote monitoring of form. A paper consent form should be used when the e-consent form is not functioning or available. If a paper consent form is used, the signed form is scanned and uploaded.

POST-ICECAP e-consent Instructions

The Site Participant Link to the e-consent instrument will be provided to the site once the site is released to enroll. No test data should be entered in the link. This is the link that only participants should be using.

It should be ensured that anyone who might be giving out the link for remote e-consent provides the Site Participant Link. Additionally, this is the link that should be bookmarked on the site's study iPad for e-consent administration in person.

The site study team members as well as the members of the CCC, and POST-ICECAP PIs will be notified by a RedCap generated email when an e-consent is submitted. These automated emails from the Redcap system are "secure" and will go out to everyone on the site's eDOA with consent responsibilities. The LAR completing the e-consent will also receive an email with a completed copy of the ICF if an email address is entered by them at submission.

When consent is obtained in person through e-consent, real-time access to the completed e-consent will not be necessary. However, the site members will still receive a secure email containing a PDF of the completed e-consent for all enrollments at their site.

If an e-consent is completed remotely, staff at the site should review the attached PDF in the notification email to confirm it was completed correctly prior to enrolling the eligible patient into POST-ICECAP. If a PDF was not attached in the email and it needs to be confirmed prior to enrollment, the research staff should contact the POST-ICECAP study manager, Natalie Fisher (brownnat@umich.edu) at (734) 846-9471 or use POST-ICECAP-contact@umich.edu

A secondary instrument, the Electronic Informed Consent Process Attestation is a required form when the consent process is completed remotely. When an e-consent Process Attestation is required the CCC will send the Principal Investigator/delegate a link to the form.

Training e-consent link

The training/test e-consent link with ICECAP consent as an example, can be used to practice entering or navigating through RedCap e-consent logistics: http://bit.ly/ICECAPTest

Click here for SIREN e-consent SOP

5. Study Team Training

Adequate training is required by the principles of the International Conference on Harmonization (ICH), and Guidelines for Good Clinical Practice (GCP).

Study team member's training must include required HSP and GCP training requirements, any Institutional training requirements, and training in all aspects of the study protocol.

5.1.1 Site PI and Primary Study Coordinator Training

Site Principal Investigators and Study Coordinators will receive training in the protocol, procedures (e.g., assessments), CRF completion, WebDCU™, and POST-ICECAP outcomes at the ICECAP Investigator Meeting, and through other scientific meetings or teleconferences, or other documentation.

5.1.2 Other Study Team Member Training

Principal Investigators and Study Coordinators are responsible for training additional members of their study teams. All study team personnel at each site will be required to undergo training prior to participation in the study. The site should maintain documentation of protocol-specific training for study team members (such as a meeting summary or minutes including those in attendance, or attestations of online or other training).

Study personnel who will be entering data into CRFs in the POST-ICECAP database on WebDCU™ will be required to complete the POST-ICECAP data training.

Study team personnel who will be maintaining regulatory compliance will be required to complete the POST-ICECAP regulatory document management training.

5.2 Outcome Assessor Training and Certification

For complete information on the training and certification of outcome assessors refer to the POST-ICECAP Outcomes Manual. All procedures for the 3 and 12 month visits outcome assessment are described in great detail in the Outcomes Manual.

Study personnel who perform the modified Rankin Scale should do the SIREN mRS training.

5.3 Site Retraining

5.3.1 Retraining for Cause.

Remedial training will be needed in case of recurring protocol violations, incorrect assessments, or frequent lost-to-follow-up of study participants. Retraining of site study team personnel will include a review of the study material specific to the problem area. Study teams will be retrained as needed by the site PI and primary study coordinator. The site PI and primary study

coordinator can retrain from online training resources or with the help of the CCC.

5.3.2 Retraining for Slow Enrollment

Study-specific refresher training will be mandated for POST-ICECAP sites that do not enroll a subject in six (6) consecutive months. Retraining will include:

1. All study team members active on the delegation of authority log will review the protocol and POST-ICECAP In a Nutshell.

2. Review of Data Training video or slides by team members as appropriate to their role.

After the above is completed, upload the PI Attestation of POST-ICECAP Retraining into the POST-ICECAP Database to document re-training. For more details regarding SIREN procedures, refer to the SIREN SOP for Hub Performance Assessment or contact your site's ICECAP site manager.

5.4 Training Resources.

POST-ICECAP training resources are located on the POST-ICECAP website.

Click here to reach POST-ICECAP Education and Training.

A POST-ICECAP specific JUST-IN-TIME training guide has been created for outcome assessors.

5.5 Protocol Change Dissemination.

Any protocol changes impacting the study team will require re-training. The training can be planned as face-to-face training, but may also include teleconferences, review of video recording, or other options as deemed appropriate by the Study PI based on the nature of the protocol change. The goal of the training is to ensure that all clinical site personnel who can attend receive the same information and are trained the same way in study procedure changes and data collection, to standardize the methods of data collection, and to ensure comparability of data across sites.

6 Safety Monitoring Plan

There are no adverse events collected as the study activities pose minimal risk to the participants. It does not involve any intervention and participants are only asked to complete questionnaires (paper, computer, and phone).

6.1 Potential Risks Specific to POST-ICECAP:

We will make every effort to accommodate participants' barriers without compromising the rigor and reproducibility of the study objectives. The study measures have been aligned with the ICECAP trial to remove redundancies. We may discover during screening or during follow-up assessments that a participant has conditions that warrant immediate treatment; a member of the research team will be available to talk to them and discuss appropriate care. A sincere effort to understand our participants' perception of respondent burden—whether the burden is psychological, physical, and/or economical - will be made.

6.2 Protection against loss of confidentiality risk:

As part of the process involved in obtaining written informed consent, all participants will be reminded that their responses are confidential and that they may refuse to participate in the project or withdraw at any time without explanation, and further, that such an action will in no way affect their future interactions with their health care provider. Only de-identified data will be transmitted to the Data Coordinating Center via the WebDCU case report forms. No paper documents with personal identifiers will be kept at DCC. Data collected via electronic adherence monitoring will be transmitted to a secured server via WebDCU™. No PHI will be transmitted. Electronic case report forms will be stored on a secure server and password-protected. The study staff is assigned a user ID and password to access the server. Study roles assigned by the Data Coordinating Center will determine the extent to which individuals will have access to case report forms or data. No hardcopy data will be stored. The PI will be responsible for ensuring that the confidentiality of the data is maintained at all times. All data will be obtained specifically for research purposes. Each subject in the study will be given a study ID that is not identifiable.

If there are questions or concerns about rights or the study, participants can contact the central IRB. Contact details are listed on the consent form.

7 Site Regulatory and Study Team Management

7.1 Regulatory Binder and Parameters Document

Required regulatory documents are defined by the POST-ICECAP Regulatory Parameters Document This document details each regulatory requirement for the site and team members and also contains instructions on which documents to upload in the POST-ICECAP Regulatory database.

WebDCU™ is the electronic regulatory study binder used in ICECAP and POST-ICECAP. All required regulatory documents must be uploaded into WebDCU™. Sites may wish to retain copies of regulatory documents locally, but only those uploaded into WebDCU™ are considered submitted and filed in the regulatory binder.

Expiring regulatory documents should be updated prior to their expiration date. WebDCU™ sends automated reminder emails to update a document at 30 and 7 days prior to a document expiring. In addition, reminders of expiring documents will also be sent to sites from the CCC. These reminders will include, but are not limited to: PI and other staff CV, training, and license expirations, FWA expiration, IRB approval renewal and/or expiration, and other outstanding regulatory documents. The site's primary study coordinator is contacted to request outstanding materials and to remind them of upcoming expirations in advance. All communications regarding expirations are documented.

7.2 Study Team Changes

Site Teams are managed within WebDCU's POST-ICECAP database. It is the responsibility of the site to update the eDOA to reflect study team changes and reconcile with other regulatory/training documentation prior to the start of trial responsibilities.

Current accurate records of the local POST-ICECAP study team must be maintained in WebDCU™. Study teams for POST-ICECAP are managed in the WebDCU's POST-ICECAP database in the Delegation of Authority Log. All sites are responsible for maintaining and reporting current and accurate personnel documentation in WebDCU™. Hubs are responsible for ensuring that their spokes are compliant with updating this information.

Please refer to the user manual on how to add/remove team members from the DOA log, or update training and documents, and how to manage user accounts in WebDCU™ under the User Management tab.

7.2.1 Change in Hub/Site Principal Investigator

The sponsor of the study is responsible for ensuring the qualifications of site investigators. Sites must notify ICECAP and POST-ICECAP Leadership of any change in Hub/Site Principal Investigator (PI) at least 30 days prior to the anticipated change. Notification should be accompanied by a current CV and NIH-required training in human subjects protection (HSP) and Good Clinical Practice (GCP) of the new Hub/Site PI. Sites should verify that the new PI has completed all regulatory requirements, prior to beginning study responsibilities. The PI changes will be submitted to NIH and the CIRB by the CCC.

7.2.2 Removal of WebDCU user accounts

The primary study coordinator at the site will notify the data manager at DCC and the site manager at the CCC when a primary team member departs and/or is no longer affiliated with the trial. The DCC data manager will close their WebDCU account and remove permissions.

7.3 Regulatory Readiness

Sites are required to be ready with regulatory documents and training prior to being released to enroll. All regulatory and training certifications are required to be uploaded to the WebDCU's POST-ICECAP database. These documents must remain current throughout the course of the study. It is the responsibility of the Hub and site to ensure regulatory compliance is maintained. The SIREN CCC will routinely monitor the database for regulatory compliance.

Overview of documents for the POST-ICECAP study start-up include:

- Ceding Request to Local IRB
- Ceding Acknowledgement from Local IRB
- Completed cIRB Tables (please reference -POST-ICECAP Regulatory Parameters Document)
- Completed Electronic Delegation of Authority Log
- Conflict of Interest
- Site IRB Approval
- IRB Approved Informed Consent Forms
- Non-English Informed Consent Forms (as required locally)
- IRB Notification of Approval Letter (Canadian sites only)
- IRB Study Communications
- Federalwide Assurance (FWA)
- HSP and HIPAA Policies
- Medical/Professional license
- CV
- Human Subjects Training (HSP) Certification
- Good Clinical Practice (GCP) Training

- mRS Certification
- WebDCU Data Training
- WebDCU Regulatory Document Management Training
- Attestation of Study Team Education & Training Protocol V2
- Completed Readiness Checklist POST-ICECAP Readiness Checklist
- Neuropsych Outcomes Training Certification

The Regulatory Parameters Document contains a description of each requirement and what needs to be uploaded into the POST-ICECAP Database/WebDCU™; this document can be found on the ICECAP website → in the tab "POST-ICECAP " under "DOCUMENTS". Once these documents are uploaded into the Regulatory database and accepted, a "Readiness Call" will be scheduled.

7.4 Readiness Call and Site Initiation

Prior to the enrollment of the first subject, site initiation (via a readiness call) will occur. The site will complete and provide a current Readiness Checklist confirming that staff have uploaded all required documents and completed training as described within the regulatory parameters document.

A "tentative" appointment for a Readiness Call will be set up by the site manager to help sites target readiness and complete required training and documents. To "confirm" the call, a completed readiness checklist will be emailed to the site manager, and all required regulatory documents uploaded into the POST-ICECAP database, at least 48 business hours prior to the scheduled call date. Upon reconciling the documents, the call will be "confirmed". The call will be rescheduled if the site is unable to provide the finalized documents and readiness checklist within 48 hours of the scheduled tentative call date.

The Readiness Call is the site initiation teleconference, equivalent to a site initiation visit. A phone call will be scheduled, coordinated, and conducted by the SIREN CCC site manager. Hub and site team members will be in attendance along with the national POST-ICECAP leadership team. During this call, site team members as well as POST-ICECAP study leadership, site manager, and study project manager will discuss any outstanding site training and planned enrollment processes. Any outstanding items (action items) if discussed during the call will need to be resolved before the site can be released to enroll.

After the call, if there are no 'action items' and the site is deemed ready, they will be released to enroll by the study site manager. If there are outstanding action items, the site manager will wait until these are completed before releasing the site to enroll. An email informing the site, ICECAP, and POST-ICECAP teams will be sent when a site is released to enroll. This email will serve as the formal communication to the site to begin enrollment.

7.5 Site Close-out

Closing to enrollment at sites that have enrolled at least one subject

If a site has enrolled at least one subject, the site IRB application will need to remain open until study results are published in the primary publication.

In order to close enrollment at a site, maintain compliance, and fulfill all regulatory requirements, the site will need to complete WebDCU documentation per the following instructions:

Spoke level

Notification: The spoke site needs to submit a letter (email correspondence is acceptable) to the Hub declaring their intention to stop screening and enrolling. The hub will submit the letter to the Study Executive Committee for review.

IRB Approval: The CCC will notify the cIRB that you are "closing to enrollment." However, the application must remain open until the end of the study is completed following primary publication. Continuing renewals will be kept current in WebDCU, to reflect that your IRB approval remains active.

Person level

Primary study team: The Hub PI, Site PI, Primary Study Coordinator, and study team members involved in regulatory affairs must remain "active" on the eDOA (no end dates added to their duties), and members will maintain site study regulatory compliance.

Non-primary study team: Study team members no longer participating in the trial can be made "inactive" by adding an end date to their role/duties on the eDOA. No further WebDCU documentation is required nor needs to be maintained for these individuals.

Regulatory Compliance During Study Closure:

- Once the cIRB acknowledges the study closure at your site, the cIRB Closeout Notification will be available in WebDCU as "IRB Acknowledgment – Site Close-Out"

7.6 Subject Log and Binder

Because WebDCU serves as both the electronic Regulatory Binder and the eCRF, sites are only required to maintain organized files of a few items. These include a Master Subject Log linking local patient identifiers and medical record numbers with the study ID number. The Master Subject Log should also include contact information for the participant. Subject files should include necessary source documents (e.g., worksheets), but need not include documents sourced from the medical record. The subject file should also include any original paper signed informed consent documents.

8 Monitoring

8.1 On-site and Remote Monitoring Including Source Documentation Verification

The purpose of source document verification and site monitoring is to ensure that the rights and well-being of human subjects are protected, that study data are accurate, complete, and verifiable, and that the study is conducted in compliance with the current approved protocol, GCP, and applicable regulatory requirements.

The POST-ICECAP site monitoring plan facilitates compliance with good clinical practice (GCP) guidelines, applicable FDA regulations (21 CFR 812 and 813), and the FDA's "Guidance for Industry. Oversight of Clinical Investigations- A Risk-Based Approach to Monitoring".

POST-ICECAP site monitoring will be managed by the SIREN CCC at the University of Michigan. The POST-ICECAP Site Monitoring Plan will be updated regularly. Information about how data is to be collected and documented is included in the POST-ICECAP Case Report Form Completion Guidelines.

The on-site Monitor will verify data entered into the POST-ICECAP Database/WebDCU™ against source documents. Source documents are original documents, data, and records. Examples include hospital records, clinical and office charts, laboratory notes, evaluation checklists, recorded data from automated instruments, study worksheets, and eCRFs (in the case of direct data entry). Monitors will query inaccuracies between the source documents and WebDCU™ database, including the omission of data, and will verify the informed consent of all study participants.

Source document verification may also be performed remotely by reviewing source documents that have been uploaded into WebDCU™ or via remote access to electronic medical records (EMR).

Click here for the POST-ICECAP Study Monitoring Plan

8.2 Central Data Monitoring

Central data monitoring is a process of data quality assessment and improvement that involves checks of logic, consistency, continuity, and pattern checking that is done by the DCC and is largely transparent to the sites.

9 Protocol Deviations and Unanticipated Problems

Protocol deviations must be assessed throughout each subject's participation in the study.

9.1 Protocol Deviation Reporting

Protocol deviations and unanticipated problems must be reported in WebDCU™ when applicable. Protocol deviations that meet the CIRB reporting requirements will be reported to the cIRB by the CCC. Protocol deviations may also need to be reported locally per local site requirements, but local reporting is not otherwise required by the sponsor.

Serious or repeated protocol deviations will require the development of a Corrective Action/Preventative Action (CAPA) plan.

9.2 Corrective Action/Preventative Action (CAPA) Plans

The Development of a CAPA plan may be initiated by the site study team, local IRB, or the SIREN-CCC. Potential triggers include protocol deviations, data quality problems, or systematic problems identified by study teams or monitors. CAPA plans must be reviewed by the site study team, SIREN-CCC site manager and monitor. The SIREN-CCC site manager, SIREN-CCC project monitors, or study leadership may approve CAPA plans.

CAPA plans are reported and documented in WebDCU™.

10 Retention of Study Records

Study records will be retained for a minimum of 3 years from the completion of the research. FDA, NIH, and local requirements may require longer retention. Sites should maintain records for the longest of all relevant requirements. FDA regulations [56 CFR 56.115(b)] also require that participating institutions retain all IRB records for at least 3 years. All records must be accessible for inspection and copying by authorized representatives of HHS and FDA at reasonable times and in a reasonable manner. Generally, it is prudent to plan to retain records in long-term storage for 7-10 years.

11 Payment to Clinical Sites

Milestones & Payment Document

Start-up payment:

1. A one-time payment of **$2,000 (inclusive of F&A costs)** to support the effort and costs of site initiation will be paid to all POST-ICECAP sites once they have completed the required trainings, submitted regulatory documents, obtained required approvals and are released to enroll subjects by the Clinical Coordinating Center. Additional sites over 50 that are released to enroll, are not eligible for this start up payment.

Per-subject payments:

1. There will be two per-patient payments i.e., after 3 months and 12 months.
2. First payment at 3 months will be after an eligible subject is enrolled and all study CRFs required from enrollment through the 3 month visit are submitted and free of queries.
3. Second payment at 12 months is when the End of Study (EOS) visit occurs within the timeline specified in the trial protocol, all study CRFs required for the EOS visit are submitted and free of queries.
4. As shown in the table below, there is an additional payment of $200 to support the completion of both the BTACT and Neuro QoL at 3 and 12-month visits.
5. If a participant dies after 1 month and before the 3-month visit - sites will be paid for the 3-month visit ($400) but not for any other visits.
6. If a participant dies after 3 months – sites will not be paid for missing visits.
7. If a participant voluntarily withdraws their consent before any visit - sites will not be paid for missing visits.
8. If a participant is lost to follow-up: sites will not be paid for missing visits.

Visit	Remote Visit	BTACT & Neuro QoL	Payment number	Payment in $
Enrollment/Intake Questions and 1 month	$0	$0	n/a	(no payment until 3 month visit)
3 month	$400	$200	**1**	$400 for the visit with an additional $200 for BTACT and Neuro QoL at 3 months ($0, $400, or $600)
6 months	$400	-	**2**	(paid at 12 months)
9 months	$400	-	**2**	(paid at 12 months)

12 month	$400	$200	**2**	$400 for each visit completed (6, 9, 12 months) with an additional $200 for BTACT and Neuro QoL at 12 months ($0, $400, $600, $800, $1000, $1200, or $1400)

All payments are inclusive of F&A.

12. Payment to participants

We encourage sites to reimburse participants for time, inconvenience, parking, and travel. Please use your institutional methods to arrange it.

The rate per visit should not exceed GSA per diem for the site location.
https://www.gsa.gov/travel/plan-book/per-diem-rates

Note: Reimbursement for participants comes from the per-subject payments to sites.

13 WebDCU™ User Manual

The User Manual is located within WebDCU's POST-ICECAP Database within the Toolbox Tab, under Project Documents.

14 Case Report Forms

14.1 CRF Study Book

The CRF study book is arranged by visit and is available in WebDCU to be downloaded from the Data Collection Schedule tab.

14.2 CRF Completion Guidelines and Timetable

POST-ICECAP Case Report Form Completion Guidelines.

15 Outcomes including Participant Tracking & Follow-Up.

15.1 Outcomes Manual of Operations

The POST-ICECAP Outcomes Manual of Operations (OMoP) delineates the POST-ICECAP primary and secondary outcomes procedures in detail. This manual includes descriptions of the outcomes-related POST-ICECAP study team roles including Outcomes Assessor and Neuropsychological Outcomes Assessor. The OMoP also details the training and certification (and expiration of certification) processes for these POST-ICECAP study roles as well as the quality assurance processes that will be used throughout the POST-ICECAP study. Next, the OMoP outlines the POST-ICECAP procedures for participant retention, scheduling of appointments, and general outcomes testing procedures. The remainder of the OMoP provides very detailed information regarding each of the POST-ICECAP outcomes.

It is highly recommended that all POST-ICECAP study personnel read sections 1 through 10.8 (~23 pages) of the OMoP. Outcomes Assessors must read the entire OMoP as part of their certification process.

15.2 Participant Tracking & Follow-Up

Participants will be followed by study staff daily while hospitalized in the ICU. This frequent contact allows for relationships to be established between study staff and the patient's family, which is important for enrollment and subsequent follow-up. To attain a high rate of follow-up, the study team will request multiple phone numbers (home, cell phones, pagers, etc.) and email, mailing, and street addresses for the subject and others, for example, his/her relatives, friends, primary doctor (if available), caregiver, and clinics. At the time of consent and enrollment, proxy respondents will be asked to provide the address and telephone number of the place where the subject will likely reside following discharge. At the time of hospital discharge, each participant's disposition will be noted (nursing home, rehabilitation facility, another acute care hospital, subject's home, relative's home) so that plans can be made for follow-up visits.

Prior to or at discharge from the hospital, participants will be given information about the study and what to expect for follow-up contacts, as well as contact information for study staff. Study staff will contact participants by telephone periodically (once per month) to maintain rapport, update contact information changes, update current living situation, and schedule a date for the 1-month telephone interview. In the event communication is lost with a participant, the local study team should begin extensive efforts to locate the individual (e.g., whitepages.com, google or other search engines, Facebook, etc.)

Study staff will then contact the participant and request at least 2 dates and times that would be agreeable to them for the 90-day follow-up assessment, preferably in person. If the patient is unable or unwilling to come to the clinic or have a staff member go to their place of residence for an in-person visit at the approximate 90-day time point.

Similar processes should be followed for subsequent telephone-based (6, 9 months) and in-person (12-month) visits.

Subjects cannot be deemed <u>"Lost to Follow Up"</u> without the POST-ICECAP Operations Committee's approval. The site PI must present a case to the Operations Committee that includes the efforts exerted to locate the study subject. The Site PI may be asked to continue their efforts prior to approval.

16 Statistical Analysis Plan (SAP)

Click here for the POST-ICECAP SAP

17 Publications and Data Sharing Policies and Procedures (link to SOP)

Please refer to the SIREN SOP documents found at
https://siren.network/nett-resources/standard-operating-procedures

The ICECAP and POST-ICECAP investigators and the SIREN Network are committed to resource and data sharing with the clinical research community both within and external to the network.

The primary results of the study will be disseminated by publication in the peer-reviewed medical literature. In accordance with the NIH Public Access Policy, the investigators will submit an electronic version of their final, peer-reviewed manuscripts (directly or through the publisher) to the National Library of Medicine's PubMed Central, no later than 12 months after the official date of publication.

The study will be registered at http://www.clinicaltrials.gov, and results of the POST-ICECAP study will be reported there within a year of trial completion. Submission of results to http://www.clinical trials.gov will be performed consistent with the requirements for applicable clinical trials per FDAAA 801 requirements.

After completion of the study and dissemination of primary study results, the CRF data will be made publicly available. With the assistance of the CCC as needed, the DCC will prepare study data for submission to the NHLBI data repository managed by BioLINCC (https://biolincc.nhlbi.nih.gov/home/) or elsewhere as arranged with the Institute. The public-use dataset will be stripped of any and all personal identifiers and will undergo a de-identification process. HIPAA-compliant de-identification will include the removal of study ID numbers and assignment of a random number to each subject, deletion of hub/spoke ID numbers and assignment of a random number to each hub/spoke, deletion of investigator or assessor name/ID, retention of the month and year and the order in which patients enrolled.

Derived variables necessary to reproduce the primary analysis will be included. All manuscripts, abstracts and press releases using the study data must acknowledge POST-ICECAP/ICECAP/SIREN investigators and the NINDS/NHLBI as the study sponsor with the relevant grant numbers.

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

18 Ancillary Study Policies and Procedures

https://siren.network/nett-resources/standard-operating-procedures

19 POST-ICECAP Frequently Asked Questions

Frequently asked questions (FAQs) are located at POST-ICECAP FAQs.

New POST-ICECAP Q&A will be posted and this page is updated regularly.

20 List of Resources for Participants

We have created a list of informational resources, support groups, and mental health resources for patients and families affected by cardiac arrest. Direct link to resource list

MOP Change Log

Date	Section	Previous Language	Updated Language
	4.1 Informed Consent Process	Eligible participants may provide informed consent at any time before the time of the first POST-ICECAP evaluation (1 month after cardiac arrest)	Eligible participants may provide informed consent at any time prior to the first POST-ICECAP evaluation. The study aims to obtain consent within 30 days of OHCA, with the day of OHCA designated as Day 0. In special circumstances, the consent window may be extended to a maximum of 45 days, consistent with the timing of the first assessment. Of note, 30-day assessment windows may receive extensions up to 60 days following discussion with the outcomes team; however, the consent window will remain capped at 45 days.
5.18.2026	**3.2 Operational Definitions Related to Enrollment**		Sometimes the initial examination may be confounded by drugs or treatments delivered during resuscitation or in the emergency department. For example, patients who wake up within a few hours after sedatives are stopped on the first day may not have been comatose. Please reach out to discuss any cases with indeterminate coma - POST-ICECAP-contact@umich.edu.
