DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Heart, Lung, and
Blood Institute
Bethesda, Maryland 20892

MEMORANDUM

DATE: June 6, 2025

TO: Study Investigators to Provide to Central and Site IRBs

FROM: Yves Rosenberg, MD, Chief Medical Research Officer, NHLBI

SUBJECT: Interim Analysis Report (RAR) dated May 20, 2025 and Final NHLBI Determinations for the "Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients (ICECAP) Trial" (UH3 HL145269; PIs: William Meurer, MD, Romergryko Geocadin, MD, and Robert Silbergleit, MD; U24 HL145272; PIs: Sharon Yeatts, PhD, Viswanathan Ramakrishnan, PhD)

The purpose of this memorandum is to inform Study Investigators of the scope and outcome of deliberations by the Strategies to Innovated Emergency Care Network (SIREN) Data Safety and Monitoring Board (DSMB) on May 30, 2025 regarding the ICECAP Trial. The National Heart, Lung, and Blood Institute (NHLBI) has reviewed the interim analysis data and DSMB's recommendations and the Institute's determination is described at the end of this letter.

We request that you provide this information to your Institutional Review Board(s).

DSMB Description and Charge

The SIREN DSMB is appointed by NINDS and tasked with independent monitoring of data and overseeing patient safety for SIREN NINDS and NHLBI-supported clinical trials including of those using exception from informed consent (EFIC). The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and monitoring the overall conduct of the ICECAP trial. The SIREN DSMB is comprised of 13 members including senior experts in neurology, cardiology, emergency medicine, hyperbaric medicine, pediatrics, internal medicine, statistics, and ethics; and convenes two times a year. Staff from the Data Coordinating Center (DCC) and NHLBI participate in the meetings as non-voting members. DSMB procedures are identified in the SIREN DSMB Charter.

ICECAP Trial Description

The **ICECAP (Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients**) **Trial** is a prospective, multicenter, randomized, response-adaptive, duration-finding, comparative effectiveness trial in a maximum of 1,800 adult comatose survivors of witnessed out-of-hospital cardiac arrest, who have been rapidly cooled to 33°C using a definitive, closed- loop (endovascular and surface) temperature control method. The primary endpoint is a weighted Modified Rankin Scale (mRS) at 90 days post-return of spontaneous circulation (ROSC). The mRS is a seven-level ordinal scale of disability, which ranges from zero (no symptoms at all) to six (death). ICECAP uses weighting of mRS states to capture changes in functional status. The potential number of treatment arms is ten (6, 12, 18, 24, 30, 36, 42, 48, 60, or 72 hours of cooling). The trial enrolls patients with shockable and non-shockable rhythm types. Within each rhythm type, patients are adaptively randomized to a cooling duration. The primary objective of this trial is to characterize, for each rhythm type, the duration-response curve for cooling and to

identify the duration that provides the maximum treatment effect, referred to as the target duration.

The trial operates under IDE G160072 whose sponsor is the ICECAP Clinical Coordinating Center (CCC) co-Principal Investigator, Dr. William Meurer, from the University of Michigan at Ann Arbor.

DSMB Findings and Recommendations – May 30, 2025

An ad hoc meeting was convened to review the May 20, 2025 Interim Analysis (RAR) which included 1,151 randomizations. The non-shockable rhythm arm had crossed the pre-specified futility boundary, and the DSMB unanimously recommended to close further enrollment into the non-shockable rhythm arm. On the question of statistical futility of the shockable rhythm type, the DSMB requested the unblinded statistical team to conduct a conditional power assessment to estimate the number of additional patients needed and the time required to cross the futility boundary or reach a conclusion for the shockable rhythm type. The Board requested that this analysis be based on current enrollment trends and results to date, using a simulation to project future scenarios. No safety concerns have been identified to date.

This information was received by the DSMB on June 3, 2025. Based on the data reviewed, the DSMB recommended stopping enrollment in both arms of the ICECAP trial.

NHLBI Leadership Meeting – June 4, 2025

The DSMB recommendations were discussed by NHLBI leadership, and NHLBI accepted these recommendations. The NHLBI has determined that enrollment in the ICECAP trial should be discontinued and follow-up should be completed on all enrolled participants as planned in the protocol. Investigators should be developing a plan for an orderly closeout.

Thank you for your time and attention.

Sincerely,

YVES D. ROSENBERG -S

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Date: 2025.06.06 13:35:03 -04'00'

Yves Rosenberg, MD,
Chief Medical Research Officer, NHLBI

Date

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