NIH SIREN Emergency Trials Network

SUBSTUDY SUPPLEMENT

PREcision Care In Cardiac ArrEst - ICECAP (PRECICECAP)

A multicenter, observational substudy to the ICECAP trial to define patterns of post-arrest injury (phenotypes) that predict optimal duration of induced hypothermia after cardiac arrest

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1 Study Operations

Participants in the parent ICECAP trial will be co-enrolled in the observational PRECICECAP substudy at a subset of approximately 12 high-performing ICECAP sites.

The SIREN Clinical Coordinating Center at the University of Michigan will serve as the Clinical Coordinating Center (CCC) for both the ICECAP trial and PRECICECAP. The SIREN Data Coordinating Center (DCC) at the Medical University of South Carolina will serve as the Data Coordinating Center for both the ICECAP trial and PRECICECAP.

1.1 SIREN Organization

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

The SIREN network consists of a DCC, a CCC, and 11 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 provides scientific, protocol, regulatory, site management, contracting and site payment support to the sub-study team. The CCC leadership includes the principal investigators, administrative director, and senior staff including the network's human subjects protection and education specialists, and lead site managers and monitors. The CCC organizes the network executive, steering, and operations committees, as well as trial specific working groups, study coordinator calls, and topic-focused working groups.

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 trials expertise and serves as voting members of the SIREN Steering and Executive Committees. The DCC has created and maintains the WebDCU clinical trial management system, including case report forms used for PRECICECAP data collection.

1.4 Contact Information and Whom to Call

For questions about PRECICECAP enrollment, study procedures and data transmission, please consult the current and detailed list of contacts maintained on the PRECICECAP website.

For immediate emergency assistance during ICECAP and PRECICECAP enrollment, please use the 24/7 ICECAP Principal Investigator Hotline at 1-833-442-3227.

For device-specific issues with the Moberg CNS bedside monitor, including connectivity issues to a subject's bedside monitor, archiving of recorded data or the CNS Monitor graphical user interface, please contact the vendor's study specific support line directly 24/7 at 1-888-662-7246. Non-urgent device questions can be sent to: support.us@micromedgroup.com

2 Enrollment Procedures

2.1 Eligibility Criteria

Eligibility criteria for PRECICECAP are:

- Subject is enrolled (randomized) in ICECAP at a PRECICECAP participating site

Exclusion criteria for PRECICECAP are:

- Moberg CNS monitor is not connected to the bedside monitor within 6 hours of ICECAP enrollment (defined as time of randomization).

It is the expectation that almost all subjects enrolled in the ICECAP trial at participating PRECICECAP sites will also be enrolled in PRECICECAP.

Enrollment in PRECICECAP is defined as connection of the Moberg CNS monitor to the patient's bedside monitor with initiation of clinical data connection (i.e. the Moberg CNS monitor is initiated). All subjects enrolled in PRECICECAP will be included in the final analysis. Time of enrollment in PRECICECAP is defined as the start time of first available cardiopulmonary waveform data aggregated on the Moberg monitor data transfer.

2.2 Subject ID Assignment

Subject identification numbers are assigned in WebDCU for potential ICECAP subjects at the time that study data is first entered in the study database, prior to enrollment. This number is the only means of subject identification used by the DCC. This subject ID remains constant after randomization/enrollment in ICECAP and for the duration of the trial.

Case report form data are collected in WebDCU using the same subject identification number assigned for the ICECAP trial. All other high-resolution data collected for PRECICECAP (EEGs, brain imaging, Moberg monitor files, electronic health record medication administrations) will be indexed using this same subject ID.

2.3 Screening Report

Screening reports are required in PRECICECAP for both scientific and administrative purposes. The denominator of patients for the screening report will be ICECAP-enrolled patients at participating PRECICECAP sites. Reasons for failed co-enrollment must be documented in WebDCU.

3 Informed Consent

The protection of human subjects is paramount in this trial and in everything SIREN does. Strict compliance with all applicable regulations is mandatory. A single informed consent form will be used for both ICECAP and PRECICECAP. The informed consent process for ICECAP and PRECICECAP can be found in the ICECAP Manual of Procedures.

PRECICECAP does not require a separate consent process because this substudy does not introduce any new or additional interventions, risks, or assessments beyond those described in the parent consent document. The substudy simply aggregates more granular detail of the same physiological, clinical, and imaging data collected in the parent trial. Collection of these kinds of data is already described in the parent consent document, and thus the LAR will have already consented to collection of these data prior to consideration and enrollment in PRECICECAP.

Subjects or their LAR may withdraw consent from participation in ICECAP at any time. Discontinuing participation in ICECAP also discontinues participation in PRECICECAP. No further data will be collected or analyzed after the time of withdrawal of consent and discontinuation of participation.

4 Clinical and Study Team Training

We will provide multiple routes for broad and site-specific clinical training. These will include annual investigator meetings held in conjunction with the annual ICECAP investigator meeting. During the first study year, we will hold periodic PRECICECAP specific interactive webinars to disseminate high-level information about the study aims and conduct, answer common questions and identify potential obstacles to implementation that are broadly relevant across sites. In addition to general informational sessions, a series of site-specific training and readiness activities will occur, as detailed below.

4.1 Clinical Team Training

It is important to have the buy-in and participation of the clinical teams managing the initial and ongoing critical care of subjects. Study teams must provide sufficient preparatory, just-in-time, and ongoing training to educate and support these clinical teams. Training should be inclusive of key elements of the study protocol and all of the clinical standardization guidelines. By the nature of the PRECICECAP study protocol, clinical team training should include the following stakeholders who will contribute to study data collection or interface with study-specific devices: ED and ICU physicians who staff units in which ICECAP patients may be bedded; ICU nurses who staff these units; and, EEG technologist responsible for initiating continuous EEG monitoring.

4.1.1 Initial Training

Clinical staff at each participating site will be trained prior to the start of the trial. All staff with potential to be involved in the enrollment and treatment of PRECICECAP subjects will be targeted for this training. Materials to facilitate this training will be provided by the SIREN CCC.

The readiness checklist will be given to the site PI and primary study coordinator prior to a readiness call. This checklist will ask the study team to describe their processes addressing important aspects of the PRECICECAP trial, including clinical standardization guidelines, and competing trials. A readiness call will be held with the site PI, study coordinator and other site investigators. From the PRECICECAP team, one of the study PIs and CCC and DCC staff will all participate in the readiness call. After successful completion of the readiness call, the site will be released to enroll.

4.1.2 Ongoing Training

Continuous on-going training of clinical staff will be required at each site. This will consist of on-line or newsletter review of educational material from the SIREN CCC. It will be the

responsibility of each Hub and site to ensure that their clinical team has received and distributed the educational material. Interval on-going training consisting of refresher lectures that combine general content on targeted management and study-specific material will be performed annually. Following enrollment of a site's first subject, the site will be contacted by the PRECICECAP leadership team for a debriefing on enrollment procedures, documentation, and data management.

4.1.3 Clinical Team Newsletter

A Clinical Team Newsletter will be e-mailed quarterly to the ICECAP sites and posted on the SIREN website. The newsletter will report updated trial information, enrollment numbers, important dates to remember, education opportunities, lessons learned, and information deemed important at the time of publication.

4.2 Study Team Training

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

Study team training is distinct from the Clinical Team Training described in Section 5. Study team members training must include required HSP and GCP training requirements, any Institutional training requirements, and training in all aspects of the trial study protocol.

4.2.1 Site PI and Primary Study Coordinator Training

Site Principal Investigators and Study Coordinators will receive training in PRECICECAP operations, CRF completion, WebDCU™ and ICECAP database at the Investigator Meeting, and through other meetings or teleconferences, or other documentation.

4.2.2 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 trial. 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 ICECAP database will be required to complete the ICECAP data training.

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

4.3 Site Retraining

Remedial training will be needed in case of recurring protocol violations or persistent transgressions from the clinical standardization guidelines. Retraining of clinical teams will be conducted by the site study team personnel and 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 PSC can retrain from online training resources or with the help of the CCC.

Consistent with SIREN standard operating procedures, sites will also be required to retrain every six months if they do not enroll a participant in that time window. PRECICECAP retraining can be performed and attested to along with ICECAP retraining, as part of a single process as appropriate.

Re-training for all sites may also be required by the study leadership as needed to address quality improvement efforts in study conduct, to implement any corrective or preventive action plans that arise, or to introduce any changes in the substudy procedures or processes that may be needed. Mandatory retraining for all sites will be required at the discretion of the sub-study leadership.

4.4 Training Resources

PRECICECAP training resources are located on the PRECICECAP website.

5 Intervention and Study Procedures

There are no study interventions in PRECICECAP. We will collect cardiopulmonary monitoring, electroencephalography, brain imaging, medication and clinical examination data with greater granularity than collected in the parent study. No new monitoring, testing, or imaging is performed for research purposes. This substudy only collects high resolution data that participating sites already acquire and record as part of routine clinical care.

5.1 Clinical Standardization Guidelines

ICECAP provides clinical standardization guidelines that describe a consistent set of practices for the routine clinical care of comatose survivors of cardiac arrest to reduce variation in background practice for participants enrolled in the parent trial. Adherence to the clinical standardization guideline whenever possible, inclusive of the approach to withdrawal of life sustaining therapies (WLST) and neuro-prognostication, is important to PRECICECAP as well as to the parent trial. PRECICECAP sites are selected for their routine clinical use of the advanced monitoring and imaging being collected in this substudy. For these sites the clinical standardization guidelines are enriched to include the following additional recommendations for standardization of routine care.

1. Routine clinical use of a structured neurological examination including additional features supplemental to the ICECAP daily assessment on hospital arrival (prior to ICECAP randomization) and daily in the ICU.
2. Routine clinical use of invasive arterial pressure monitoring
3. Routine clinical use of brain CT imaging at admission
4. Routine clinical use of continuous electroencephalography recorded from ICU arrival until at least 12 hours after rewarming
5. Routine clinical use of brain magnetic resonance imaging on day 3-5 after cardiac arrest

Details of these data elements (e.g. MRI sequences, EEG montages and devices, etc) are left to local clinical practice.

Refer to the ICECAP clinical standardization guidelines document for more extensive discussion of the purpose, terminology, and monitoring of routine clinical care standards in the parent trial. Please note that transgressions from the clinical standards are not research protocol deviations, and that sites are always expected to provide patient-centric care appropriate to the individual in their care.

5.2 Study procedures

5.2.1 Pre-enrollment neurological assessment

Subjects who are enrolled in ICECAP will have undergone a pre-randomization neurological assessment to ensure ICECAP eligibility. Because awake patients do not receive post-arrest hypothermia, this assessment will typically occur after initial post-arrest stabilization but prior induction of hypothermia. At PRECICECAP participating sites, this assessment should include evaluation of major brainstem reflexes (pupillary light reflex, corneal reflex, cough, gag), motor exam, and assessment of level of responsiveness. To aid in retrospective abstraction of presenting neurological assessment, this assessment should be clearly documented in either a clinical note or non-clinical communication (e.g. email) to the site's PRECICECAP study coordinator.

5.2.2 Initial brain CT imaging

Subjects at PRECICECAP participating sites undergo brain CT imaging as routine clinical care early after cardiac arrest.

5.2.3 Connect Moberg CNS monitor to bedside clinical monitor(s)

Subjects at PRECICECAP participating sites undergo routine cardiopulmonary ICU monitoring, including invasive arterial blood pressure monitoring, as routine clinical care. PRECICECAP will capture these waveform and vital sign numerical data using the study-supplied Moberg CNS monitor. Instructions for setup of the Moberg CNS monitor are in Section 5.3. The Moberg CNS monitor will be connected to the bedside ICU monitor (with cardiopulmonary data), definitive temperature device, and the continuous EEG (cEEG). Other neuromonitoring devices (ICP, PbtO2, quantitative pupillometry, etc) that may be used optionally at sites should also be connected. Connect the Moberg CNS monitor as soon as possible post-arrest, ideally within two hours of ICECAP randomization but **never more than 6 hours after ICECAP randomization** (See Section 2.1, Exclusion Criteria). If ICU admission is anticipated to be delayed by > 2 hours, the Moberg CNS monitor may be connected in the emergency department (ED).

5.2.4 Connect Moberg CNS EEG amplifier to clinical EEG

Subjects at PRECICECAP participating sites undergo routine continuous EEG (cEEG) monitoring. cEEG will be initiated as soon as possible after cardiac arrest and continued for 72 hours post-arrest or for at least 12 hours after return to normothermia (whichever is longer) as part of standard clinical care. The Moberg CNS monitor includes its own EEG amplifier, which allows recording of cEEG for research purposes in parallel with routine clinical monitoring. The PRECICECAP study team will work with the site PI and EEG technologists to tailor site-specific EEG acquisition procedures based on each site's local clinical hardware. Generally speaking, use

of jumper-splitter cables allows simultaneous clinical and research monitoring from the same clinical electrodes affixed to the subject's scalp. On initiation of clinical EEG monitoring, a PRECICECAP study investigator or EEG technologist will use these jumper cables to ensure EEG capture on both the Moberg CNS monitor EEG amplifier and any clinical EEG system used by the enrolling institution. The EEG signal can be split in this way without degradation in signal quality. See section 6.3 for additional information on Mober CNS monitor system configuration.

5.2.5 Clinical monitoring and daily CRF completion

PRECICECAP enrolled patients will undergo daily structured neurological assessments by a study investigator. This assessment is complementary to that required by the ICECAP trial and includes several additional data elements including the timing of assessment in relation to last sedative and analgesic administration, quantitative results of prognostic testing if performed (somatosensory evoked potential, neuron specific enolase, pupillometry), and those requisite components to calculate Sequential Organ Failure Assessment scores not already included in the ICECAP CRFs. When magnetic resonance imaging is performed, vital signs at the time of image acquisition are also recorded. This supplementary information in the PRECECICAP daily CRF is completed daily on post-arrest days 1-5.

5.2.6 Brain magnetic resonance imaging (MRI)

PRECICECAP participating sites obtain brain MRI on post-arrest day 3-5. This should occur *after* hypothermia and rewarming for the ICECAP trial are completed and the subject is normothermic. Among comatose patients, MRI contributes to guideline-concordant neurological prognostication. Among awake patients, MRI can identify anticipated neurological deficits and inform rehabilitation. Note that EEG must typically be removed prior to MRI, unless FDA-approved MRI-compatible non-ferromagnetic EEG electrodes are used. It may be necessary to disconnect and then reconnect the EEG for MRI so that the MRI can be obtained in the requisite time frame.

5.2.7 Collection and flow of data

<u>WebDCU data entry</u>

Case report forms (CRFs) will be completed in WebDCU. Automated emails to the site investigators and study coordinators will prompt completion of delayed forms. PRECICECAP CRF completion policies parallel ICECAP's policies.

<u>Imaging portal data upload</u>

Image DICOM files should be deidentified by the study site at the time of their export from the

site's Picture archiving and communication system (PACS) with removal of patient name, medical record number, other account numbers, date of birth, and any other identifiers embedded beyond those allowable in a HIPAA-limited data set. Image DICOMs will include subject ID number and date/time of acquisition. Sites with established protocols for DICOM deidentification developed for other trials should follow their local protocols. The PRECICECAP leadership team will work collaboratively with sites that do not have an established precedent to develop procedures that ensure adequate deidentification.

Image DICOMs are then uploaded to the imaging portal within four weeks of PRECICECAP enrollment. This portal is hosted on Stanford University RedCAP, an NIH-funded HIPAA compliant research database. The Imaging Portal Guide contains details on this secure upload process. Frequently asked questions can be found on the PRECICECAP FAQ page.

IBM Cloud data upload

Moberg CNS Monitor is connected as above. Real-time data collection on the Moberg CNS Monitor concludes five days (120 hours) after PRECICECAP enrollment, or at death or discharge when this occurs prior to 5 days after enrollment. Data should be downloaded at the time collection is completed. Sites will be responsible for uploading data from the Moberg CNS Monitor device to the IBM cloud space where the data will be accessed by the PRECICECAP study team. As part of the readiness call for each site, a primary team member responsible for the data upload should be identified to ensure accounts are set up before the site is released to enroll.

Medication data should be uploaded to the IBM cloud space periodically, at a minimum after every five patients or once every twelve month. Participating PRECICECAP sites use an electronic health record (EHR, most commonly Epic or Cerner) that maintain a medication administration record (MAR) including all intermittently dosed medications and titrations of continuous infusions. These EHRs allow export of the MAR in a comma separated value or other delimited file format. The detailed MAR for each patient is uploaded into the IBM cloud space, where it is parsed to a standardized format for data harmonization.

Data Security

All data streams used in PRECICECAP use multiple layers of data protection. First and foremost, the data collected will be highly limited datasets without any personal identifying information and with very limited protected health information (dates and times). Linkage of data is only by the assigned study subject identification code. No sensitive identifiable human subject research data are collected. All imaging and EHR data and metadata are deidentified or redacted except for dates and subject identification code. WebDCU, IBM Cloud, and Stanford REDCap are HIPAA and 21 CFR 11 compliant platforms. Each has robust physical and virtual

protections including data encryption at rest storage, and rigid user access controls. Data exports for analysis can be fully deidentified using scrambled subject codes and jittered dates and times.

5.2.8 Table of Data Acquisition

	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5
Moberg CNS Monitor	---------->					
cEEG	---------->					
Head CT	X					
Brain MRI				X		
Structured Neurologic Exam	X	X	X	X	X	X

5.3 Moberg Device Procedures

The Moberg CNS Monitor will be used to integrate physiologic data collected from all bedside monitors. The Moberg CNS Monitor collects data from over 30 medical devices via digital interfaces. The data are collected at the native resolution (data sampling rate) of the source device providing a high definition and time-synchronized record of the participant's physiology (as opposed to a static electronic medical record). The Moberg CNS Monitor is FDA cleared and provides a nurse-friendly display as well as embedded instructional material to streamline setup and reduce errors in data collection. It will be checked daily for proper functioning by nursing staff or research staff.

Additional technical support regarding the configuration and use of the PRECICECAP Moberg CNS monitor can be found in the PRECICECAP-Moberg Instruction Manual.

6 Safety Monitoring Plan

PRECICECAP is a purely observational study of data already acquired for clinical purposes using approved, commercially available diagnostic monitoring and imaging. The only incremental risk anticipated in PRECICECAP is exposure to an inadvertent breach of confidentiality. Significant breaches of confidentiality without injury will be reported as Unanticipated Problems Involving Risks to Participants or Others. Harm or interventions to prevent harm resulting from breaches of confidentiality will be reported as adverse events. Any breach of confidentiality will be reported in WebDCU, and assessed in a manner consistent with existing ICECAP safety monitoring and other procedures including Independent Medical Safety Monitor review of all serious adverse events. Any event resulting specifically from PRECICECAP participation will be reviewed by the PRECICECAP leadership team. Adverse events reported in relation to the ICECAP trial do not need to be separately reported to PRECICECAP.

The SIREN DSMB providing oversight of ICECAP will also provide oversight of PRECICECAP.

7 Site Regulatory and Study Team Management

7.1 Regulatory Binder and Parameters Document

PRECICECAP requires no additional regulatory documents beyond those required by the ICECAP trial. The only contents of the study binder for PRECICECAP are worksheet source documents specific to PRECICECAP CRFs. The master subject log and any paper consent forms are for the parent ICECAP study and not the substudy.

7.2 Change in Hub/Site Principal Investigator

It is expected that the ICECAP Site Principal Investigator (PI) will also serve as the PRECICECAP Site PI. Procedures pertaining to change in Site PI will follow the ICECAP process.

7.3 Regulatory Readiness

PRECICECAP requires no additional documentation of regulatory readiness beyond that required by the ICECAP trial.

7.4 Readiness Call and Site Initiation

Prior to the enrollment of the first PRECICECAP subject, site initiation (via a readiness call) will occur. For sites starting both ICECAP and PRECICECAP enrollment concurrently, this call will be scheduled to coincide with the required ICECAP readiness call. During this call, site team members as well as PRECICECAP study leadership, site manager, and study project manager will discuss site training and 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.

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 PRECICECAP leadership team and relevant CCC and DCC personnel. A site overview and discussion on study conduct will take place during the call.

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. An email informing the site and PRECICECAP teams will be sent when a site is to enroll. This email will serve as the formal communication that the site is ready to enroll.

7.5 Site Close-out

It is our expectation that PRECICECAP sites will co-enroll at least 5 ICECAP/PRECICECAP subjects annually, and at least 2 in the first 6 months the site is open for co-enrollment. Meeting this minimum benchmark is necessary for PRECICECAP to meet its target sample size. Participating sites have been selected in part based on their expected enrollment volumes. Failure to meet the 6-month benchmark will trigger a phone call between PRECICECAP leadership and the site investigator team. **In cases where site investigators no longer feel it is feasible to meet these targets, or cases in which fewer than 5 subjects are enrolled after the first year, the site will be closed out.** Closeout procedures are detailed below. In addition to these, the Moberg CNS monitor on loan to the study site will be reallocated to another new or existing PRECICECAP site.

8 Monitoring

Monitoring is a process of ensuring the integrity and accuracy of the conduct of the clinical trial and the data collected. Broadly speaking, this process includes on-site and remote site monitoring and central data monitoring. Monitoring of enrollment and data collection in this substudy will be performed by the ICECAP team as part of monitoring of the parent trial.

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 trial data are accurate, complete, and verifiable, and that the trial is conducted in compliance with the current approved protocol, GCP, and applicable regulatory requirements.

PRECICECAP site monitoring will be managed by the SIREN CCC and incorporated into existing ICECAP study monitoring processes, which include both remote and onsite source document verification. The 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''.

Click here for the 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 Quality Control of Data Collection and Substudy Performance

Anticipated quality control issues that may arise in PRECICECAP cap include missed or delayed enrollment, transgressions from clinical standardization guidelines, technological or process related problems leading to incomplete collection or transmission of data, incomplete redaction of potential identifiers in medication administration data or DICOM image data. Quality control and feedback will be addressed cooperatively through PRECICECAP-specific efforts directed by the substudy PIs and project director, and through parent study processes directed by the CCC. Quality issues that are also reportable protocol deviations or unanticipated problems must be managed using the processes established for the parent trial.

9.1 Protocol Deviation and Unanticipated Problem Reporting

Potentially reportable protocol deviations and unanticipated problems involving risk to subjects or others must be reported in WebDCU™. 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. Local reporting is the responsibility of the site PI.

Protocol deviations will require the development of a Corrective Action/Preventative Action (CAPA) plan at the discretion of the PRECICECAP and parent trial leadership.

9.2 Corrective Action/Preventative Action (CAPA) Plans

CAPA plans may be required by the leadership for instances or patterns of problems related to either quality of data collection or study performance, or in response to identified protocol deviations or unanticipated problems. CAPA plans will always be required in response to reportable protocol deviations or problems, but may also be required for other important issues or transgressions. Development of a CAPA plan may be initiated by the site study team, local IRB, or the SIREN-CCC. 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 in the Issues table on the CIRB tab.

10 Retention of Study Records

Study records will be retained in accordance with ICECAP policies and procedures.

11 Payment to Clinical Sites

Start-up payment:

A one-time payment of **$1,000 (inclusive of F&A costs)** will be paid to PRECICECAP sites, once they have completed the required training, submitted regulatory documents, obtained required approvals and are released to enroll subjects by the CCC.

Per-subject payments:

All approved, participating sites will be eligible for a single per-subject payment of **$2,000 (inclusive of F&A costs)** after an eligible subject is enrolled in PRECICECAP; all PRECICECAP specific CRFs are submitted and free of queries; the subject's Moberg CNS data file(s) are uploaded and verified; and imaging DICOMs are uploaded and verified (if the imaging of interest was performed).

12 Case Report Forms

12.1 CRF Study Book

The CRF study book is maintained in project documents under the Project Setup / CRF Collection Schedule tab in WebDCU™.

12.2 CRF Completion Guidelines

PRECICECAP CRF Completion Guidelines will be incorporated into the parent study completion guidelines document. CRF completion policies parallel ICECAP's policies.

12.3 CRF Completion Timetable

Study CRFs are required to be completed within timelines as described in the CRF Completion Guidelines. See link above.

13 Participant Tracking & Follow Up

PRECICECAP data collection will end on hospital discharge. All other follow-up data is described within the MOP for ICECAP.

14 Statistical Analysis Plan (SAP)

The PRECICECAP SAP can be found on the PRECICECAP study website.

15 Publications and Data Sharing Policies and Procedures

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

The PRECICECAP publications policy will be consistent with the overarching SIREN and ICECAP publications policies. Any variations from these will be documented in a substudy-specific addendum to the ICECAP publications policy.

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

The SIREN Data Coordinating Center (DCC) at the Medical University of South Carolina (MUSC) will be responsible for the management of the clinical database. CRF data for PRECICECAP will be included in the ICECAP parent trial Public Use Dataset prepared by the DCC. The ICECAP Manual of Procedures details the anticipated timeline, and the DCC approach to de-identification and creation of Public Use Data Sets.

Source physiological data acquired from the Moberg CNS monitor, imaging DICOMs or derivative results from feature extraction and modeling using these source data will not be included in ICECAP Public Use Data Set. The PRECICECAP investigators favor publicly sharing these voluminous data too, and intend to do so if sufficient resources are available and it is technologically feasible. Any data sharing plans for high-resolution source data will be developed collaboratively with the funders to ensure compliance with NIH policies and best practice.

16 PRECICECAP Frequently Asked Questions (link)

Frequently asked questions (FAQs) are located at PRECICECAP FAQs. New Q&A are posted and this page is updated regularly.