March 25, 2022

University of Michigan
William Meurer
Associate Professor Emergency Medicine and Neurology
Taubman Center B1-354F
1500 E. Medical Center Drive
Ann Arbor, Michigan 48130

Re: G210126/S002
Trade/Device Name: Pediatric Influence of Cooling duration on Efficacy in Cardiac Arrest Patients
Dated: February 21, 2022
Received: February 23, 2022
CMS Category: B
Annual Report Due: May 26, 2022

Dear William Meurer:

The Food and Drug Administration (FDA) has reviewed the supplement to your Investigational Device Exemption (IDE) application regarding your pivotal study for a significant risk device proposing revisions to the P-ICECAP clinical protocol including the replacement of the 6-hour cooling duration arm with a "zero-hour" additional cooling arm. FDA identified some outstanding issues in your application, and has therefore determined that your study is approved with conditions. You may implement the changes in your study (in accordance with the conditions of approval listed below) using a revised informed consent document which corrects deficiency numbers 2 through 9. Your investigation is limited to 40 US institutions and 50 US subjects (with interim reports submitted to the DSMB and FDA – see staged conditions).

Your IDE application has been approved with conditions as a staged study. You may request approval to expand enrollment in your study when you have submitted the following:

1. Detailed interim safety reports submitted to FDA and the DSMB after every 10 subjects enrolled and treated (with at least 30 day follow up data). The purpose of these reports is to identify otherwise unrecognized ongoing safety issues appropriate for informing stopping decisions.
2. Detailed minutes for the DSMB meetings (open and closed sessions) following each interim safety report.
3. A comprehensive clinical report (including at a minimum, adverse event information, and temperature and outcomes data for each subject) on the first 40 subjects enrolled and treated (with all follow-up information available).

These staged conditions have been implemented to address the following concerns:

In the May 26, 2021, Conditional Approval letter for G210126 ("P-ICECAP"), FDA communicated the following to you in approval condition 3 (emphasis added):

> *You have proposed the P-ICECAP study as a consented study, obtaining consent from subjects or their parent/guardian/legally authorized representative (LAR) within 6 hours following application of standard of care (SOC) therapeutic hypothermia treatment (cooling via site specific cooling devices). This approach to consent is acceptable as long as the current SOC at the study site is therapeutic hypothermia…the sites that will be permitted to enroll subjects in the P-ICECAP study need to have demonstrated that they have previously established therapeutic hypothermia protocols as the SOC treatment in pediatric cardiac arrest subjects,..change in treatment from normothermia to therapeutic hypothermia is considered a research intervention. Obtaining informed consent before the hypothermia intervention will not be feasible and as such, in order to include these sites in the P-ICECAP trial, your study would need to be performed under 21 CFR 50.24, Exception from Informed Consent Requirements for Emergency Research (EFIC). As such, under the proposed consented P-ICECAP study, FDA will require that any study admitted into the P-ICECAP trial submit verification to you that therapeutic hypothermia is the established SOC therapy for pediatric cardiac arrest at their site…Only clear indications of an established hypothermia protocol for pediatric cardiac arrest, other than the desire to participate in the P-ICECAP trial, will be acceptable.*

In your July 9, 2021, response, you modified your trial's position regarding initial SOC therapeutic hypothermia with the clarification that

> *…with nearly all of our sites…a majority have used a target of 33 degrees at some point within the last year. The sites are uniformly using targeted temperature management… From a practical perspective, sites will set the target temperature for the device to their local routine care after admission… intensive care unit physicians will set targets from 33 to about 37 degrees*.

Our interpretation of your response was that, consistent with our condition of approval, all study sites indeed used device-controlled targeted temperature management (TTM) as SOC to maintain pediatric cardiac arrest patients at a temperature below normothermia (i.e., 37° C), with a "majority" using "a target of 33 degrees." Based on that inference, we approved (August 3, 2021) your protocol's inclusion criteria change of "[t]he requirement that a participant is cooled to 34 degrees will be altered and will be changed to a requirement of initiation of targeted temperature management using a temperature control device." However, your clarification of study centers' SOC practices regarding temperature management raised two new concerns (Study Design Considerations #4 and #5 communicated in our August 3, 2021 letter) regarding P-ICECAP:

> *[SDC #4] The P-ICECAP study is an adaptive allocation clinical trial designed to determine if increasing durations of induced hypothermia are associated with better neurobehavioral outcomes and to identify the optimal duration of induced hypothermia for neuroprotection in comatose survivors of childhood cardiac arrest. Your study design does not include a normothermia control arm. Induction of hypothermia for cardiac arrest in the pediatric population has a Class 2a recommendation from the American Heart Association (AHA) (level of evidence B-NR), and a recent study (THAPCA) evaluating cooling to mild hypothermia in pediatric cardiac arrest demonstrated no difference in any of the outcome measures (e.g., including survival and neuro outcome) as compared to the normothermia control arm. Accordingly, and consistent with prior*

recommendations, FDA suggests you consider including a normothermia arm for the P-ICECAP study.

[SDC #5] You proposed protocol revisions as outlined in Amendment G210126/A001 to permit sites to practice their current temperature management protocol to the institution's target until consent is obtained. FDA is concerned this change may risk jeopardizing safety and/or effectiveness inferences at the conclusion of the study. Specifically, the first primary objective of your study is "[t]o determine whether increasing durations of cooling are associated with better outcomes or recovery, implying efficacy of hypothermia versus no cooling." The fundamental eligibility criterion related to that objective had previously been, "Eligibility will require that a core temperature of <34° C be obtained by 240 minutes after cardiac arrest ROSC." This criterion is now changed in your modified protocol, and FDA is concerned that the heterogeneous enrollment characteristics related to disparate initial temperature management strategies may ultimately confound the results, thereby potentially making the study uninterpretable with regard to this primary objective. To try to address our concern, we recommend you consider pre-specifying initial target-temperature subgroups and/or require enrollment caps for subjects not initially cooled to 34 degrees within 6 hours.

In our teleconference on March 16, 2022 we were surprised to learn that ~90% of your sites' investigators do not employ targeted hypothermia as their SOC, as this fact is not consistent with our prior Condition of Approval above. In your current submission G210126/S002, you have now proposed replacing the 6-hour duration cooling arm with a "zero hour" cooling arm. It seems that your definition of the "zero hour" cohort will be a non-pre-specified mixture of initial cooling followed by warming to normothermia, no cooling followed by continued normothermia, no initial cooling followed by cooling, initial cooling followed by deeper cooling to 33°C, or initial cooling to 33°C followed by maintenance of 33°C. Accordingly, our concern over heterogeneity remains.

You also suggested that the majority of pediatric cardiac arrest subjects arrive at the study sites already hypothermic, irrespective of the sites' SOC management. Based on our review of Table S1 "Therapeutic hypothermia after out-of-hospital cardiac arrest in children" (N Engl J Med 2015;372:1898-908, Supplementary Appendix), we believe this assumption may not be true (median first measured body temperature 36° C, upper IQR 37° C). Accordingly, we continue to believe that varying approaches to temperature management for up to 6 hours prior to randomization may seriously confound the results and jeopardize interpretability for your stated objectives, i.e., determine (i) whether the duration-response implies cooling efficacy versus no cooling, and (ii) the shortest duration of cooling that provides the optimal treatment effect. Additionally, we also explained in the teleconference our concern that the variability in initial patient management, based as it would be on individual clinicians' prerogatives, risked exposing enrolled subjects to cycled temperature management interventions (e.g., hypothermia followed by warming followed by randomized re-cooling) that could pose additional, unrecognized harm to pediatric patients. Although you agreed with us that such scenarios should be avoided, your protocol has no provisions to do so.

Your trial was previously approved with the understanding that appropriate equipoise existed among investigators and clinicians regarding the use of normothermia and hypothermia; that assumption no longer appears valid. The Additional Safeguards for Children (21 CFR 50 subpart D) must be considered when pediatric patients will be enrolled in a clinical trial. The risk of treating children with

out of hospital cardiac arrest with different durations of hypothermic or normothermic TTM in P-ICECAP is more "than a minor increase over minimal risk" (21 CFR 50.53) and therefore use of these durations of TTM must offer a prospect of direct benefit to the individually enrolled pediatric subject. The risk must be justified by the anticipated benefit, and the anticipated risk-benefit profile must be at least as favorable as that presented by accepted alternative treatments (21 CFR 50.52). The information you recently provided suggests the vast majority of pediatric intensive care units (PICUs) and clinicians use normothermic TTM, and appears to suggest that even though clinical guidelines for treatment of pediatric patients state that hypothermic TTM is a "reasonable" treatment option, the risks of different durations of hypothermic TTM may not be justified by the benefit given routine practice. As such, we are concerned that P-ICECAP may not meet the requirements under subpart D.

In addition, your protocol modifications, although they appear intended to address the issue of the absence of a normothermic control arm, have unfortunately magnified our concern that the trial may yield uninterpretable results regarding the safety and/or effectiveness of hypothermic targeted temperature management (TTM) in the vulnerable population of pediatric cardiac arrest patients. Given that you have not responded to our questions about your statistical analysis plan, we are challenged to determine whether the proposed plan will result in interpretable results.

When it is considered scientifically necessary to conduct a clinical investigation in children, it is imperative that the clinical investigation be well designed to collect interpretable data. Key elements of well-designed clinical investigations include selection of appropriate control groups and study endpoints that are relevant in the pediatric population, and a well designed statistical analysis plan with adequate power calculations. Studies that are not well-designed expose children to unnecessary risks, are unlikely to yield informative study results and as a result may be considered unethical. Based on your submission, we are concerned "there is reason to believe that risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained" (21 CFR 812.30(b)(4)), and that the investigation plan is not adequate (21 CFR 812.30(b)(5)(i).

To address the above concerns, FDA will conduct substantially enhanced oversight of the trial, as outlined in the staged conditions above, in order to assure that the ongoing trial can fulfill the ethical, scientific, and regulatory obligations required when conducting a pediatric clinical trial.

Alternatively, we strongly advise you to modify your protocol as follows:

a. A clinical investigation in children must be well-designed to collect interpretable data. Key elements of well-designed clinical investigations include selection of appropriate control groups. Trials that are not well-designed expose children to unnecessary risks, are unlikely to yield informative study results and as a result may be considered unethical. To best address this concern, we suggest that you design a stand-alone randomized study that will include a control arm of true normothermic TTM. This arm should enroll sufficient subjects from the outset of the trial, and the statistical analysis plan should be modified such that your objective of determining whether the duration-response implies cooling efficacy versus no cooling can be rigorously evaluated in a direct manner. Similar to your current statistical plan, we would accept an adaptive study design that closes enrollment to this control arm if an interim analysis yielded clinical and statistical results justifying doing so.

b. Modifications to the enrollment and randomization processes should be codified within the protocol such that occurrences of the cycled TTM mentioned above (and may pose additional, unrecognized harm to pediatric patients) are specifically prevented from taking place. For example, you may wish to designate clinically discordant initial and subsequent randomized TTM strategies as triggering cross-over to a non-randomized treatment arm, with analysis populations defined accordingly. Please make the appropriate revisions to your protocol to address this safety concern.

If you choose to modify your protocol as recommended, please submit these protocol revisions under a new IDE supplement and we will re-evaluate the staged status of your study.

You must also obtain institutional review board (IRB) approval before implementing this change in your investigation as required by 21 CFR 812.35(a) because FDA believes this change affects the rights, safety, or welfare of subjects.

Approval Conditions

This approval is being granted on the condition that, within 45 days from the date of this letter, you submit information correcting the following issues:

Enrollment of Pregnant Subjects

1. You have provided insufficient justification for enrollment of pregnant people in this trial. As such, please exclude enrollment of pregnant individuals (when known) until you have provided sufficient information to address the following (alternatively, you may revise your protocol to explicitly exclude pregnant individuals):

   a. The protocol states that "each PICU has a usual practice for this," presumably this means that each PICU has a usual practice for determining pregnancy and/or initiating hypothermic or normothermic TTM in pregnant people. However, you have not provided data on how many institutions use therapeutic hypothermia compared to normothermia in pregnant people or how many institutions have a different SOC for pregnant people. Please provide evidence that the pregnant person would not have access to TTM outside the research setting.

   b. We note that the potential for this trial to hold out the prospect of direct benefit that is not otherwise available outside the research setting is only one of 10 required conditions outlined in 45 CFR part 46, subpart B, Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research, Department of Health and Human Services (HHS), regulations that FDA recommends be satisfied for FDA-regulated clinical research. Additional conditions for enrollment of pregnant people include nonclinical studies and clinical studies that provide data for assessing potential risks to pregnant women and fetuses when appropriate and obtaining the pregnant person's informed consent.

      Please provide sufficient scientific justification for the enrollment of pregnant people in P-ICECAP. We recommend this justification include (1) reasonably foreseeable risks to the pregnant person and fetus, (2) a literature summary of nonclinical studies and clinical studies that provide data to assess the risks and benefits of TTM in pregnant people, (3) the anticipated number of pregnant people who

will enroll in the trial, (4) how the data generated from the pregnant subjects will inform use and duration of use of TTM, including therapeutic hypothermia and normothermia, in this population, and (5) address the procedures for subjects known to be pregnant prior to randomization and for subjects identified as pregnant after randomization. Identify the objective eligibility criteria for pregnant persons in the protocol. In addition, the informed consent document should describe any foreseeable risks or discomforts specific to the pregnant subject and the fetus (see Approval Condition 6 below).

Informed Consent

2. The informed consent form (page 4) states, "Your child will receive usual intensive care unit treatment whether they are in the study or not." Although the form goes on to explain "the main difference" of study participation will be assignment to hypothermic TTM or normothermic TTM, this initial statement may be misleading. The informed consent must clearly identify that the intervention to which the child is randomized may not be the SOC at the treating PICU and may not be the intervention the attending physician would choose to treat the potential subject. Please revise this statement accordingly. You could consider the following language or something similar:

   "This study will employ different durations of keeping lower body or normal body temperatures. Your child's temperature may be kept at a temperature that is lower, higher or the same as what would normally be used in this hospital. Your child's temperature may be kept at a temperature that would not routinely be used by your child's doctor. All the other treatments your child will receive are the usual intensive care unit treatments they would receive whether they are in the study or not."

3. The informed consent form (page 4) states, "If your child is already cold, they will be slowly rewarmed to 33 (or 36.8 °C if he/she is assigned to normal temperature for the whole 5 days)." Please clarify "rewarmed to 33" as this is not considered a normal temperature. Additionally, the informed consent does not address the procedures for when the child temperature is normal or above normal and the procedures that may occur in these situations. Please correct this deficiency.

4. The informed consent form (page 4) identifies that the study team will collect "some additional information about you and your family, and how your child was doing before the cardiac arrest." Please provide additional information about the data that will be collected in the hospital and after discharge (at 3 months and 12 months) in the informed consent form.

5. The "What Are the Possible Risks and Discomfort of the Study?" section of the informed consent form (page 5) describes possible risks following "cardiac arrest." Although including possible risks/discomforts after cardiac arrest may be informative, the document should describe the possible risks and discomforts of cooling following cardiac arrest and any potential risks associated with shorter or longer durations of cooling. Please make these necessary changes to the "What Are the Possible Risks and Discomfort of the Study?" section of the informed consent form.

6. The "Unforeseen Risks" section of the informed consent form identifies unknown risks to a pregnancy, embryo or fetus, and the "Pregnancy" section identifies that "cooling appears to be safe." If you choose not to exclude pregnant individuals from the P-ICECAP study and address approval condition 1 above, please include in the "What Are the Possible Risks and Discomfort of the Study?" section any unique possible risks and discomforts to the pregnant person or fetus.

7. Language in several sections of the informed consent form imply that the subject will be cooled. For example, the "Why are we doing this study?" section (page 3) states, "the different treatments we are studying are different lengths of cooling," the "Unforeseen Risks" section (page 5) states, "Since the length of time cooling is used is what we are studying," and the "Costs" section states, "Temperature control started prior to your consenting to participate in the study and so cooling is part of standard medical care." The assent form for subjects 14 to 18 years of age (page 1) states, "For this study, your body was kept cooler than regular temperature." Please modify the informed consent documents to identify that cooling may not be SOC at all institutions and not all subjects will be cooled.

8. Under the "Alternatives to Participation" section (page 6), the informed consent states "Most often with standard or routine care, the temperature is kept between 33-37°C for about 3-5 days." Per our discussion on March 16, 2022, and your document titled "Default.Report.pdf" providing site survey data, this statement is incorrect as the vast majority of trial sites use normothermic TTM as SOC. Please correct this statement and include a numerical estimate of the number of sites and/or clinicians that use normothermic TTM. You could also provide an estimate of the chance that a child would normally receive hypothermic TTM.

9. If a change in guardianship occurs during the trial and/or a subject reaches the age of majority at any point during the trial, including the inpatient and outpatient parts of the trial, the informed consent process should be repeated, and consent by the new LAR and/or "adult" subject must be documented using the written informed consent form approved by the IRB. The informed consent form must be signed and dated at the time of consent as required under 21 CFR 50.27(a). Please make this informed consent process clear.

In your submission that responds to the deficiencies listed above, please identify your response as an amendment to G210126/S002 and reference the date of this letter. As we render only one decision per application, if you include additional changes beyond the scope of these deficiencies with your response, such changes may raise new issues that impact our decision.

Your response should be identified as an IDE amendment referencing G210126/S002, and must be submitted following eCopy guidelines to:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
IDE Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

The Federal Food, Drug, and Cosmetic Act (the Act), as amended by section 1136 of the Food and Drug Administration Safety and Innovation Act (FDASIA), authorizes FDA to require an electronic copy (eCopy) for certain types of submissions. An eCopy is an exact duplicate of a paper submission, created and submitted on a CD, DVD, or other electronic media, accompanied by a single paper copy of your signed cover letter. This authorization applies to the original, amendments, supplements, and reports, as applicable, for your submission type.

For more information about FDA's eCopy program, including the technical standards for an eCopy, refer to the guidance document, "eCopy Program for Medical Device Submissions" at https://www.fda.gov/media/83522/download. In addition, we strongly encourage you to visit FDA's eSubmitter website at https://www.fda.gov/industry/fda-esubmitter/cdrh-esubmitter-program in order to develop an eCopy in accordance with the technical standards prior to sending it to FDA.

Please note that the above condition(s) of approval should be satisfied within 45 days from the date of this letter or we may take steps to propose withdrawal of approval of your IDE application.

If you would like a meeting or teleconference with the review team and management to discuss your planned approach for responding to the deficiencies in this letter, please submit your request for feedback as a Submission Issue Q-Submission (Q-Sub). Please submit a valid eCopy of the Submission Issue Q-Sub to the address listed above. The eCopy must be accompanied by a single paper copy of your signed cover letter. Your submission should reference this IDE, identify the specific deficiencies you wish to discuss, and indicate your preferred feedback mechanism (i.e., email, meeting or teleconference). For additional information regarding Q-Subs, please refer to the Guidance for Industry and FDA Staff on Medical Devices: Requests for Feedback and Meetings for Medical Device Submissions at https://www.fda.gov/media/114034/download. FDA's guidance represents FDA's proposed approach to this issue.

If you have any minor clarification questions concerning the contents of the letter, please contact Catherine P. Wentz at 301-796-6339 or Catherine.Wentz@fda.hhs.gov.

Sincerely,

Nicole G. Ibrahim -S

Nicole Ibrahim
Director
DHT2B: Division of Circulatory Support,
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Office of Product Evaluation and Quality
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