October 19, 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/A003
Trade/Device Name: Pediatric Influence of Cooling duration on Efficacy in Cardiac Arrest Patients
Dated: September 15, 2022
Received: September 19, 2022
CMS Category: B
Annual Report Due: May 26, 2023

Dear William Meurer:

The Food and Drug Administration (FDA) has reviewed the amendment to your Investigational Device Exemption (IDE) supplement proposing to conduct a new pivotal study (P-ICECAP) for a significant risk device. You have not fully addressed the issues cited in our July 28, 2022 letter. While FDA identified some outstanding issues in your application, FDA has determined you have provided sufficient data to support continuation of your human clinical study; this means that there are no subject protection concerns that preclude continuation of the investigation. Your supplement therefore remains approved with conditions, and you may continue your investigation after you have obtained institutional review board (IRB) approval. Your investigation is limited to 40 US institutions and 50 US subjects.

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 concerns outlined in our March 25, 2022 conditional approval letter.

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.

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.

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:

1. In our Approval Condition 1, we stated, "It appears that you have not modified the draft Statistical Design Report to incorporate either the staged nature of enrollment or the firewalls, if any, needed to maintain the intended blinding in the setting of iterative interim reports." You responded, "[G]iven the low sample size for the initial safety analyses, and the lack of binding hypothesis tests, we lack clarity on what additional details the agency believes are needed in this document." Our request was for you to identify and reconcile any impact[s] that knowledge of the 50-patient safety cohort's interim results may have on the otherwise-blinded trial's statistical analysis plan that includes a 150-patient, 3-arm burn-in period. We are concerned that if knowledge of the interim results is not properly accounted for in the statistical analysis plan, it may significantly bias the trial conclusions and call into question whether there is reason to believe that risks outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained (21 CFR 812.30(b)(4)). If you believe the safety analysis will have no impact, please articulate your reasoning within the protocol and the Statistical Design and Power document, and provide FDA with both a red-lined and clean copy of these documents.

2. In Approval Condition 2 of our June 16, 2022 letter, we reiterated our opinion that the outcomes of this trial, as currently designed, would be unable to "imply" efficacy of hypothermic TTM ("hypothermia") as compared to normothermic TTM ("normothermia"). Accordingly, we requested that you revise the primary objective because "it is misleading and suggests that the trial may be unethical as it is not designed to meet its stated objectives." In our July 28, 2022, letter, we stated that because your chosen study design does not comprehensively address the objective of relative normothermic/hypothermic efficacy, language in the protocol and related documents (including the informed consent document) it was not appropriate to imply either that hypothermia is recognized to be superior to normothermia or that the trial will evaluate this possibility. In approval condition 2a of the letter, we presented 4 examples of language which continued to imply that P-ICECAP will be able to demonstrate clinical and/or statistical superiority of hypothermia as compared to normothermia. In response, you have now struck the language highlighting the current ambiguity on the effectiveness of normothermia as compared to therapeutic hypothermia. Although doing so removed "normothermia" from the text, this approach is problematic and inappropriately misleading. For example, p.20/73 of the tracked-change protocol (31 July 2022) now states that the P-ICECAP trial is strongly supported by recent International Liaison Committee on Resuscitation (ILCOR) consensus statements (Kleinman et al., 2018) and American Heart Association Pediatric Advanced Life Support Guidelines (de Caen et al., 2015; Duff et al., 2019) on the grounds that those

organizations identify duration of cooling as a research priority for further trials. However, the language that you deleted had also identified within the references a foundational need to determine whether therapeutic hypothermia is in fact superior to controlled normothermia. Indeed, your Risk Analysis points out (Maconochie, 2020) that "…there is inconclusive evidence to support or refute the use of TTM 32°C to 34°C compared with TTM 36°C to 37.5°C (or an alternative temperature) for children who achieve ROSC but remain comatose after OHCA or IHCA." Your removal of this fact is misleading. Please retain these and associated details regarding knowledge gaps in the use of targeted temperature management. We continue to recommend that P-ICECAP include a normothermia control arm; if it does not, we require that the protocol, statistical analysis plan, safety monitoring plan, oversight committee charters, and informed consent document all clearly and unambiguously articulate that P-ICECAP is not designed to address clinical or statistical questions relating to the choice of normothermia versus hypothermia in the treatment of pediatric cardiac arrest in order to ensure these documents do not include misleading information. Please address the specific examples below of sections within your protocol where misleading information remains and diligently review your protocol to ensure that there is **no** language that implies that your trial will answer the important question of whether therapeutic hypothermia is superior to normothermia – see also Study Design Consideration 1 below:

a. The section of your protocol cited above (p.20/73 of the tracked-change protocol) should be revised to be consistent with the following:

> "The International Liaison Committee on Resuscitation (ILCOR) consensus statements and American Heart Association Pediatric Advanced Life Support Guidelines (de Caen, 2015, Duff, 2019, Kleinman, 2018) have identified scientific knowledge gaps and clinical research priorities in pediatric resuscitation research. These priorities include the need for further studies to determine 1) whether therapeutic hypothermia is superior to controlled normothermia and 2) the duration of target temperature management for pediatric CA resuscitation research. P-ICECAP will not include a normothermia (control) arm and therefore will not address the first priority (superiority of therapeutic hypothermia to controlled normothermia). It may answer questions related to duration of target temperature management, and it may address a THAPCA-OH limitation by including children with milder encephalopathy post-OHCA."

b. Page 20/73 of the tracked-change protocol still contains the statement "If the optimal duration of therapeutic hypothermia to improve survival and neurobehavioral outcome in children can be identified, such findings would conclusively change clinical practice across the entire care spectrum of pre- hospital, emergency department, intensive care and rehabilitation for pediatric OHCA patients." This statement was identified as our second example in approval condition 2a where the language implies that hypothermia is superior to normothermia. Please remove or modify this statement. You may consider the following language:

> "If the optimal duration of therapeutic hypothermia to improve survival and neurobehavioral outcome in children can be identified, such findings may change clinical practice for pediatric OHCA patients with respect to therapeutic hypothermia duration, but it will not answer the related question of whether hypothermia should be used over normothermia."

c. The language used to respond to the 3rd and 4th examples identified in approval condition 2a requires additional revision. You have replaced “efficacy of cooling versus no cooling” in the third example and “that cooling is effective versus no cooling” in the fourth example with “a dose(duration) response effect.” These changes are acceptable. However, the sentence identified in the 3rd example (page 41 of the tracked protocol) now states “an increasing treatment effect across some set of durations **would** [emphasis added] imply a dose (duration) response effect,” and the sentence in the 4th example (page 42 of the tracked protocol) now states “an increasing treatment benefit in at least one part of the duration-response curve, then this **would** [emphasis added] demonstrate a dose (duration) response effect in improving neurological outcomes. Use of the term “would” is presumptive and as such, misleading. Please replace the term “would” with “may.”

Please make the necessary changes to your protocol and provide FDA with both the red-lined and clean version of your revised protocol.

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 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.

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.

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

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.

Please note that the above conditions 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.

CDRH would like to offer you a teleconference to occur within 10 business days from the date of this letter in order to provide clarification regarding the information provided in this letter. If you wish to schedule this teleconference, please propose three dates and times for the meeting using the contact information listed below.

Additionally, 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.

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,

Rachel E. Neubrander -S

Rachel Neubrander, PhD
Acting 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 (please note this list of Study Design Considerations (SDC) contains the same SDCs identified in the July 28, 2022 conditional approval letter with the following exceptions – 1) SDC 1 has been revised based on your response to SDC 1 provided in the July 28, 2022 letter, and 2) you were able to sufficiently address SDC 2 from the July 28, 2022 list of SDCs. Please consider addressing the following concerns:

Clinical/Protocol

1. In previous interactions, we stressed that a "zero hour" randomization arm was not synonymous with "normothermia." In Study Design Consideration 1 of our July 28, 2022 letter, we clarified that "we believe the issues involving 'normothermia' are not semantical, but rather they will be key to any eventual inferences of safety and effectiveness." You agreed and removed "normothermia" from various locations within P-ICECAP's IDE documents. From our review of the current Amendment, we note the following:

    a. In Section 2.1 (Rationale) of the revised protocol, you state:

        > There are a total of 10 possible treatment arms exploring 0 through 96 hours of cooling duration…The overarching goal of this project is to identify clinical strategies (duration of cooling) that will improve the neurobehavioral outcomes of children after OHCA.

    b. In Section 3.2 (Randomization and Allocation), you state:

        > Participants will be potentially randomized over the course of the trial to the following possible durations of cooling (in h): 0, 12, 18, 24, 36, 48, 60, 72, 84 and 96.

    c. In Section 4 (Selection and Enrollment of Participants), you state:

        > At all participating sites, the usual clinical practice during the course of P-ICECAP for comatose pediatric OHCA survivors will be TTM to targets of 33-37 °C on arrival in the PICU; any definitive servo-regulated surface temperature control device may be used.

    d. In Section 4.1 (Inclusion Criteria and Rationale), you state:

        > All participants will be randomized within 6 hours of ROSC and after the initiation of targeted temperature management. Enrollment is defined as the time of randomization.

    e. On p. 1/27 of your most recent "Statistical Design and Power" analysis plan (18 February 2022), you clarify the following:

The 6-hour duration has been replaced with a no-additional cooling arm. (Some patients will receive cooling prior to randomizations). Any residual references to a 6-hour arm refer to a no-additional cooling or 0-hour arm.

f. In Section 5.1 (Interventions, Administration, and Duration) of the revised protocol, you state:

Duration of cooling will be measured from the time that cooling is started as indicated by activation of a definitive cooling device (see 5.2 for definition) set to a target of 33°C (targets from 32- 34°C and maintained continuously prior to randomization also qualify as start of cooling.

Taken together, we believe that P-ICECAP's characterization of "0 hour" remains inappropriately inconsistent, confusing, and likely misleading. Furthermore, we are concerned that the substantial heterogeneity of subjects within the potentially key "0 hour" randomization arm as currently defined could be problematic and may jeopardize safety or effectiveness inferences. For example, it appears to us that the "0 hour" cohort could include subjects who have received:

- 120 hours of 36.8°C
- 6 hours of 33°C followed by 16 hours of rewarming and 98 hours of 36.8°C
- 1 hour of 32°C followed by 16 hours of rewarming and 103 hours of 36.8°C
- 2 hours of untargeted hypothermia followed by 4 hours of 34°C followed by 16 hours of rewarming and 100 hours of 36.8°C

Although pre-randomization temperature may confound all randomization arms, we believe the impact could be most pronounced on "0 hour" subjects, as all other subjects will be maintained at 33°C for at least 12 hours without temperature variability. Therefore, we strongly recommend that you revise the trial's documents throughout to more accurately characterize "0 hour" and to more consistently and clearly identify the limitations inherent to the "0 hour" randomization arm.

2. 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.

3. 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.

4. Although you are free to make the proposed protocol revisions as outlined in this Amendment, FDA is concerned that they 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, you may want to consider pre-specifying initial target-temperature subgroups and/or require enrollment caps for subjects not initially cooled to 34 degrees within 6 hours.

5. As stated in approval condition 7 of our July 28, 2022 letter, we identified a statement in the informed consent document that still suggested that subjects randomized to zero-hour cooling will have therapeutic hypothermia. Please carefully review all your trial-related documents and ensure that neither the protocol nor the ICD have any remaining language that implies that all subjects will be cooled.

Statistical

6. As you have amended the protocol (G210126/S002) to replace the 6-hour cooling arm with a no-additional cooling arm, we recommend you discuss whether the initially proposed dose-response curve for different cooling durations still applies.

7. 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.

8. 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.

9. 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.

10. 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.

11. 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.

12. In the posterior distribution, $YYYY$ is defined as the final response for each subject. However, according to the longitudinal analysis, $YYYY$ is the imputed 12-month response based on 3-month data. We recommend you clarify whether $YYYY$ is the observed or imputed 12-month data. Additionally, the $yyYY$,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.

13. It appears that you plan to calculate the posterior probabilities that the mean response on dose dd 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.

14. 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 $PPPP(MMMMMM)$. 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.

15. 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.

16. The trial may stop accrual for expected success if $PPPP(MMMMMM) > 0.95\ ffffPP\ dd = 96\ hPP$. However, according to the SAP, d varies from 1 to 10. We recommend you clarify.

17. 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.

18. 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.

19. 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.

20. 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.

21. 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.

You may propose changes to address these Study Design Considerations as part of your submission (IDE amendment) that responds to the approval with conditions deficiencies provided in this letter. If you intend to propose changes to your study to address these Study Design Considerations, in the absence of a response to deficiencies, 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.