NIH SIREN Emergency Trials Network

POST-ICECAP

STUDY PROTOCOL

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:
Pending

Protocol Version 1

Protocol Signature Page

I have reviewed and approved this protocol. My signature assures that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

Sponsor's Signature	Date of Signature (DD MMM YYYY)

I have read this protocol and agree that it contains all the necessary details for carrying out the study as described. I will conduct this protocol as outlined herein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the interests of the study subjects.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practices (GCP).

Investigator's Signature	Date of Signature (DD MMM YYYY)

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Table of Abbreviations

CCC	Clinical Coordinating Center
co-I	Co-Investigator
co-PI	Co-Principal Investigator
CRF	Case Report Form
DCC	Data Coordinating Center
DCR	Data Clarification Request
DCU	Data Coordination Unit
ED	Emergency Department
EMS	Emergency Medical Services
ICU	Intensive Care Unit
IRB	Institutional Review Board
LAR	Legally Authorized Representative
mRS	Modified Rankin Scale
MUSC	Medical University of South Carolina
NIH	National Institutes of Health
PI	Principal Investigator
ROSC	Return of Spontaneous Circulation
ROC	Resuscitation Outcomes Consortium
SAE	Serious Adverse Event
SIREN	Strategies to Innovate Emergency Care Clinical Trials Network
SSL	Secure Socket Layer
SOP	Standard Operating Procedures

TABLE OF CONTENTS

BRIEF SYNOPSIS

Title	**P**atterns **o**f **S**urvivors Recovery **T**rajectories in the **ICECAP** Trial (**POST-ICECAP**)
Phase	Phase III
Methodology	Prospective cohort study ancillary to an ongoing multi-center, randomized trial
Funding Agencies	R01NS127959-01A1 NINDS/NHLBI
Study Duration	June 2023 to June 2028
Study Center(s)	SIREN Trial Network
Objectives	**Primary**: Describe between-patient variability in the improvement of functional, cognitive, and quality of life outcomes from 3 to 12 months after OHCA. **Secondary**: 1. Determine whether changes are associated with illness severity scores and critical care interventions performed during the acute care stay. 2. Determine whether receipt of acute inpatient rehabilitation versus outpatient therapy/no therapy/skilled nursing facility within 1 month of hospital discharge is associated with greater improvement in recovery outcomes from 3 to 12 months. 3. Determine whether non-Hispanic Black and Hispanic/Latinx patients have less favorable changes in recovery outcomes between 3 and 12 months and explore mechanisms for such disparities.
Endpoints	**Primary:** Performance-based measures of functional outcome (Modified Rankin). **Secondary**: Performance-based measures of cognitive function: 1. NIH toolbox Age-corrected Standard Score for 3 and 12 months in-person visits; Brief Test of Adult Cognition by Telephone (BTACT) total score at 1-, 6-, and 9-month phone visits. 2. Patient-reported Health-Related Quality of Life as measured on NIH Neuro-QoL at 3 and 12 months in-person visits
Participants	1000 OHCA survivors
Main Inclusion Criteria	● Age ≥ 18 years ● Coma after resuscitation from OHCA ● Patients who were either screened or enrolled in the ICECAP trial ● Received targeted temperature management ● The patient survives to hospital discharge or 1 month, whichever occurs first ● Signed ICF by a patient or an authorized representative

Major Exclusion Criteria	● Neither English nor Spanish speaking ● Terminal non-cardiovascular illness (life expectancy <1 year) ● Hospice as disposition ● Severe mental illness requiring urgent psychiatric care ● Current alcohol/substance abuse that would impede the ability to complete protocol ● Pre-existing conditions that could confound outcome determination e.g., dementia. ● Known inability to follow up (e.g., no reliable phone or internet access)
Study Visits	Telephone Interview (or in-person): 1, 6, and 9 months after OHCA In-person Interview: 3 and 12 months after OHCA
Study Measures	**Intake Questionnaire:** ● Socio-demographics ● Experiences of Discrimination Scale ● Pre-morbid Modified Rankin Scale ● Pre-morbid 4-item PTSD scale **Every Visit:** ● Modified Rankin Scale ● Brief Test of Adult Cognition by Telephone ● PHQ-8 (Depressive symptoms) ● GAD-3 (Anxiety) ● PCL-5 (PTSD Symptoms) ● Self-reported questionnaire capturing healthcare and rehab utilization ● ADL & IADL assessments ● Fatigue assessment *Disability Rating Scale for patients who are unable to follow commands. **In-Person Only (3 and 12 months):** ● NIH Neuro-QoL ● NIH Toolbox ● Kansas City Cardiomyopathy Questionnaire (KCCQ-12) ● Social Support Instrument
Duration of study	12 months after OHCA

Statistical Methodology	Primary analyses will be performed on patients w/ mRS<5 (awake patients; anticipated n=750) at 1 month, but descriptive/exploratory analyses will be performed on those w / 1-month mRS=5 (n=250). We will analyze these two strata separately as patients with disorders of consciousness will have qualitatively different recovery and systematically different exposures to modifiers like rehabilitation (ineligible for inpatient acute rehabilitation). Each Aim focuses on the change in function, cognition, and HRQoL from 3 to 12 months; i.e., the period beyond the ICECAP endpoint. To test the hypotheses for our Aim 1, initial illness severity (total OHCA score primary predictor, PCAC secondary predictor), early coronary angiography, and duration of hypothermia are associated with a change from 3 to 12 months in mRS (primary outcome), NIH-Toolbox and Neuro-QoL (secondary outcomes). The same analytic approach will be used to address Aims 2 and 3, with the primary predictors being the receipt of inpatient acute rehabilitation (vs. outpatient rehabilitation/no rehabilitation/discharge to a skilled nursing facility; Aim 2) or race/ethnicity (non-Hispanic Black race, Hispanic/Latinx ethnicity vs non-Black/non-Hispanic patients [reference group]; Aim 3).

SYNOPSIS

Many patients now survive out-of-hospital cardiac arrest (OHCA); however, gaps in knowledge about long-term outcomes result in a fragmented and underdeveloped continuum of care to achieve recovery. Recovery is defined as significant improvement in functional and cognitive outcomes and health-related quality of life (HRQoL). OHCA Survivors with favorable recovery patterns may potentially go back to work and/or social roles. Prior studies assessing recovery domains after OHCA are small, limited to single centers and short-term outcomes, i.e., 1-3 months. Identifying individual patient patterns of recovery over longer-term, and the ability to predict who will be likely to need more intensive support after discharge, would allow interventions to be targeted more efficiently. It is also crucial that we offer patients and their families the best information available about a patient's prospects for continued recovery even in the absence of modifiable intervention targets. This study will be among the first to focus on a new equitable science of OHCA survivorship itself, seeking empirically derived targets for preserving or restoring recovery.

To accomplish these goals, we propose "Patterns Of Survivors' recovery Trajectories in the ICECAP trial (POST-ICECAP)", an ancillary study to the NINDS and NHLBI-funded ICECAP trial, conducted within the NIH-funded Strategies to Innovate Emergency Care Clinical Trials Network (SIREN). The goal of POST-ICECAP is to describe recovery in a large, well-characterized, racially/ethnically diverse, representative cohort of US OHCA patients. We will enroll 1,000 patients who were screened for ICECAP and survived to hospital discharge. The parent ICECAP trial includes a telephone follow-up visit at 1 month and an in-person visit at 3 months. The ancillary study will add two telephone/videoconferencing visits at 6 and 9 months and an in-person visit at 12 months after OHCA.

For Aim 1, we will describe between-patient variability in recovery (i.e., improvement in functional, cognitive, and HRQoL outcomes) from 3 to 12 months after OHCA and test whether changes are associated with illness severity scores and critical care interventions performed during the acute care stay. Aim 2 will test whether receipt of acute inpatient rehabilitation (vs outpatient therapy/no therapy/skilled nursing facility) within 1 month of hospital discharge is associated with greater improvement in recovery outcomes from 3 to 12 months. Finally, in Aim 3, we will test whether non-Hispanic Black and Hispanic/Latinx patients have less favorable changes in recovery outcomes between 3 and 12 months and explore mechanisms for such disparities.

1. STUDY OBJECTIVES

Primary:

Describe between-patient variability in the improvement of functional, cognitive, and HRQoL outcomes from 3 to 12 months after OHCA.

Secondary:

1. Determine whether changes are associated with illness severity scores and critical care interventions performed during the acute care stay.
2. Determine whether receipt of acute inpatient rehabilitation versus outpatient therapy/no therapy/skilled nursing facility within 1 month of hospital discharge is associated with greater improvement in recovery outcomes from 3 to 12 months.
3. Determine whether non-Hispanic Black and Hispanic/Latinx patients have less favorable changes in recovery outcomes between 3 and 12 months and explore mechanisms for such disparities.

2. BACKGROUND

2.1 Burden of Cardiac Arrest Survivorship

In the US, nearly 1,000 adults experience a sudden OHCA each day.[1,2] An electrical malfunction is triggered by a disruption of the heart's rhythm, and the heart ceases to pump blood to the brain, lungs, and other organs.[3,4] Coronary artery or other heart disease is the most common etiology.[3] Over 15% (60,000/year) of all OHCA patients survive to hospital discharge,[5,6] thanks to effective public health campaigns for cardiopulmonary resuscitation,[2,7] defibrillators,[8-10] and advances in bundled post-arrest intensive care,[11-16] based on the American Heart Association's original five links of the *'Chain of Survival'* **(Figure 1).** Now that more patients are surviving OHCA, we must identify strategies to ensure that patients live long, healthy, disability-free lives. Indeed, national[5,17] and international[18] scientific bodies recently issued a scientific statement declaring that OHCA survivors have "unique and complex needs that are inadequately addressed by

current treatment recommendations".[5] POST-ICECAP will address major knowledge gaps surrounding the key 'sixth link' in the Chain of Survival: 'survivorship' or the recovery phase.

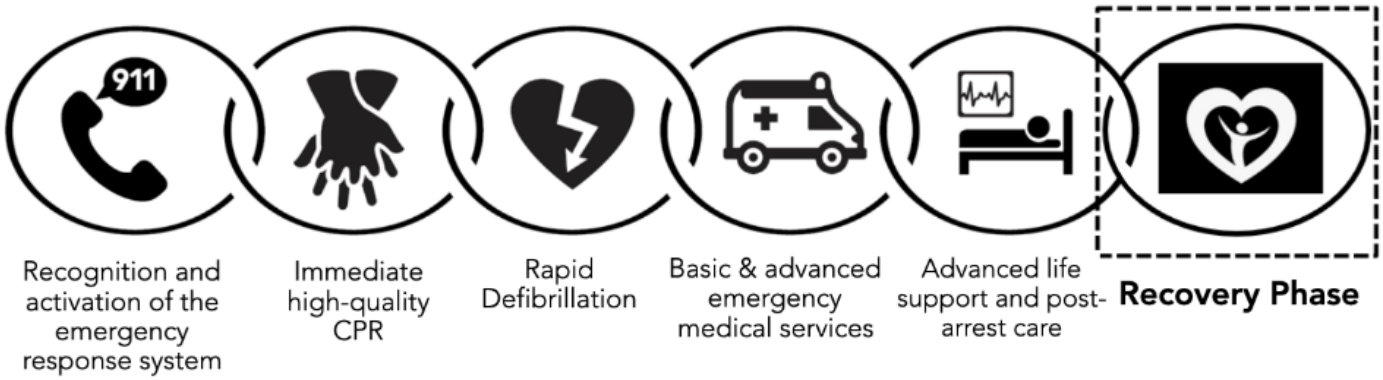


Figure 1. The Sixth Link of Chain of Survival: From Survival to Recovery

2.2 The conceptual framework for recovery after OHCA is grounded in the World Health Organization's International Classification of Functioning Disability and Health (WHO-ICF).

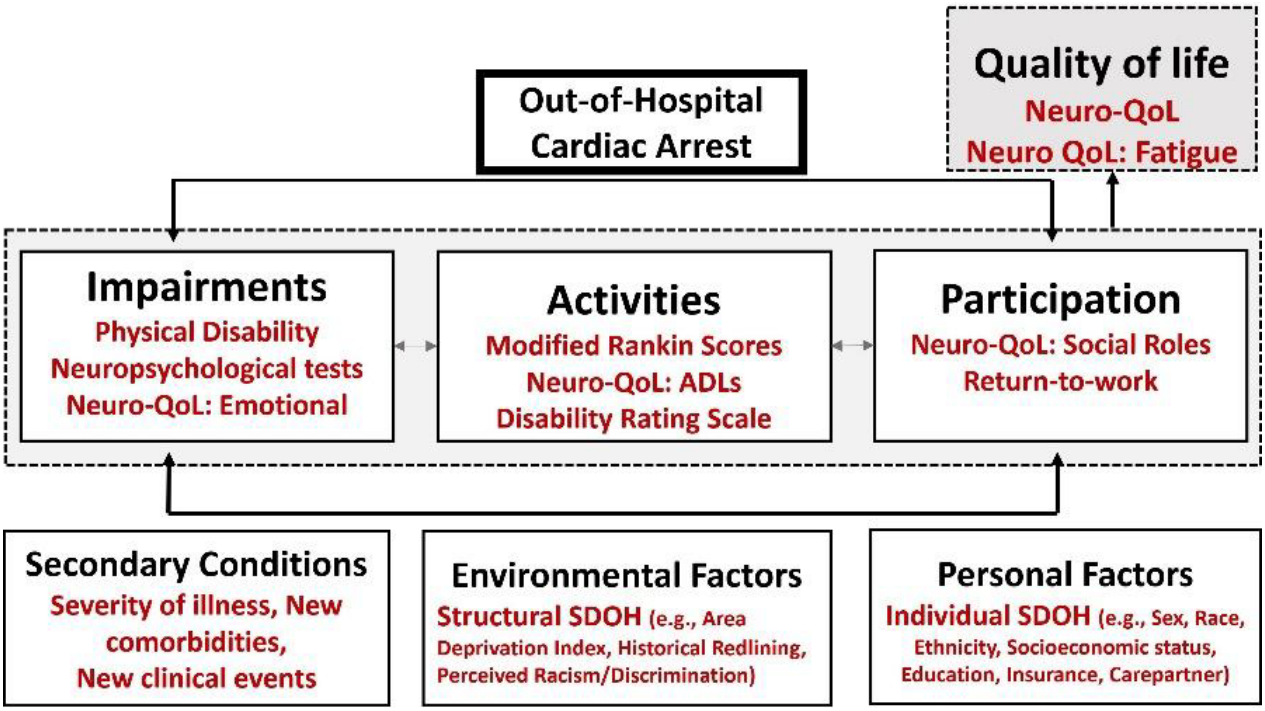


Figure 2. Proposed OHCA Recovery Framework, an adaptation of WHO-ICF model,[48] demonstrating 1) the three primary domains of recovery (impairments, activity or functional limitations, and HRQoL/participation restrictions), 2) Influence of factors related to clinical course, individual and structural components of Social Determinants of Health (SDOH), on functional and cognitive recovery & HRQoL.

OHCA is a particularly challenging condition to manage clinically, due to the heterogeneous nature of the injury. OHCA survivors with apparently similar brain injury profiles can experience very different functional, cognitive, and HRQoL outcomes.[19-24] This variability may be partly attributable to differences in personal biology, including a complex interplay between premorbid and injury-induced pathophysiology.[12,25-29] However, our prior research suggests that recovery is determined in part by potentially modifiable factors, including aspects of critical care,[12,15,30-34] intensity of rehabilitation services after hospital discharge,[19,35] and the physical and social environments,[35-39] in which recovery takes place. In **Figure 2** we present a biopsychosocial framework that encompasses multiple domains of recovery related to impairments in structure and function, activity limitations, participation restrictions, and poor HRQoL and that contextualizes the important predictors affecting variability in recovery. Identifying factors that are associated with patient heterogeneity in recovery is the critical first step toward evidence-based personalized recovery plans and treatments.[26,40-42]

2.3 Understanding why recovery continues for many months in some patients, while others plateau or regress, will inform future OHCA intervention trial design, assist patients and families in planning transitions of care, and allow for personalized interventions and plans of care. Currently, referral to acute rehabilitation after hospital discharge is not routine, in part because the clinical evidence is weak or absent about whether an OHCA patient should expect continued recovery, or if further rehabilitation efforts are futile.

2.4 Rationale

We propose the first national study of factors associated with recovery from 3-12 months post-resuscitation in patients who experienced an out-of-hospital cardiac arrest (OHCA). Patients are now almost 3 times more likely to survive to hospital discharge after OHCA (~60,000 survivors per year) compared to 10 years ago.[1,2,5,43] However, over 50% of survivors have a persistent neurological impairment, ranging from mild cognitive deficits to disorders of consciousness or coma,[5,6,12,29,41,44] due to hypoxic-ischemic injury to the brain. *Recovery* is defined as significant improvement in functional and cognitive outcomes, and health-related quality of life (HRQoL). Patients with good recovery can return to employment and/or social roles.[13,19,20,22,25,41,45-57]

The paucity of data about long-term recovery after acute hospitalization is a major reason that there are no clear guidelines for after-hospital care or intense rehabilitation for OHCA. Most data about functional or cognitive recovery focus on short-term outcomes, i.e., 1-3 months after OHCA.[5,6,28,58] In a recent, single-center pilot study, we found substantial variability in recovery after 3 months,[19,35] suggesting that 3-month recovery status does not dictate recovery status at 12 months.

Currently, clinical practice and rehabilitation efforts are optimized for recovery outcomes assessed at 1-3 months after OHCA. Patients and families don't know whether to expect further improvement after 3 months or if there is a ceiling beyond which no further recovery is likely. Together with ICECAP, this proposed study will provide the best evidence to date about patients' longer-term recovery prospects after OHCA. It may generate evidence for systematic referral to acute inpatient rehabilitation for most patients and the characteristics of those patients most likely to benefit from such rehabilitation. Our study may also point to racial and/or ethnic disparities in recovery, as well as intervention targets to reduce such disparities. As such, this study represents a critical step toward understanding and supporting widespread, equitable recovery after OHCA.

2.5 Supporting Data

In preparation for this proposal, we analyzed data from a prospective, observational pilot study[35,53,59] of 261 diverse (24% Hispanic/Latinx and 19% Black) adult (mean 56±16 years) OHCA survivors (40% women) with the ability to follow commands and participate in an interview at 1-month after OHCA between 2/1/2016 and 1/31/2020. We measured participants' functional outcomes (modified Rankin Scores; mRS) and cognitive impairment [Repeatable Battery for Neuropsychological Status (RBANS)[50,60]] at 1, 3, and 12 months post-OHCA. We also examined biopsychosocial factors including **demographics** (age, sex), **social determinants of health** including self-reported race/ethnicity, caregiver status, individual-level socioeconomic status (SES): insurance, education level, income, occupation, structural-level SES: Area deprivation index[61-63]), **clinical factors** (comorbidities, components of OHCA severity score[64,65], in-hospital factors, hospital length of stay), and **discharge disposition** (inpatient acute rehabilitation, outpatient rehabilitation, no rehabilitation, skilled nursing facility).

2.5.1 Functional Recovery Variation from 1 to 12 Months. We confirmed our prior observations[19] that in nearly half of the participants, there are clinically important differences between long-term (12 months) and early (1 month) functional outcomes (**Figure 3**). Most (63%, n=127/201) maintained good functional status or improved, but over one-third (37%, n=74/201) of patients had a poor functional recovery pattern, defined as death, or persistent unfavorable functional outcomes, i.e., mRS between 3-5, or any worsening of mRS from 1 to 12 months.[35]

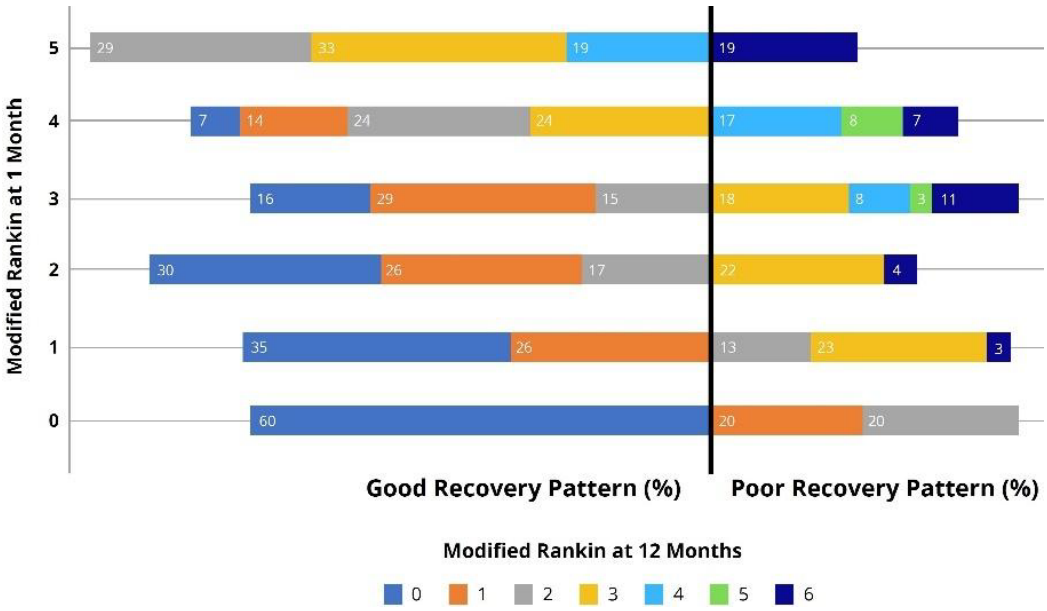


Figure 3. Functional status (mRS) at 1 and 12 months after OHCA. Good Recovery Pattern is maintenance of mRS 0-2 or improvement, and Poor Recovery Pattern is persistent mRS 3-5, worsening mRS or death.

2.5.2 Similar Variation in Cognitive Recovery Patterns from 1 to 12 months. Among the 64% (n=117/182) with cognitive impairment at 1 month (≥80 on RBANS, a threshold used for moderate traumatic brain injury), 30% (n=55/117) had persistent cognitive impairment at 12 months (poor recovery pattern), while 34% (n=62/117) showed improvement (good recovery pattern).[36]

2.5.3 Variation from 3-12 Months. Because the OHCA recovery studies with the longest follow-up tend to end at 3 months, we estimated variation in further recovery from 3-12 months. We found that one-third of patients (n= 66) had a change in their functional outcome between 3 and 12 months (**Figure 4**), including those with a favorable status at 1 month (n=14, 31%; Trajectories 2 & 3) and those with an unfavorable status

at 1 month (n=52, 39%; Trajectories 6 & 7). POST-ICECAP will explore what factors influence whether a patient experiences a good or poor recovery pattern from 3 to 12 months after OHCA.

Selection of performance-based and patient-reported outcomes of Recovery in POST-ICECAP.

2.5.4 Functional outcome (Performance-based Outcome, Primary Study Outcome) includes difficulties with or dependence on others for everyday activities and is a critical patient-centered outcome.[5,25,58] Almost half of OHCA survivors have persistently poor functional outcomes.[6,19,20,22,66,67] This poor functional recovery leads to low participation in social and leisure activities, inability to return to work, and poor family relationships.[57,66,68,69] POST-ICECAP will evaluate a well-established measure of functional outcome, the Modified Rankin Scale,[58,70-72] to yield a detailed picture of functional recovery over 12 months after OHCA.

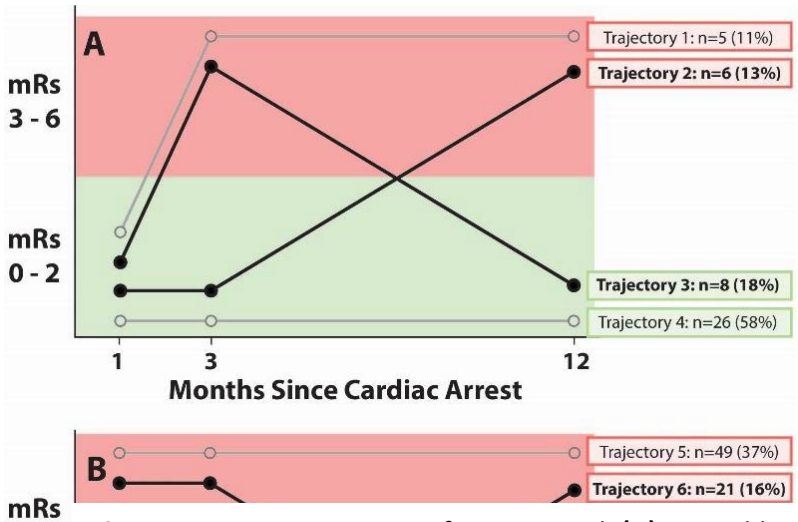


Figure 4. Recovery Patterns of Patients with **(A)** Favorable functional outcomes (mRS 0-2), **(B)** Unfavorable functional outcomes (mRS 3-5) at 1-month after OHCA.

2.5.5 Cognitive Function (Performance-based Outcome, Secondary Study Outcome). Mild to severe cognitive impairment occurs in 25–60% of OHCA survivors[20,48,50,55,66,73,74] and persists months to years after hospital discharge.[6,28,75,76] In our pilot cohort, we found a high prevalence of cognitive impairment at 1 and 12 months, with the most prominent impairments in attention, immediate memory, and delayed memory **(Figure 5)**.[20] OHCA survivors with cognitive dysfunction generally have worse HRQoL and social functioning, a lower likelihood of returning to work, and more psychological distress than those without cognitive dysfunction.[6,54,55,57,77] POST-ICECAP will collect serial measurements to reliably quantify individual cognitive outcomes using the global Age-adjusted standardized cognition score (primary cognitive outcome) and sub-types summary scores derived from a battery of neuropsychological tests (NIH toolbox) and a validated brief telephone-based test.

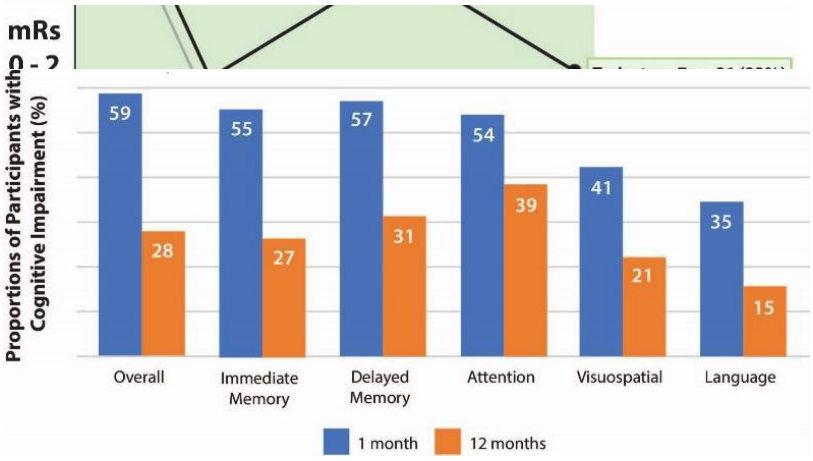


Figure 5. High prevalence of cognitive impairments across all sub-types at 1 and 12 months, using the threshold for moderate traumatic brain injury.

2.5.6 Health-related Quality of Life and Societal Participation (Patient-reported, Secondary Outcome). Quality of life is the most important consideration of OHCA survivors.[5,23,58,78,79] HRQoL estimates inform health

economic assessments of intervention cost-effectiveness, and therefore identifying factors that are associated with HRQoL is key for identifying potential intervention targets and evaluating treatments. Perhaps because clinical expectations were so low for decades, current practice yields HRQoL scores in OHCA patients that are 0.5-1 SD below norms for their age.[69] Subgroup analyses show that younger patients (18-44 years) have 0.4 SD lower HRQoL than older patients, and women have significantly lower scores than men (0.35 SD lower).[69] However, we have shown that societal participation improves over 12 months and is strongly correlated with functional recovery.[22] POST-ICECAP will estimate HRQoL and societal participation and identify changes in overall and physical, social, emotional, and cognitive health sub-scales between 3 and 12 months after OHCA. The primary HRQoL outcome will be the total summary score on NIH Neuro-QoL.

2.5.7 OHCA survivors with disorders of consciousness (DoC) are a critical but neglected subgroup**.** We have documented that withdrawal of life-sustaining treatments (WLST) for patients with DoC (i.e., unresponsive and not following simple commands) within a few days after OHCA is widespread[27,80] and estimated to be responsible for as many as 20,000 additional OHCA-related deaths per year.[81]This is due to limited data on long-term recovery from DoC and a belief among clinicians that these patients will show no long-term improvement. The *2018 American Academy of Neurology practice guideline update* makes clear that recovery from DoC after acute brain injury can occur later than previously believed, with meaningful functional improvement in a substantial minority.[82] We have recently shown that up to 20% (190/975) of patients discharged from the hospital after OHCA have a severe functional disability and, of those, 23% do not follow commands at discharge.[83] We and others have reported recovery of consciousness in up to 20% of OHCA survivors discharged to in-person acute rehabilitation while still unconscious.[84-86] Nearly half (41%) of those who regained consciousness after discharge also experienced meaningful functional improvements that were not yet apparent at 3 months. The proposed study will aid in the identification of those who may recover.[28] POST-ICECAP will be the largest study to systematically examine the natural clinical course (over 12 months) of patients who remain unresponsive before hospital discharge.

2.5.8 Selection of factors that may influence recovery in POST-ICECAP.

To improve clinical care, we seek to identify potential targets for interventions that are associated with improved outcomes after OHCA. In POST-ICECAP we will investigate the prospective associations of clinical factors and interventions in the acute care setting, post-discharge rehabilitation services, and social determinants of health with continued recovery or regression on functional, cognitive, and HRQoL outcomes.

2.5.8.1 OHCA severity of brain injury set the stage for variability in recovery: Whether long-term outcomes are associated with OHCA illness severity scores that predict survival and functional status at hospital discharge is a knowledge gap.[41,42,87-89] We derived and validated one score, the Pittsburgh Cardiac Arrest Category (PCAC),[12,31,90,91] based on the motor and brainstem subscales of the Full Outline of UnResponsiveness (FOUR) scores[92-94] and cardiovascular and respiratory subscales of the Sequential Organ Failure Assessment (SOFA) score.[95,96] POST-ICECAP will leverage the comprehensive and systematically collected physiological and

biomedical data in the parent ICECAP trial to examine how these physiological assessments are associated with recovery from 3-12 months.

2.5.8.2 Clinical interventions, including ICECAP randomized duration of hypothermia, may influence recovery. Hypothermia is a guideline-recommended treatment for comatose survivors of OHCA,[1,97] but whether the duration of hypothermia influences long-term recovery patterns is unknown. Human data about prolonged duration of hypothermia after OHCA are lacking,[98] but mechanistic and preclinical outcome data suggest potential benefits.[99-101] Hypothermia is delivered in conjunction with many other critical care interventions, including specific blood pressure goals,[102] mechanical ventilators settings[103], renal replacement therapy,[33] sedation and neuromuscular blockade regimens,[104] and treatments (e.g. early coronary angiography).[105-109] While the ICECAP parent trial will examine associations between the duration of hypothermia and 3-month outcomes, POST-ICECAP will test whether the duration of hypothermia is associated with continued recovery from 3-12 months. For primary analyses, we will also test if angiography performed within 24 hours is associated with greater improvement in recovery.

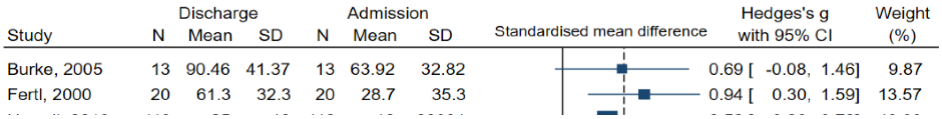


Figure 6. Forest plot showing a beneficial effect of inpatient rehabilitation on functional Independence Measure (FIM) score between admission and discharge.

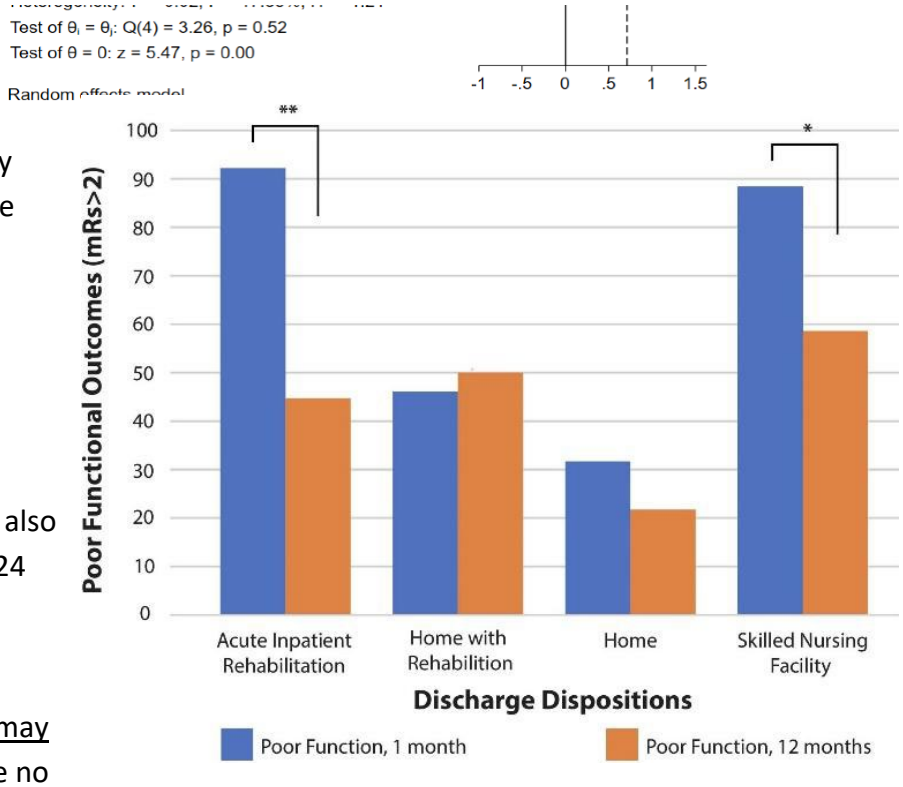


Figure 7. Proportion of patients with poor functional outcome at 1 and 12 months, by discharge disposition

2.5.8.3 Inpatient acute rehabilitation may improve recovery. Currently, there are no guidelines or recommendations for neurorehabilitation for OHCA survivors in the US.[5] Whether inpatient acute rehabilitation is commonly provided to OHCA survivors is a major knowledge gap. Outside of reports[19,35,110] from a few tertiary care centers, including our own, the proportion of OHCA survivors who receive physical, occupational, speech, or physiatry evaluations and disposition to continue rehabilitation after hospital discharge is not known. A recent systematic review found patients improved between admission and discharge from inpatient acute rehabilitation after CA (medium-large effect size) **(Figure 6)**.[111] In our data, patients who received inpatient acute rehabilitation (vs other discharge dispositions) after acute care hospital stay were significantly more likely to progress from poor functional outcomes to good

functional outcomes between 1 and 12 months (**Figure 7**). In models adjusted for demographics, clinical characteristics, and social determinants of health, patients who received acute inpatient rehabilitation were 3 times more likely to achieve a good functional recovery pattern.[35]

In two geographically distinct cohorts, we have shown that a substantial proportion of patients with poor functional status at hospital discharge return to home, either with no rehabilitation or with home healthcare.[110] There are significant sex-based disparities in receipt of inpatient acute rehabilitation.[112] These patients may be an unrecognized "at-risk" group, potentially with unfavorable social determinants, who experience worsening or flat recovery patterns from discharge to 12 months. POST-ICECAP will be the first prospective multicenter study to **(a)** describe with a high degree of granularity the in-hospital rehabilitation evaluations/services received before discharge and the rehabilitation services offered and received after hospital discharge, **b)** examine what factors, either clinical (e.g., medical complexity, the severity of impairments at discharge) or sociodemographic (e.g., insurance, presence of a caregiver, sex, race/ethnicity), are associated with these decisions about alternative discharge dispositions, and **(c)** test whether attending an inpatient acute rehabilitation within 1 month after surviving OHCA is associated with recovery.

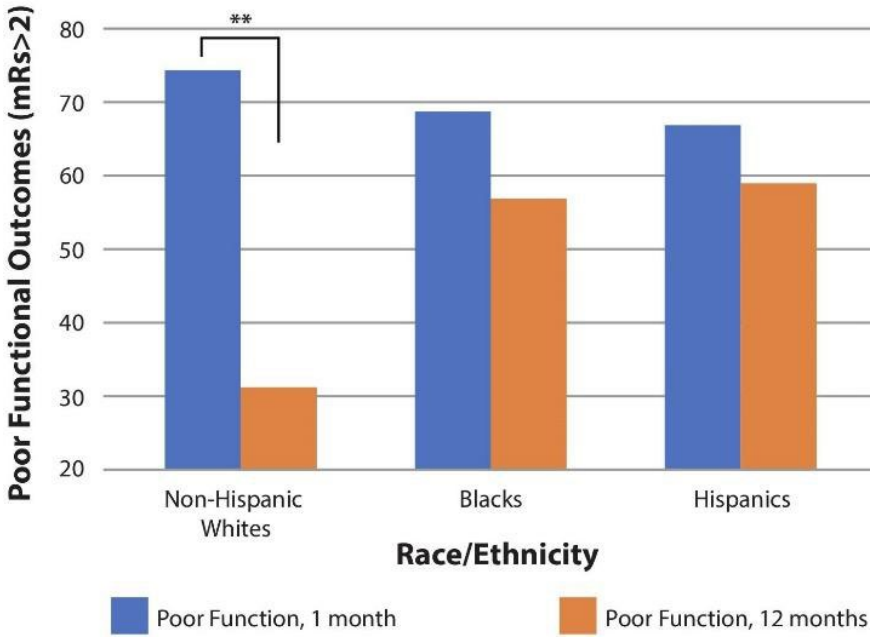


Figure 8. Proportion of patients with poor functional outcomes at 1 and 12 months by Race/Ethnicity

2.5.8.4 Social determinants of health (SDOH) influence recovery after OHCA**.** Prior research identified racial and ethnic disparities in OHCA incidence and mortality.[113-122] There is a gap in our knowledge about racial/ethnic disparities in longer-term recovery after OHCA. Understanding which SDOH contributes to racial and ethnic disparities after OHCA is critical for reducing those disparities. Limited data on other cardiac and critical care illnesses indicate that historically marginalized groups are at higher risk of poor functional outcomes with worse HRQoL, impaired societal participation, and perhaps because of inequity of follow-up care or employment security, compared with White patients.[123-128] No national data exist for OHCA survivors.

In our study of 201 patients discharged from the hospital after OHCA, multiple social factors were associated with improvement or worsening between 1 and 12 months. For example, the proportion of non-Hispanic Whites who had poor function (mRS>2) decreased 50% from 1 to 12 months, but only 10% of Blacks and 8% of Hispanics exhibited similar improvement (**Figure 8**). In multivariable models, Black race and Hispanic ethnicity,

poor insurance, non-working status, absence of a caregiver/spouse, and high area deprivation index as an indicator of neighborhood SES, were independently associated with a poor cognitive recovery pattern from 1-12 months after OHCA. The disparities we found are clearly multifactorial, with self-reported race aligning with other individual-, structural-, and hospital-level factors at several points in the course of recovery after OHCA. Structural racism and race-based stressors may also contribute to these disparities. POST-ICECAP will deepen our understanding of where disparities exist in OHCA recovery and may point to targets for interventions to reduce health disparities in OHCA.

2.5.8.5 Post-Intensive Care Syndrome (PICS) and Psychological Distress in OHCA survivorship. Our pilot data suggest that many patients continue to improve on functional, cognitive, and psychological or HRQOL measures after 3 months, but some deteriorate on 1 or more dimensions. One of the ways the field describes new or worsening deficits is through the concept of PICS. Our serial measurements include the PICS components (function, cognition, and psychological distress), and we will be the first national study to document the prevalence and predictors of PICS or recovery from 3 to 12 months after OHCA. POST-ICECAP will be the most comprehensive study of the psychological dimension of OHCA recovery ever conducted.

OHCA occurs suddenly and often without warning in apparently healthy individuals, young or old, of any sex.[129] Survivors experience 2-3 weeks of critical illness.[53] The psychological experience of OHCA is traumatic and life-altering.[78,79] Nearly 1/3 of OHCA patients screen positive for posttraumatic stress disorder (PTSD) at 1 and 12 months after OHCA,[24,53,130] a rate that is 2.5 to 3 times greater than other acute cardiovascular conditions (32% for OHCA vs 11-15% for acute coronary syndrome or stroke).[131-135] Similarly, depression and generalized anxiety are very common among OHCA survivors (14%-45%).[50-52,56,59,136,137] We have shown that psychological distress coexists with cognitive and functional impairments at 1 and 12 months after OHCA.[59] Only 10% of survivors had no measurable psychological distress or functional or cognitive impairments at 1 month (**Figure 9**).

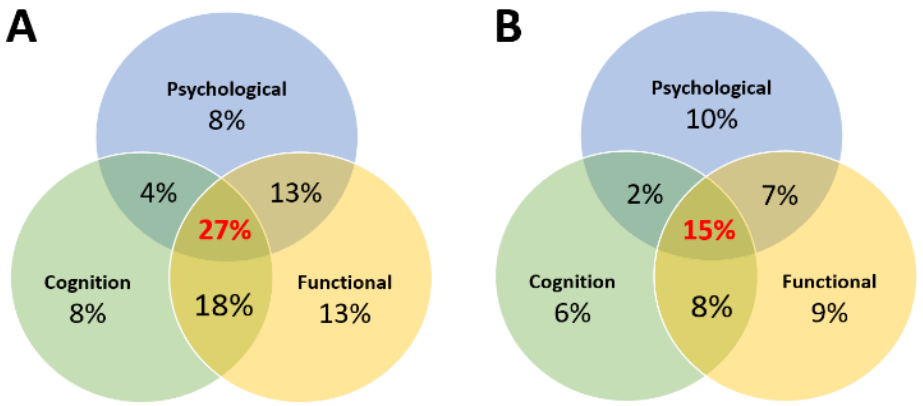


Figure 9. The prevalence of post-intensive care syndrome components, and co-occurrence of psychological distress with functional and cognitive deficits at **(A) 1 month**, **(B) 12 months** after OHCA. *% denotes proportion of patients.*

In summary: POST-ICECAP will address a critical knowledge gap by describing long-term recovery after OHCA in a national cohort of US patients, including unresponsive DoC patients, identifying between-patient

variability in recovery after 3 months, and estimating how acute care factors, receipt of inpatient acute rehabilitation, and race/ethnicity (likely through SDOH) relate to recovery in OHCA survivors (**Figure 10).**

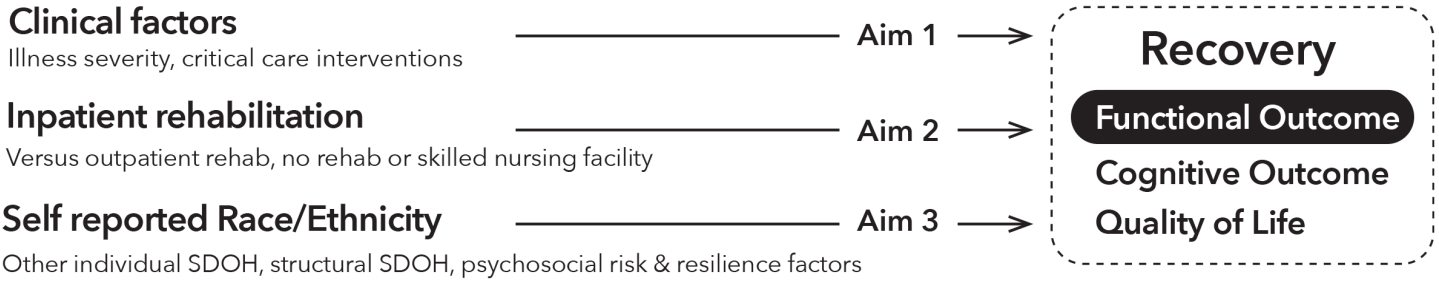


Figure 10. Conceptual Figure

3. STUDY DESIGN

3.1 Study Design

POST-ICECAP is a prospective cohort study of patients who survive to hospital discharge or 1 month after OHCA, whichever occurs earlier. Participants will complete two in-person visits at 3 and 12 months (primary outcomes assessment), and three telephone visits at 1, 6, and 9 months post-OHCA. For patients enrolled in ICECAP, 1- and 3-month visits will be conducted under the parent ICECAP trial. We will administer validated measures of functional outcomes, cognitive performance, HRQoL, rehabilitation details, and a biopsychosocial questionnaire. See **Figure 11** for study visits.

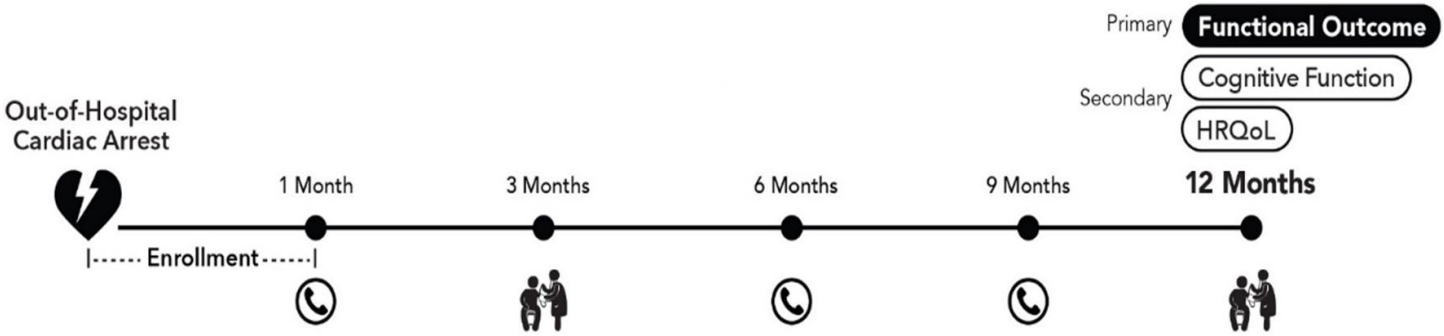


Figure 11. Study Schema showing the distribution of POST-ICECAP visits across ICECAP participants and ICECAP screen failures. Please note: for ICECAP participants 1- and 3-month visits will be conducted under the parent ICECAP trial.

3.2 Clinical Sites

Hub and spoke hospitals from the SIREN network who are participating in the ICECAP trial will be eligible for participation in POST-ICECAP. Approximately 50 hospitals are anticipated to enroll an average of 5 subjects per year. The enrollment period is anticipated to be 4 years (estimated accrual rate of 21 subjects per month).

4. SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Study Population

Study population will comprise adults, enrolled in or screened for the ICECAP trial, who survived to hospital discharge or 1 month after an OHCA, whichever comes first. Detailed inclusion/exclusion criteria are listed in **Table 1**. POST-ICECAP will recruit from a racially and ethnically diverse population of OHCA survivors in the US that is often difficult to engage in research and is recognized by the NIH as requiring special efforts to ensure adequate representation in clinical studies. Enrolling a diverse cohort of OHCA survivors by using the geographically diverse SIREN/ICECAP sites is a major strength of our proposal.

Table 1. Inclusion Criteria	**Exclusion Criteria**
● Age ≥ 18 years ● Coma after resuscitation from OHCA ● Patients who were either screened or enrolled in the ICECAP trial ● Received targeted temperature management ● The patient survives to hospital discharge or 1 month, whichever occurs first ● Signed ICF by a patient or an authorized representative	● Neither English nor Spanish speaking ● Terminal non-cardiovascular illness (life expectancy <1 year) ● Hospice as disposition ● Severe mental illness requiring urgent psychiatric care ● Current alcohol/substance abuse that would impede the ability to complete protocol ● Pre-existing conditions that could confound outcome determination e.g., dementia. ● Known inability to follow up (e.g., no reliable phone or internet access)

4.2 Informed Consent and Enrollment

At all ICECAP sites, screen failure data is entered on all patients with an emergency department diagnosis consistent with cardiac arrest (ICD-10 code of I-46, I-49.01, I47.2, R96, R98, R99, or equivalent codes in another diagnostic system) that are treated in the ED but not enrolled. Research teams will evaluate eligibility of patients based on criteria listed in **Table 1** and invite these patients or their proxies to participate in their preferred language of English or Spanish. Screen failures for ICECAP might be approached in the hospital after an introduction by the treating team or even after hospital discharge before the first POST-ICECAP evaluation (1-month post-OHCA). Research teams are already involved with subjects enrolled in ICECAP and will approach for POST-ICECAP consent during the hospitalization as soon as it has been determined that the patient is likely to survive hospitalization (e.g., when being released from the ICU) or any time before 1 month after OHCA. Of note, proxies may consent for patients who do not yet have the capacity for themselves (e.g., those with disorders of consciousness and unable to follow commands). Participants are considered to be enrolled in POST-ICECAP if (1) they (or their proxy) have provided informed consent and (2) they have been discharged alive from the initial hospitalization or survived beyond 1 month after OHCA.

5. STUDY ASSESSMENTS

5.1 Measurement timepoints

To minimize participant burden, for subjects enrolled in ICECAP, POST-ICECAP will not repeat measures collected as part of the overlapping 1 and 3 month visit with the parent ICECAP trial (i.e., mRS at 1 and 3 months, neuropsychological testing, and HRQoL assessment). POST-ICECAP will still capture these measures for ICECAP screen failures. Beyond 3 months post-arrest, both subjects enrolled in ICECAP and ICECAP screen failures will follow the same collection schedule. The study team will contact participants via telephone at 6 and 9 months after OHCA and plan an in-person assessment at 12 months (POST-ICECAP primary outcome assessment) (**Figure 11**). At each of the 5 study visits, participants will complete measures of functional outcome, cognitive function, and psychological distress. At the in-person 3-month and 12-month visits, participants will 1) complete a neuropsychological outcome assessment, 2) complete a computerized adaptive testing assessment of HRQoL, 3) provide details on health care utilization, including rehabilitation services received, and 4) complete a brief psychosocial questionnaire. If unable to attend in-person visits at 3 or 12 months, we will substitute NIH toolbox with a telephone-based cognitive assessment. For patients with DoC at any of the follow-up visits, functional outcomes will be collected from a telephone interview with a caregiver.

5.2 Efficiencies provided to POST-ICECAP by ICECAP trial

5.2.1 Screening and access to patients. The ICECAP research teams have surveillance strategies in place to screen all OHCA patients at participating hospitals. Research teams track ICECAP randomized patients through 3 months and ICECAP screen-failures through hospital discharge. The latter are included by design to measure the generalizability of the ICECAP randomized population. Thus, POST-ICECAP can use research teams that already have contact and entrée to approach all the OHCA patients admitted at their hospitals and do not need to create or directly support the screening process.

5.2.2 Baseline and clinical care data. Research teams for ICECAP prospectively collect, audit, and monitor detailed information about the patient comorbidities, OHCA-related factors, acute hospital events, and procedures performed during hospitalization. POST-ICECAP can use the data already collected for subjects enrolled in ICECAP, saving hundreds of hours of research staff time compared to collecting these de novo.

5.2.3 Duration of hypothermia. In the parent ICECAP trial, adaptive randomization is used to assign patients to one of ten possible durations of hypothermia (6, 12, 18, 24, 30, 36, 42, 48, 60, or 72 hours). In the subset of patients who were randomized in ICECAP and then enrolled in POST-ICECAP, we can test whether hypothermia duration influences recovery trajectories beyond the 3-month ICECAP primary outcome.

6. OUTCOMES

6.1 Primary Efficacy Outcome

The primary outcome measure will be the mRS at 12 months after 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. The mRS will be determined by a site investigator or research staff certified by the CCC in the performance of the scale.

6.2 Secondary Efficacy Measures - Patient Reported Outcomes

Neuro-QOL is a set of self-report measures that assesses the HRQoL of adults with neurological disorders. Neuro-QOL consists of item banks and scales that evaluate symptoms, concerns, and issues that are relevant across disorders - along with measures that assess areas most relevant for specific patient populations.

The Neuro-QOL tool includes carefully developed and rigorously calibrated comprehensive item banks of patient-reported outcomes that are relevant to people with neurological disorders. The item banks include: Physical Health (e.g., Mobility; Fine Motor/ADL; Fatigue; Sleep Disturbance), Social Health (Ability to Participate in Social Roles & Activities; Satisfaction with Social Roles & Activities), Emotional Health (e.g., Depression, Anxiety, Stigma, Positive Affect & Well-Being; Emotional-Behavioral Dyscontrol), Cognitive Health (ie, Cognitive Function; Communication).

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

6.3 Secondary Measures - Neuropsychological Outcomes

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

We have selected measures that comprise the cognitive domain of the NIH Toolbox and are designed to leverage advantages unique to the NIH Toolbox tests including computerized administration (which allows precise and reliable timing), the availability of characterized composite scores, and the anticipation that the Toolbox cognitive battery will be commonly utilized in future neurological trials allowing for cross trial comparisons and aggregation of trial results.

Furthermore, this particular combination of tests has been carefully designed to be comprehensive, with special emphasis on measures of domains that have been found to be most significantly impacted in previous studies of cardiac arrest, namely learning, memory, attention and executive functioning. The NIH Toolbox tests can be subdivided into crystallized (i.e., general knowledge base) and fluid (i.e., thinking and reasoning) measures, providing information about both patients' premorbid and current functioning. A fluid composite

score will be obtained for fluid measures (i.e., those expected to change with injury). A stability composite score will be calculated for crystallized measures (i.e., those not expected to change with injury). The use of two distinct composite scores rather than combining all into a single composite measure will result in both greater sensitivity of the fluid composite as well as provide us with a separate estimate of premorbid functioning.

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

Neuropsychological testing has been limited to 45 minutes to an 1 hour to enhance patient compliance and minimize patient fatigue. Patients who cannot tolerate the complete battery of tests and interviews in one session may be scheduled for a second session. Study participants will be evaluated at 3 and 12 months following ROSC. Study team members responsible for neuropsychological outcome assessment will be trained and certified per ICECAP study procedures.

6.3.1 Brief Test of Adult Cognition by Telephone (BTACT) encompasses a wide range of cognitive domains and ability levels based on well-established, traditional neuropsychological tests.[138,139] The BTACT is brief (10-15 minutes), is available in English and Spanish, with good psychometric properties[140], and robust normative

sample that includes adults and older adults with and without cognitive decline.[141] These advantages led to the inclusion of the BTACT in the NIH Common Data Elements for TBI.[142]

6.3.2 The Disability Rating Scale (DRS) measures and tracks recovery in all three WHO-ICF categories: impairment, disability, and handicap for patients with DoC.[143,144] The DRS includes measures of eye-opening, verbalization, and motor response (derived from the Glasgow Coma Scale); cognitive understanding of feeding, dressing, and grooming; degree of assistance and supervision required; and employability. Scores range from 0 (no disability) to 29 (extreme vegetative state). DRS has in-person or telephone administration,[145] and has good test-retest, interrater reliability,[146] and concurrent and predictive validity.[143,147] We will score DRS from a structured interview with the participant's primary caregiver.

6.4 Key Predictors and Modifiers of Outcome

6.4.1 Disposition and Rehabilitation details (Primary predictor; Aim 2). Study teams at each site will utilize medical records to document evaluations performed before hospital discharge by a physical, occupational, speech therapist, and physiatrist and concordance between recommended and actual dispositions. We will categorize discharge disposition into 1) inpatient acute rehabilitation, 2) inpatient subacute or skilled nursing facility, 3) home with outpatient therapy or 4) home with no prescribed therapy. For patients who receive any form of rehabilitation within 1 month of discharge, we will collect the duration and the total number of therapy sessions attended.

6.4.2 Self-reported race and ethnicity (Primary predictor, Aim 3) is the current gold standard and superior to measures derived from other sources.[148,149] Participants will be asked by the POST-ICECAP team to identify their ethnicity and then asked to identify their race on categories defined by NIH and US Census Bureau.

6.4.3 Psychological distress**.** *1: PTSD symptoms.* The PTSD Checklist (PCL-5)[150] is an extensively validated, 20-item scale developed by the National Center for PTSD that corresponds to *DSM-5* criteria for PTSD and will be keyed to the OHCA. We will use the continuous score and the National Center for PTSD's recommended cut-off point of 36 to categorize participants as likely having PTSD.[151] The PCL-5 has been validated for telephone administration[152] and has performed well in our OHCA participants.[53] *2: Depression and 3: Generalized (non-cardiac) Anxiety Symptoms* are common after OHCA[23,56,153] and are modifiers of functional and cognitive outcomes.[55,56] We will use the validated Patient Health Questionnaire (PHQ-8) to measure depressive symptoms[154,155] and the GAD-2 to measure generalized anxiety.[156]

6.4.4 Social Factors. Biological sex of participants is collected by ICECAP. POST-ICECAP will collect information about gender identity, caregiver status and involvement in day-to-day care, social support, education, occupation and socio-economic status as determined by the NIH. We will collect participant (or caregiver) reports about perceived racism and discrimination. We will assess two unique neighborhood-level indicators of SES (Area Deprivation Index,[62] Social vulnerability index, and Historical Redlining[157]).

6.4.5. Healthcare Utilization. At each assessment, we will ask participants about interval hospitalizations, medical procedures, or outpatient visits. We will extend the existing ICECAP data on medical comorbidities and confirm any new medical diagnoses at each encounter (e.g., hypertension, heart failure, diabetes).

7. POTENTIAL RISKS: The respondent burden has been shown to vary in intensity and degree, depending upon the risk level of the research, the procedures that the research entails, and the individual participant's condition, mental state, and support systems. Though this study poses minimal risk to participants as it does not involve any intervention and participants are only asked to complete questionnaires (paper, computer, and phone), 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; therefore procedures for participants with alcohol/drug impairments, inability to communicate, providing safety in suicidal participants, or reporting COVID-19 symptoms will be made. A sincere effort to understand our participants' perception of respondent burden—whether the burden is psychological, physical, and/or economical - will be made.

8. TRAINING

POST-ICECAP will use the training infrastructure of the ICECAP trial. The Clinical Coordinating Center (CCC) will execute POST-ICECAP sub-contracts as amendments to the ICECAP master contract and will train and monitor site performance. SIREN utilizes multiple methods to optimize the education and training of site personnel including face-to-face training at investigator meetings and online modules and certifications for re-training or training of new personnel. We successfully adapted all of these methods to remote training and monitoring during the COVID-19 pandemic. At all POST-ICECAP enrollment locations, the site principal investigator, study teams, treating physicians, inpatient nursing staff, and outcome assessment investigators will receive appropriate training prior to study initiation. Training decay will be minimized with scheduled recertification and/or refresher training of study and clinical staff. Personnel responsible for outcomes assessment will be recertified frequently to ensure inter-rater reliability.

Clinical principal investigators from the study leadership will evaluate each site prior to initiation to provide and assess adequacy of training and organization. Investigator meetings will occur periodically to address any impediments to subject enrollment, discrepancies in treatment between centers, and protocol violations of concern. In addition, this will afford an opportunity to discuss any changes in the standard of care during the study period.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Plan: Plan for ensuring transparency and unbiased reporting

Confidence and rigor in research are threatened[169] when there is selective reporting, selective adjustment for covariates, or performance of multiple unreported tests, all of which result in non-reproducible findings rather than trustworthy/reproducible evidence. To avoid this threat, we will post our methods and analysis plan on the Open Science Framework.

9.1.1 Primary analyses will be performed on patients with mRS<5 (awake patients; anticipated n=750) at 1 month, but descriptive/exploratory analyses will be performed on those w/ 1-month mRS=5 (n=250) (DoC patients). We will analyze these two strata separately as patients with DoC will have qualitatively different recovery and systematically different exposures to modifiers like rehabilitation (ineligible for inpatient acute rehabilitation). Each Aim focuses on the change in function, cognition, and HRQoL from 3 to 12 months; i.e., the period beyond the ICECAP endpoint.

9.1.2 Primary Aim 1 analyses. Among patients with mRS<5 at 1 month, we will examine/report the crosstabulation of 3-month mRS with 12-month mRS and the scatterplots of 12- versus 3-month scores on NIH-Toolbox and Neuro-QoL. While we anticipate that the 3- and 12-month outcomes will be substantially correlated, one of the primary rationales for conducting POST-ICECAP is our belief that these correlations will fall far short of 1.00, due to substantial between-person variability in the change from 3 to 12 months in each outcome. To test the hypotheses that initial illness severity (total OHCA score primary predictor, PCAC secondary predictor), early coronary angiography, and duration of hypothermia are associated with change from 3 to 12 months in mRS (primary outcome), NIH-Toolbox and Neuro-QoL (secondary outcomes), we will perform separate repeated measures ANOVAs/ANCOVAs with Time (3 vs 12 months) as the within-person repeated factor, one predictor and the *a priori* covariates (including Black race and Hispanic/Latinx ethnicity) as between-person factors, and the Time*Predictor and Time*Covariate interaction terms. The significance of the Time*Predictor term will be based on a 2-tailed, α=0.05 F-test. In the primary analysis, mRS will be treated as a continuous variable, but we will conduct a sensitivity repeated measures ordinal regression analysis where mRS is treated as an ordinal variable. Also, the effect of duration of hypothermia will be modeled as a 2-df quadratic curve, by including a squared term in the analysis, because we anticipate that its relationship to the outcomes is likely to be U-shaped (or inverted U-shaped) with the optimal duration lying somewhere in the middle of the distribution. Of note, we prefer the repeated measures model approach over modeling the 12-month outcome and including the 3-month outcome as a covariate, because POST-ICECAP is an observational study, and this alternative approach, while having greater statistical power, is more prone to bias.[171]

In addition to the analysis of the duration of hypothermia described above, we will conduct an intention-to-treat analysis of its effect, with no covariates, in the subset of ICECAP participants for whom the duration of hypothermia was randomly assigned. Again, the relationship will be modeled as a quadratic curve.

9.1.3 Primary Aims 2 and 3 analyses. The same analytic approach will be used to address Aims 2 and 3, with the primary predictors being the receipt of inpatient acute rehabilitation (vs. outpatient rehabilitation/no rehabilitation/discharge to a skilled nursing facility; Aim 2) or race/ethnicity (non-Hispanic Black race, Hispanic/Latinx ethnicity vs non-Black/non-Hispanic patients [reference group]; Aim 3). Secondary analyses for

Aim 2 will categorize patients into 4 groups –inpatient acute rehabilitation, outpatient rehabilitation, skilled nursing facility, and home without rehabilitation – in order to explore differences among the latter three groups. Aim 2 analyses will exclude those whose 1-month mRS=0 since these patients would not be eligible for inpatient acute rehabilitation. Secondary analyses for Aim 3 will estimate mediation models evaluating the extent to which the associations of race/ethnicity with change in outcomes might be mediated through perceived racial discrimination, individual-level SES, neighborhood-level SES, psychosocial risk, and resilience factors.

9.2 Statistical and clinical basis for the sample size calculation

In the primary sample (those with mRS<5 at discharge, anticipated n=750) we anticipate 10% attrition,[53] resulting in n=675 with both 3- and 12-month mRS. We note that with complete data for 2 repeated measures (Y_3 and Y_{12}), the power to detect an association between X and ΔY (=Y_{12} -- Y_3) equals the power to test the Time*Predictor interaction term in the planned repeated measures analyses described above. N=675 with complete data provides ≥80%/90% power to detect Pearson (or partial) correlations of 0.109/0.126 between a predictor and the change from 3 to 12 months in function, cognition, or HRQoL (Aim 1), adjusting for 8 covariates; with multiple imputations, the effective sample size will slightly exceed 675 making these estimates of power somewhat conservative.[174] Assuming 35-45% receive inpatient acute rehabilitation and the exclusion of up to 5% due to their having mRS=0 at 1 month (ineligible for the Aim 2 analysis), N=641 provides ≥80%/90% power to detect an effect size of d=0.24/0.27 for the t-test comparing the mean change in outcomes from 3 to 12 months of these patients versus those not receiving inpatient acute rehabilitation (Aim 2). For other outcomes (cognition and HRQoL), we anticipate an additional 10% missing data due to those with mRS≥5 at either 3 or 12 months not being able to provide data (leaving n=607 with both 3- and 12-month data), resulting in ≥80%/90% power to detect Pearson correlations of 0.115/0.133 or larger and d=0.25/0.29 or larger. For Aim 3, the anticipated race/ethnic distribution of 35% non-Hispanic Blacks, 10% Hispanic/Latinx, and 55% non-Hispanic non-Blacks will provide ≥80%/90% power to detect d=0.25/0.29 for the comparison of 3- to 12-month change in function between non-Hispanic Blacks vs non-Hispanic non-Blacks and d=0.26/0.30 for the change in cognition or HRQoL. Although underpowered to detect associations with Hispanic ethnicity, we believe it is important to examine these.

The above demonstrates that the proposed POST-ICECAP study is adequately powered to detect “relatively small” associations with 3- to 12-month changes in those with 1-month mRS<5. The analyses of the subgroup with mRS=5 at discharge will be descriptive/exploratory; we will not perform/report significance tests but will report 95% confidence intervals for parameters of interest.

10. DATA MANAGEMENT

10.1 Data Management Overview

Data management will be handled by the DCC, which is housed in the Data Coordination Unit, of the

Department of Public Health Sciences, College of Medicine, Medical University of South Carolina (MUSC). All activities will be conducted in coordination with the study PIs, the sites, and the CCC. The data validation procedure will be implemented in two stages. First, the automated data checks will flag items that fail a rule, and the rule violation message will appear on the data entry screen at the time of data entry. The Study Coordinator at a site will see these rule violations and will be requested to address it. His/her choices are to: (1) correct the entry immediately; (2) correct the entry at a later time; or (3) if the entered data are confirmed to be correct, dismiss the rule by checking that option provided by the WebDCU™ system. Any changes made to the data will have a full audit trail. Secondly, for some checks that are more complicated, additional consistency checks will be run periodically after data entry occurs at the site. All data items that fail the programmed consistency checks will be queried via the data clarification request (DCR) process initiated by the DCC data managers.

In addition to the study database, the DCC will provide the site staff password protected access to a standard set of web-enabled tools, including subject visit calendar, subject accrual status, case report form completion status, and outstanding DCR status pertaining to their respective sites.

10.2 Data Acquisition and Central Study Database

The entire study will be conducted using an electronic data acquisition method where all clinical data on enrolled subjects will be data entered (single-keyed) by the site personnel into a web-based data management system, WebDCU™. In order to provide user-friendly and easy-to-navigate interfaces, the WebDCU™ data capture screens are designed based upon individual CRFs. Prior to study start, the system is validated to ensure the data entry screens mirror the CRFs and that the pre-programmed data rules appropriately detect incorrect data. The data will be managed after data entry via data queries from the DCC.

The latest version of each CRF will be available as a PDF file within the study database for use as worksheets and source documents by study personnel. This process facilitates version control of these study related documents, particularly since documents may evolve over the course of the study. This user-friendly web-based database system, developed by the DCC, will be used for data entry, data validation, project progress monitoring, subject tracking, tracking, user customizable report generation and secure data transfer.

10.3 Core Trial Database

Although POST-ICECAP requires a separate database, given its inclusion of ICECAP screen failures, it will be seamless to link POST-ICECAP data with ICECAP data using the shared ICECAP subject ID or screen failure ID. The DCC programmers will maintain the core clinical database. The relational database is based on the study CRFs using Microsoft SQL Server. The study database is programmed with extensive consistency checks (e.g., data type, range and logic checks) to flag potential data entry errors, including missing required data, data out of pre-specified range, and data conflicts and disparities within each CRF and across different CRFs. All validation parameters are outlined in the Data Management Plan maintained by the DCC.

10.4 Reporting Module

The WebDCU™ system also has a real-time reporting component that allows authorized users to view protocol specific reports as data listings and in a summary format, overall and by site, at any time during the study via the password protected system. The reports are presented in a manner that protects the integrity of the study (e.g., blinded assessment). The DCC will provide authorized study personnel access to a standard set of web-enabled tools on the WebDCU™. These tools allow the authorized research personnel to receive regular updates on accrual status and CRF status of enrolled subjects. Examples of available reports include subject enrollment logs, basic subject demographics, CRF completion rate and number of data queries outstanding and resolved. Like all reports generated on the system, data reported are in real time.

10.5 Security, Privacy, and Confidentiality

The DCU employs several layers of data protection to ensure data security. The first part of security is physical protection of the hardware systems employed by the DCU. The facility housing the DCU hardware is protected 24/7 by multiple layers of security, including electronic building and facility access secured by magnetic locks, onsite-personnel, monitored and recorded closed-circuit television, person-traps, and mandatory identity logging of all outside visitors. By limiting access, ensuring only authorized personnel have access, and tracking all entry, we can ensure this risk is minimal.

The network and system security is ensured by implementing multiple layered firewalls and a network intrusion prevention system for identifying and blocking malicious network activity in real time. Vulnerability scans are also run daily to ensure server and network hardening and preventing known application and OS vulnerabilities. Antiviral, Trojan, and worm protection is achieved by using Microsoft Forefront, updated on a daily basis. All communication with the web server and client is encrypted via SSL to make certain network traffic 'sniffing' poses no threat.

10.5.1 Audit Trail Function for WebDCU™: To maintain electronic records in the database as adequate and accurate, WebDCU™ system tracks all changes made to any patient-related and dynamically managed electronic records. This audit-trail information is created with a computer generated time-stamp and the user name in chronological order, when the original data is modified or deleted.

10.5.2 Data Redundancy: The Volume Shadow Copy Service is enabled for all DCU file servers and web servers used in the storage of clinical trial related documents and website files in order to provide a quick recovery solution for lost data. This allows for "point-in-time" copies of all edited files to be maintained in a hidden file space on the server. The copies or "snapshots" of edited files are taken 3 times daily.

10.5.3 Backup (Disaster Recovery): The databases housed in the WebDCU™ are backed up in two steps. The Microsoft® SQL server maintenance plans are set up to initiate the internal data integrity checkup procedures and to produce off-line backup copies of the database prior to IBM® Tivoli Storage Manager (TSM) backup. The TSM then delivers the full data backup to all DCU servers used in the storage of the database on at daily basis. The TSM completely backs up all system files (i.e., system registry, operating system, software, etc.) and user data files on the server. In the event of a weather related emergency or other situations where the university

implements emergency procedures, the DCU also begins emergency full backup of all servers and other procedures in accordance with the DCU's Emergency Operation SOP.

10.6 Quality Assurance / Site Monitoring

Upon entry of CRFs into the study database, quality control procedures will be applied at each stage of data handling in order to ensure compliance with GCP guidelines, integrity of the study data, and document processing system reliability. Both remote and site data and source document monitoring will be employed in a coordinated fashion. Coordination and reporting of monitoring findings, data queries, site visits, and other performance metrics are centrally consolidated within a monitoring module incorporated into WebDCU™. All sites will undergo source document monitoring by the study site monitors from the CCC. Site monitors will review source documents and case report form information, and perform multifaceted quality assurance and protocol compliance reviews.

Site Monitors will also be able to generate DCRs when discrepancies are found during source to database verification. The DCRs will be generated, communicated to the sites, and resolved on the secure study website.

The study monitoring plan will define a baseline rate of monitoring visits, and items such as informed consent documentation that will undergo 100% source document monitoring. Additional monitoring visits will be conducted using a data-driven risk-based sampling strategy. Site monitoring will include a combination of on-site and remote source document verification.

Monitoring findings are reported to the study leadership and will be used to identify and correct problems in data collection and protocol performance. Corrective action plans will be collaboratively formed and implemented with sites. Creation, implementation, tracking, and closure of corrective action plans are also performed with the online monitoring module.

11. HUMAN SUBJECTS

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

11.1 Institutional Review Board (IRB) Review and Informed Consent

In accordance with NIH guidance NOT-OD-16-094, the POST-ICECAP trial will utilize a single IRB. In conjunction with the ICECAP trial, the SIREN Emergency Research- Central IRB (ER-CIRB), Advarra will serve as the IRB of record for all sites. All SIREN sites agree to rely upon the ER-CIRB for SIREN trials as a condition of their grant awards and/or master agreements. CIRB approval for POST-ICECAP will be obtained for all participating enrollment sites.

The ER-CIRB will be responsible for the initial and scheduled continuing review of applications, modifications, review of SAE, unexpected problems, and other reportable occurrences, and review and approval of informed consent documents.

The ER-CIRB will be administered in close collaboration with the SIREN Clinical Coordinating Center (CCC). Interactions between the POST-ICECAP sites and the ER-CIRB occur primarily through the CCC Site Managers who already work closely with the sites on all aspects of trial management. CCC Managers in turn will work closely with the ER-CIRB Coordinator at Advarra.

Applications, informed consent documents, study team composition, certifications, site sign-off confirmations, adverse events, and other required information are collected in the WebDCU system, the SIREN Clinical Trial Management System (CTMS), and the IRB Information Technology platform (IRB- IT). Data transfers between IRB- IT to WebDCU reduce duplicative document submissions. All study-specific IRB communications and documents, including initial and continuing scheduled approvals, stamped, applications, notifications, and queries will be maintained in WebDCU as per prior regulatory activities.

POST-ICECAP sites will be responsible for meeting regulatory obligations, such as overseeing the implementation of the approved protocol, training and certification of investigators, stamped consent forms, conflict of interest management plans, and reporting unanticipated problems and study progress to the CIRB.

11.2 Subject Confidentiality

Case report form data and other records that leave the site will be identified only by the Study Identification Number (SID) to maintain subject confidentiality. Any material records will be kept in a locked file cabinet. Electronic records will be appropriately secured using compliant safeguards. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the NIH, the OHRP, the sponsor, or the sponsor's designee.

Return of results of the study to participants, and other study updates and thanks will be facilitated by a separate central database of contact information for participants. Contacts may opt out of this database at the end of a subject's participation or anytime afterward.

11.3 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the NIH, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

12. STUDY ORGANIZATION

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

The SIREN Clinical Coordinating Center at the University of Michigan will provide overall project management

for the study. Participating sites will be involved through an amendment to the ongoing master agreement between the SIREN CCC and SIREN Hubs. Hubs are responsible for subcontracting with and organizing clinical spoke sites. The SIREN Data Coordinating Center will provide all data management functions.

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

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

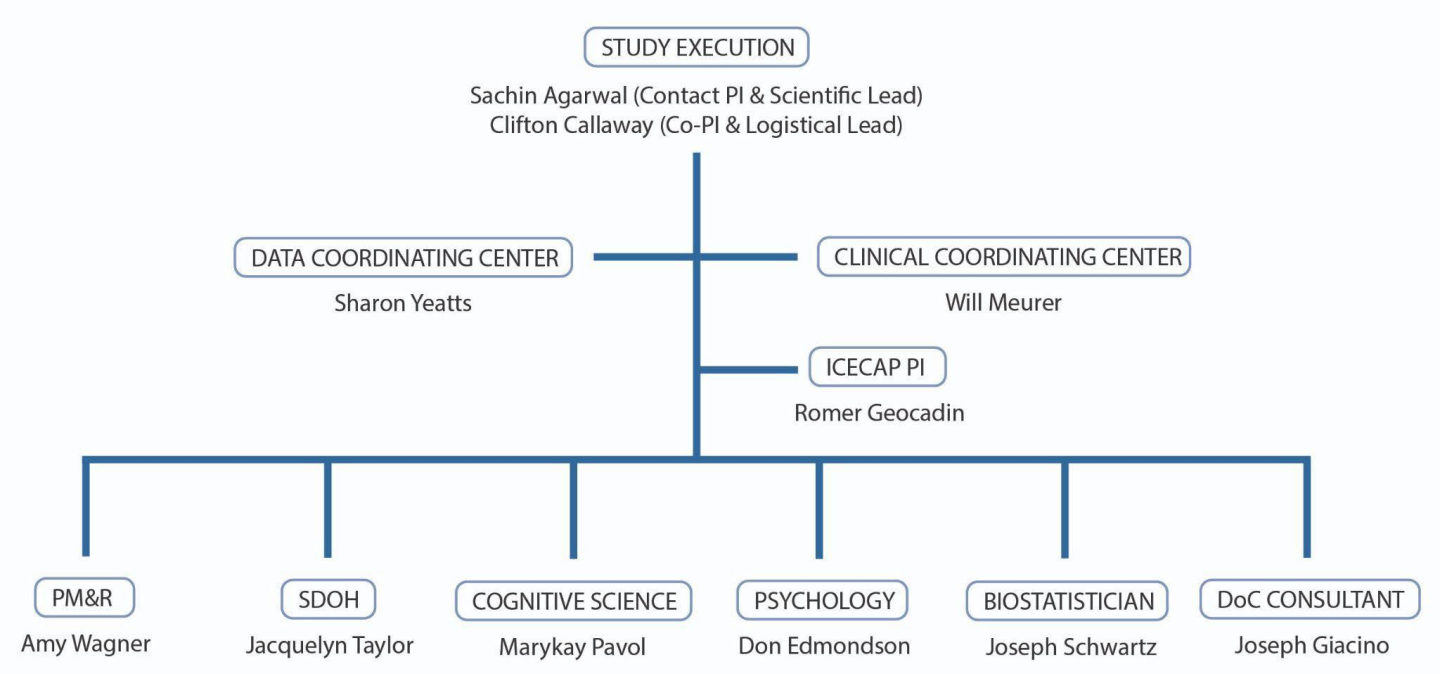
12.1 Organizational Structure of the Investigative Teams

12.1.1 The Steering Committee is charged with the overall conduct of the study. Dr. Agarwal will be responsible for chairing the Committee, which will include all investigators at CUIMC, Co-PI Callaway, Co-I Meurer, and Co-I Yeatts. Members of the Steering Committee will meet on a bimonthly basis. The Steering Committee will also be responsible for the final research dissemination of the study's findings.

12.1.2 The Project Advisory Subcommittee is charged with aiding Dr. Agarwal in the successful completion of the study. This subcommittee will be co-chaired by Dr. Agarwal and Dr. Callaway. Co-Is Edmondson, Meurer, and Geocadin will be additional members. This Subcommittee will meet in person every month for 12 months, and then every 3 months during the remainder of the study. The frequency of meetings will be reassessed periodically and increased if necessary. The agenda of the meetings will focus on addressing issues that arise during the study, with the overall goal of completing the study.

12.1.3 The Data Management and Analysis Subcommittee will be responsible for data management for all collected data, and the performance of all statistical analyses proposed in the study. Dr. Agarwal will co-chair this committee with Dr. Schwartz. Other key members of this group will include a CU data analyst and a data manager from the Data Coordinating Center at the MUSC.

12.1.4 Social Determinants of Health and Access to Rehabilitation Subcommittee will be responsible for compiling and coding the social determinants of health, coding physical therapy/occupational therapy/Physiatrist notes for patterns of referrals, and determining biopsychosocial factors influencing access to acute inpatient rehabilitation. Dr. Taylor and Dr. Wagner will co-chair this committee and meet with Dr. Agarwal and Dr. Callaway every 3 months.



Overall Structure of the POST-ICECAP Study Team

13. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the standard operating procedures developed by the SIREN and trial leadership available at https://siren.network/nett-resources/standard-operating-procedures

All presentations, abstracts, and manuscripts will include attribution of funding to the NIH and will be made available for review by the sponsor and the NIH.

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