August 3, 2021

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/A001
Trade/Device Name: Pediatric Influence of Cooling duration on Efficacy in Cardiac Arrest Patients
Dated: July 9, 2021
Received: July 12, 2021
CMS Category: B
Annual Report Due: May 26, 2022

Dear William Meurer:

The Food and Drug Administration (FDA) has reviewed the amendment to your Investigational Device Exemption (IDE) application regarding your pivotal study (P-ICECAP) for a significant risk device. You have corrected the deficiencies cited in our May 26, 2021 approval with conditions letter. Your application is therefore approved, and you may continue your investigation after you have obtained institutional review board (IRB) approval. Your investigation is limited to 40 US institutions and 900 US subjects.

We would like to point out that approval of an IDE application does not ensure that the results of this investigation will provide a reasonable assurance of the safety and effectiveness of your device or assure a determination of clearance/approval for your premarket submission.

Your study may meet the definition of an applicable clinical trial, which requires mandatory registration and results information submission to http://www.clinicaltrials.gov. Please see the final rule "Clinical Trials Registration and Results Information Submission" (81 FR 64982; Sept. 21, 2016) and 42 CFR Part 11. For information on informed consent requirements related to applicable clinical trials set forth in 21 CFR 50.25(c), please see "Guidance for Sponsors, Investigators, and Institutional Review Boards Questions and Answers on Informed Consent Elements, 21 CFR 50.25(c)" at https://www.fda.gov/media/82634/download.

FDA will waive those requirements regarding prior approval of a supplemental IDE application for investigational sites (21 CFR 812.35(b)) provided that the total number of investigational sites does not exceed the limit identified in this letter. Under this waiver, the study may be initiated at new sites, up to the approved limit, and updated information required by 21 CFR 812.20(b) on participating investigators and associated Institutional Review Boards (IRBs) and the IRB approval documentation may be submitted all at

once in your IDE annual progress report. You must, however, submit a supplemental IDE application, and receive FDA approval, prior to expanding the investigation beyond the site limit specified in this letter. In addition, you must maintain current records as required by 21 CFR 812.140 and submit reports as required by 21 CFR 812.150. If a reviewing IRB requires any significant changes in the investigational plan or in the informed consent that may increase the risks to subjects or affect the scientific soundness of the study, then this change must be submitted to FDA for review and approval prior to initiating the study at that investigational site (21 CFR 812.35). Minor changes requested by the IRB may be made without prior FDA approval. FDA also will waive the requirement for 6-month current investigator lists (21 CFR 812.150(b)(4)) provided that current investigator information is submitted every 12 months as part of the IDE annual progress report.

FDA acknowledges that your investigation will include foreign sites. FDA does not have jurisdiction over foreign sites; therefore, you may proceed at those foreign sites at your discretion. We encourage you however, to follow a uniform protocol at the domestic and the foreign investigational sites. Please note that FDA will accept data from studies conducted outside the United States if you demonstrate that the data are adequate to support a premarket submission (e.g., an IDE, or a marketing application or submission). Section 812.28 of the IDE regulation provides the requirements for studies conducted outside the United States that began on or after February 21, 2019, and are submitted in support of a premarket submission. For additional information please refer to the FDA Guidance "Acceptance of Clinical Data to Support Medical Device Applications and Submissions", available at: https://www.fda.gov/media/111346/download.

For studies conducted outside the United States that began before February 21, 2019, and are submitted in support of a premarket approval (PMA) application, FDA will accept the data if the data are valid and the investigators have conducted the studies in accordance with the "Declaration of Helsinki" or the laws and regulations of the country in which the study is conducted, whichever afford greater protection to the human subjects. If the country's standards are used, you must state in detail any differences between the country's standards and the "Declaration of Helsinki" and explain why the country's standards afford greater protection to the human subjects.

Furthermore, to export a device that is not in commercial distribution in the U.S. you must comply with Section 802 of the Federal Food, Drug and Cosmetic Act (the act). Detailed information regarding export requirements for investigational devices is available at: https://www.fda.gov/medical-devices/exporting-medical-devices/exporting-unapproved-devices.

For clarification regarding FDA decisions and recommendations for IDEs, please refer to the FDA guidance "FDA Decisions for Investigational Device Exemption Clinical Investigations: Guidance for Sponsors, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff," available at: https://www.fda.gov/media/81792/download.

In order for your study to serve as the primary clinical support for a future marketing approval or clearance, FDA has provided additional study design considerations as an attachment to this letter. These recommendations do not relate to the safety, rights or welfare of study subjects and they do not need to be addressed in order for you to conduct your study. You are reminded that prior to implementing any significant modifications to the approved investigational protocol you must obtain FDA approval, and, if appropriate, IRB approval for the changes.

FDA encourages sponsors to collect clinical trial data in accordance with the Guidance for Industry: Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies (https://www.fda.gov/media/98686/download) and to enroll patients that would reflect the demographics of the affected population with regard to age, sex, race and ethnicity. Reference is made to 21 CFR 812.25(c) regarding description of patient population and to 21 CFR 814.15(b)(1) with regard to the need for data, including foreign data, to be applicable to the U.S. population and U.S. medical practice. We recommend that you include a background discussion of prevalence, diagnosis and treatment patterns for the type of disease for which your device is intended. This should include age-, sex-, race-, and ethnic-specific subgroup prevalence, identification of proportions of women and minorities included in past trials for the target indication, and a discussion of your plan to address any factors identified or suggested, which may explain potential for under-representation of women, minorities, and specific subgroups, if applicable. We recommend that you include a summary of this information in your protocol and investigator training materials. Consideration should be given to enrollment of investigational sites where recruitment of needed populations for study can be more easily facilitated.

Future correspondence concerning this application should be identified as an IDE supplement referencing the IDE number above, 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

Information to help you understand the function and duties of a sponsor, titled, "Sponsor's Responsibilities for a Significant Risk Device Investigation," is available at: https://www.fda.gov/medical-devices/device-advice-investigational-device-exemption-ide/sponsors-responsibilities-significant-risk-device-investigations-nov-1995. Additionally, information which you should provide to participating investigators, titled, "Investigators' Responsibilities for a Significant Risk Device Investigation," is available at: https://www.fda.gov/medical-devices/device-advice-investigational-device-exemption-ide/investigators-responsibilities-significant-risk-device-investigations-nov-1995.

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.

Background regarding the assigned CMS category and the process for requesting re-evaluation of the category is provided in guidance: "FDA Categorization of Investigational Device Exemption (IDE) Devices to Assist the Centers for Medicare and Medicaid Services (CMS) with Coverage Decisions," which is available at https://www.fda.gov/media/98578/download. Additional information about Medicare coverage related to Investigational Device Exemption (IDE) studies is available at https://www.cms.gov/Medicare/Coverage/IDE/index.html.

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 Ibrahim, Ph.D.
Director
DHT2B: Division of Circulatory Support,
Structural and Vascular Devices
OHT2: Office of Cardiovascular Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure
Additional Recommendations and Considerations

ADDITIONAL RECOMMENDATIONS AND CONSIDERATIONS

The recommendations and/or considerations below do not relate to the safety, rights or welfare of study subjects and they do not need to be addressed in order for you to conduct your study.

Study Design Considerations

FDA suggests the following additional modifications to your clinical protocol for your consideration. Study Design Considerations 1-3 and 6-21 are repeated from FDA's letter issued on May 26, 2021.

Clinical

1. The proposed primary effectiveness measure of P-ICECAP is a composite of the average Vineland Adaptive Behavior Scales–Third Edition (VABS-3) at 12 months and survival at 12 months. Specifically, you propose to measure VABS-3 scores (which can range from 20-140) among surviving subjects, consistent with the published VABS-3 manual. You additionally propose to assign a VABS-3 score of "0" to non-surviving subjects. It is not clear to us if this VABS-3/mortality composite represents a previously un-implemented use of the VABS-3 scale for a clinical trial, nor if this proposed composite has been previously tested and/or validated. While we agree with you that "for out of hospital cardiac arrest, the primary outcome measure must concurrently account for survival rate and neurobehavioral functioning among survivors," we do not agree that you have provided an adequate justification for why death should be considered 20 points below the lowest attainable neurocognitive score in the ordinal VABS-3; the appropriateness of adding the interval value of 20 to the outcome of death is unclear to us. Importantly, P-ICECAPS's proposed secondary endpoint metrics related to neurological outcome (Pediatric Cerebral Performance Category (PCPC) and Pediatric Resuscitation after Cardiac Arrest (PRCA)) and ICECAP's primary outcome measure (modified Rankin Scale (mRS)) all incorporate death as part of the unadjusted scales. You state that the added 20-point margin assigned to non-survivors will prevent "excessively reward[ing] a cooling duration, in the setting where this duration primarily improves survival only by transitioning patients from death to severe neurobehavioral impairment." Clinically, however, the difference with VABS-3 = 20, and death may very likely not truly reflect an "additional" neurobehavioral impairment equivalent to 20% of the age-corrected standardized mean (100). We acknowledge the example scenario (in which mortality and lower-score mortality diverge substantially) you provided in your statistical analysis plan that you believe justifies your proposed approach. However, you also state, "This example is extreme, as we do not expect recovery and mortality to diverge nearly this much." Accordingly, we are concerned that your trial design risks assigning undue statistical value to survival with poor neurological outcome as compared to death, and that this fact may jeopardize clinical interpretability of your trial. Therefore, please better clarify why you believe your modification to the VABS-3 metric (i.e., its conversion into a composite with survival) is justified for this trial in which you expect mortality to be 45-55%. In so doing, we recommend that you consider modifying your primary effectiveness measure to be the similar to the approach used in THAPCA-OH, for which favorable outcome was defined as 12-month survival with VABS-2 score ≥ 70 , as this approach would seem to better align clinical and statistical results in P-ICECAP.

2. You state that you will exclude individuals with pre-existing conditions that may confound the outcome determination. However, you do not delineate those specific conditions individually. For example, you

plan to use a 3-month Vineland Adaptive Behavioral Scale (VABS-3) to predict 12-month outcomes and cite Somlene et al (2019) to support this approach. Although this article is not overt in clarifying the factors that impact the ability for 3-month data to predict 12-month outcome, it is clear that pre-cardiac arrest neurological status is a confounder. However, you do not exclude individuals with pre-cardiac arrest neurodevelopmental disorders. In order to allow consistency in recruitment, and confidence in outcome analysis based on the 3-month outcome data, it is important to have as clear inclusion and exclusion criteria as possible. If there are specific conditions known to impact the outcome determination, these conditions should be specified and delineated in the exclusion criteria. Please consider making the appropriate revisions to the exclusion criteria.

3. Currently your informed consent form indicates that enrollment is expected to occur over 5 years. Your protocol ("Brief Synopsis") indicates that the study will continue over 7 years. Since follow-up is only out to 1 year, we are unsure as to why there is a 2-year gap between the duration of expected enrollment (5 years) and study completion (7 years). We recommend you clarify and make any necessary corrections to your documents (informed consent and/or protocol).

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.

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 <u>initial</u> 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.

<u>Statistical</u>

6. Multiple imputation is proposed as part of the missing data strategy. We recommend you provide additional mathematical details for the multiple imputation method, including the regression models and

predictor variables to be used. The predictor variables should be chosen either because they are correlated with the missing variable, the reason for missingness, or both.

7. According to the statistical analysis plan (SAP), you plan to use multiple imputation as well as longitudinal modeling to predict 12-month outcomes in the primary endpoint analysis. It is unclear whether or how these two methods will be used together in the analysis. We recommend you clarify this issue. In addition, please clarify whether multiple imputation will be used in the sensitivity analysis and/or the primary analysis.

8. In the dose-response model, different regions of the model appear to be connected into one long formula (page, "P-ICECAP Statistical Design D 5"), and the end of the formula is cutoff by the paper margin. We recommend you provide the mathematical formula of the U-shaped dose-response model in a clear format.

9. In Figure 1 (illustration of the U-Shaped Model), the cooling durations 6, 12, 18, 24, 36, 48, 60, 72, 84, and 96-hours are shown as d=1,…,10. Please note that as the durations are not equally spaced, it is not appropriate to use 1,…,10 to represent these time durations in the figure. We recommend you use the actual duration in plots of the dose response curves.

10. You provided prior distributions for parameters used in the dose-response curve. We recommend you provide additional rationale regarding the choice of the prior distributions such as the mean of the baseline response, width of the plateau, etc.

11. In the posterior distribution, Yi is defined as the final response for each subject. However, according to the longitudinal analysis, Yi is the imputed 12-month response based on 3-month data. We recommend you clarify whether Yi is the observed or imputed 12-month data. Additionally, the yi,3 in the posterior distribution is noted as the longitudinal modeling with 3 months while it appears to be the observed 3 months response in the longitudinal analysis section.

12. It appears that you plan to calculate the posterior probabilities that the mean response on dose d is greater than a dose of 6 hours. However, the mathematical formula presented in the SAP shows an unconditional probability. We recommend you provide a clear definition for probability that the mean response on each dose *d* is greater than the mean response with dose of 6 hours.

13. You plan to estimate two parameters of target dose. However, target dose is not clearly defined. We recommend you clarify whether the target dose is the maximum effective dose or the shortest duration of cooling that provides the maximum treatment effect (as defined in the study objective). In addition, the probability of being the maximum effective dose for different cooling durations share one common notation $Pr(Max)$. We recommend you use an appropriate notation with an index for different cooling durations. Please note that the notation for Pr(ED95) has the same issue.

14. During the response adaptive randomization, subjects will be randomized in block sizes of 10. It is unclear how this blocked randomization is used in the response adaptive randomization (RAR) design setting. We recommend you provide a detailed description of this block randomization process as well as the overall randomization algorithm.

15. The trial may stop accrual for expected success if $Pr(Max) > 0.95\ for\ d = 96\ hr$. However, according to the SAP, d varies from 1 to 10. We recommend you clarify.

16. A primary study objective is to determine, in pediatric comatose survivors of out-of-hospital cardiac arrest (OHCA), the shortest duration of cooling that provides the maximum treatment effect as determined by the primary endpoint. We recommend you clarify whether the target dose or maximum effective dose is consistent with this study objective.

17. In the simulation, the aim 2 is defined as "determination of the shortest duration that provides maximum treatment effect is clinically defined by selecting an ED95 that is within 1 or 2 durations of the true ED95". It appears that ED95 is considered the target dose in this context. Please confirm.

18. The operating characteristics are presented in Table 3. However, the meaning of the column heads are not clear. We recommend you provide a clear interpretation of the column heads for Table 3.

19. In the secondary outcome analysis, you mention that "continuous secondary outcomes (change in PCPC from baseline to 12 months and PRCA at 12 months) will be analyzed in a similar nature as the primary outcome", which implies Bayesian methodology. However, you further provided regression model and significance testing for these outcomes. We recommend you clarify the method that will be used for these endpoints.

20. We were unable to locate a clear study objective for the secondary outcome analysis. We recommend you clarify the statistical significance discussed in the secondary outcome analysis section.

Other

21. We recommend you provide FDA with the DSMB Charter and membership when available.

If you intend to propose changes to your study to address these Study Design Considerations you should submit an IDE supplement.

If you would like FDA's feedback on your plans for addressing any additional recommendations and considerations, please submit a Pre-Submission. Your submission should reference this IDE, identify the specific Study Design Considerations and/or Future Considerations you wish to discuss, and indicate your preferred feedback mechanism (i.e., email, meeting or teleconference). Additional information regarding Pre-Submissions is available in 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.

March 25, 2022

University of Michigan
William Meurer
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1500 E. Medical Center Drive
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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,
Structural and Vascular Devices
OHT2: Office of Cardiovascular Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health