June 16, 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/A001
Trade/Device Name: Pediatric Influence of Cooling duration on Efficacy in Cardiac Arrest Patients
Dated: May 16, 2022
Received: May 17, 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 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. You have also proposed to proceed with a staged approach for the P-ICECAP study. You have not fully addressed the issues cited in our March 25, 2022 letter, and in particular, you have not provided sufficient detail in your protocol to adequately describe the staged trial and the proposed interim safety analyses. Your supplement therefore remains approved with conditions, and you may implement that change in your study using a revised informed consent document which corrects deficiency numbers 4-12. 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.

**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:

**Clinical Protocol**

1. In our Conditional Approval letter dated March 25, 2022, we requested that a normothermia control arm be added to the study design, and in the absence of this requested control arm, your proposed study would be conditionally approved as a staged trial with enhanced FDA oversight of safety. This is necessary in order to ensure that P-ICECAP does not exceed the risk threshold allowable under 21 CFR 50 subpart D, specifically that the anticipated benefits of different durations of cooling than are generally used in clinical practice as proposed in P-ICECAP justify the risks (21 CFR 50.52). In addition, this is to ensure that there is no 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)). You have made the decision not to add a normothermia control arm and, although you state in one subsection of the protocol (i.e., "11.5 Subpart D determination") that you will conduct the requested interim analyses, you have made no revisions to the protocol to include these required interim analyses. Without these specific protocol revisions to identify that the required interim safety analyses will be conducted, and a specific description of the analyses to be performed and reviewed by the FDA and DSMB, we remain concerned that the protocol does not accurately reflect the proposed plan.

   In order to meet the requirements under 21 CFR 50, subpart D, please update your protocol (and informed consent document as necessary) to include the new staged aspect of the trial, the required interim analyses, and details regarding these interim analysis intended to address the outstanding safety concerns related to this study design. Please provide FDA with both a redlined and clean copy of the updated protocol and informed consent document(s).

2. The primary objective of your trial, specifically "*To determine whether increasing durations of cooling are associated with better outcomes or recovery, implying efficacy of hypothermia versus no cooling*," is unchanged from the original IDE submission. As we have discussed with you, we do not agree that the outcomes of this trial, as currently designed, will "imply" efficacy of hypothermic TTM compared to normothermic TTM. As such, the proposed trial design is not adequate to meet this objective. Please revise this objective as it is misleading and suggests that the trial may be unethical as it is not designed to meet its stated objectives. You may consider revising your primary objective to the following:

*"To determine whether increasing durations of cooling are associated with better outcomes or recovery."*

**Enrollment of Pregnant Subjects**

3. In response to approval condition #1 in our March 25, 2022 letter (related to sections 4.0 and 4.6 of the protocol), we acknowledge that you have added "known pregnancy" as an exclusion criterion and provided your rationale for exclusion of this patient population because there is insufficient data to evaluate risks and benefits in this patient population and the low number of estimated pregnant subjects will not result in data adequate to inform hypothermic TTM use in this population.

   However, the revisions to the protocol (subsection 4.6) state that a patient with a "*known, pre-existing*" pregnancy will be excluded. This subsection states the protocol does not define procedures for screening for pregnancy, noting that "*each PICU has a usual practice for this*." The protocol states that if a pregnancy becomes known after randomization, the clinical team will decide whether further cooling is "*reasonable*." This approach to excluding pregnant people from the trial is unacceptable. Please incorporate pregnancy screening into the screening procedures of your protocol for all subjects of childbearing potential (e.g., subjects who have entered puberty and/or are Tanner Stage ≥2), exclude all patients with a positive pregnancy test from the trial and add information about pregnancy testing to the Informed Consent Document (ICD).

**Informed Consent**

4. You have addressed Approval Condition #2 that identified that you did not describe that the intervention to which the child is randomized may not be the standard of care (SOC) at the treating Pediatric Intensive Care Unit (PICU) and may not be the intervention the attending physician would choose to treat the potential subject by revising the language in the "More Detailed Information" Section of the ICD. Please also include this information in the "Summary of Key Information" Section following the sentence that states "*If your child participates in this study, your child will be assigned to a length of cooling or fever prevention in the Pediatric Intensive Care Unit (PICU)*."

5. You have partially addressed Approval Condition #3 that identified the Informed Consent Document (ICD) does not discuss procedures for when the child temperature is normal or above normal and the procedures that may occur in these situations. The revised ICD describes the plans for cooling or rewarming based "*upon arrival*." The described temperature management changes should occur after parental permission is obtained and based on the temperature at "*randomization*" not "*upon arrival*." Please revise the description of the temperature management from "*upon arrival*" to "*at time of randomization*."

6. You have not adequately addressed Approval Condition #4 that identified deficiencies in the description of the additional information that would be collected from the parent about themselves and their family. We note that this deficiency is also relevant to SDC #6. The ICD states, "*Since some of the questions we ask are about you as the parent or your family, you will be participating in the research study as well*." The protocol states, "*we still consider these data to be participant information, and do not consider parents themselves to be participants in the trial.*" Please align the

information about parents as subjects in the protocol and ICD and provide additional information to support whether the data collection from parents will be exempt from informed consent or document how informed consent will be obtained. We remind you that unless your proposed data collection from the subject's parent will not be linked to the subject (i.e., no patient identifiers will be retained), the research is not likely to be determined exempt by an IRB under 45 CFR 46.104(d)(1-6).

7. You have not adequately addressed Approval Condition #5 that identified deficiencies in the description of risks and discomforts. The ICD must describe any foreseeable risks or discomforts to subjects in this trial as required under 21 CFR 50.25(a)(2). You have added additional information about risks, but you have also removed information about risks that are included in the protocol. We note the ICD identifies the risks of bleeding, infection, fever, cardiac arrhythmias, "*shifting of blood electrolyte and sugar levels*", discomfort or shivering and skin problems. The revised ICD does not describe all the risks included in the protocol (e.g., risks of seizures, neurological worsening, and repeat cardiac arrest) and does not identify that cardiac arrhythmias may require intervention, that bleeding disorders may require blood products, the types of infections (i.e., pneumonia, urinary tract infections and blood stream infections) to which subjects are at risk or the types of skin problems. The ICD does not describe the potential risks of fluctuating temperature management based on body temperature at randomization and the arm to which subjects are randomized, or that there are limited data about use of therapeutic hypothermia for longer durations. In addition, the language used may not be understandable by all LARs. This section of the ICD also states the trial "*may have*" risks.

   Please revise the ICD to include all the risks described in the protocol, the risks of longer durations of cooling and the risks of fluctuating temperature management. The statement that the study "*may have*" risks is inaccurate and should be corrected to identify that participation in this study "has" risks. Additionally, please ensure that the language used is understandable to the LAR (see Approval Condition #10).

8. In response to Approval Condition #9 (Section 4.4 of the protocol), we acknowledge your addition of the statement "*Written informed consent should be obtained from either the new guardian or the competent participant attaining legal adulthood*" to the "Change in Guardianship (4.4.2)" subsection. However, your description of this process remains confusing, especially the language retained in the third paragraph of this section that states that an LAR or participant may reaffirm enrollment by signing an "*additional consent form but are not required to do so*." Please clarify this informed consent process as requested in our March 25, 2022, letter. You may wish to consider the following or similar language:

   > *"If a change in guardianship occurs during the trial and/or a subject reaches the age of majority at any point during the trial, the new LAR and/or adult subject will be offered the opportunity to withdraw from the trial and the informed consent process will be repeated. The consent by the new LAR and/or "adult" subject will be obtained using the written informed consent form approved by the IRB and documented in accordance with 21 CFR 50.27(a)."*

General

9. The ICD uses the Celsius temperature scale in some sections and both the Celsius and Fahrenheit scale in other sections. Please describe the temperature management using both the Celsius and Fahrenheit scales to improve understanding.

10. As required under 21 CFR 50.20, the information in the ICD must be in language understandable to the subject or the LAR. The language used in the ICD, especially the risk section, is likely not understandable to most LARs. When you are revising your ICD, please ensure that the language in the ICD is understandable to the LAR. We recommend consent forms be written at an eighth grade or lower reading level based on recommendations made by the working group formed by the National Cancer Institute (NCI), along with the Office for Protection from Research Risks (now the Office of Human Research Protections, OHRP) and FDA in the 1998 "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" as described in the FDA Draft Informed Consent Information Sheet: https://www.fda.gov/media/88915/download

11. Please make the following changes to the "Key Information" section of the Informed Consent Document:

    a. This section states, "*The goal of this study is to find out if, and how, controlling childrens' [sic] temperatures by cooling their body in the days after cardiac arrest can help the brain recover*." This statement is confusing and inaccurate. Please revise this sentence to align with the objectives of the trial and improve readability. You may consider the following or similar language:

    *"The goal of this study is to find out if cooling children's bodies for longer durations than are used in clinical practice can help the brain recover after cardiac arrest."*

    b. This section states, "*Other than how long the temperature is controlled, children in the study get the same care for cardiac arrest as children not in the study*." This statement is not accurate because all subjects will have temperature control (i.e., TTM) for 5 days. Please revise this sentence to identify that except for how body temperature is managed, subjects will receive routine PICU SOC for out of hospital cardiac arrest (OHCA). You may consider the following or similar language:

    *"Except for body the management of body temperature, children in this study will get the same care for cardiac arrest as children not in the study."*

    c. This section includes the statement, "*this study will help us learn how to treat other children like yours in the future*." Please replace the word "*will*" with "*may*." The sentence should read: "*this study "may" help us learn…*".

    d. This section states, "*Participation may also have risks. Longer or shorter durations of cooling assigned in the study may be safer or less safe*." This trial has risks, so please replace the words "*may also*" with the word "*has*." In addition, to provide complete information, please

identify that cooling, especially prolonged cooling, may be less safe than normothermic TTM. You may wish to consider the following or similar language:

*"Participation in this study has risks. Longer or shorter durations of cooling assigned in the study may be safer or less safe, and cooling, especially prolonged cooling, may be less safe than keeping your child at a normal body temperature."*

12. Please make the following revisions to the "More Detailed Information" section of the Informed Consent Document:

    a. The "Why are we doing this study?" section states, "*we don't know for sure if this cooling helps or how long to cool*" and it may be that "*simply keeping the child at a normal temperature is best.*" You have not identified that there may be more risks associated with cooling, especially extended durations of cooling. In addition, your word choices may be misleading. Please remove the words "*for sure*" and "*simply*" and describe the potential for increased risks associated with cooling. You may wish to consider the following or similar language:

    *"We don't know if this cooling helps or how long we should cool to give the best chance of brain recovery. It may be that cooling is not better than keeping your child at a normal body temperature. Cooling, especially longer durations of cooling, may put your child at higher risks for medical problems, than keeping your child at a normal temperature"*

    b. The benefits section states, "*Being part of the study may help doctors learn whether to keep a child at a normal or colder temperature and how long to keep children at a colder temperature after out of hospital cardiac arrest in the future*" and "*Others may not benefit directly if a much different length of cooling turns out to be better*." 21 CFR 5025(a)(3) requires the ICD provide a description of any benefits that may reasonably be expected from the research. We do not agree that it is reasonable to expect this trial will identify whether normothermic TTM is superior to hypothermic TTM. Please edit the language in these sentences accordingly. You may wish to consider the following or similar modifications:

    *"Being part of the study may help doctors learn how long to keep children at a colder temperature after out of hospital cardiac arrest."*

    *"Others may not benefit directly if a much different length of cooling turns out to be better or if maintaining bodies at a normal temperature is better than cooling."*

    c. The "Voluntary Participation/Withdrawal" section identifies that a subject may withdraw from the trial at any time and that there will be no penalty or loss of benefits. However, the ICD does not identify that refusal to participate in the trial will not involve penalty of loss of benefits to which the subject is otherwise entitled as required under 21 CFR 50.25(a)(8). Please include language in the ICD that states refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled as required under 21 CFR 50.25(a)(8).

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.

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.

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, Ph.D.
Director
DHT2B: Division of Circulatory Support,
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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 March 25, 2022 conditional approval letter with the following exceptions – 1) you were able to sufficiently address original SDCs 7 and 8 (Assent Forms), and 2) 4 additional Clinical/Protocol SDCs were added (items 7-10 below) based on your May 16, 2022 response *[received at FDA May 17, 2022]*):

Clinical/Protocol

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 $\geq 70$ , 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. 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. Language in multiple areas of the protocol (and in the Informed Consent Documents [ICDs]) suggest that subjects randomized to zero-hour cooling will have received therapeutic hypothermia as SOC at the time of admission to the PICU. For example, per the Attachment 2 IRB protocol revisions, page 29, "Assent will only be possible after the cooling period;" page 30, "Slow rewarming to a temperature of 36.8°C will occur over approximately 16 hours for those participants assigned to cooling durations greater than zero;" and page 40, "in the absence of a normothermia control arm…" The language in the protocol (and the ICDs) does not consistently identify the scenario in which a subject who is admitted to a clinical site in which normothermic TTM is standard of care will be randomized to "zero-hour" cooling, and as such will not receive therapeutic hypothermia. Please review and revise both the protocol and ICDs accordingly (see also Approval Condition 7 above).

6. Unless your proposed data collection from the subject's parent will not be linked to the subject (i.e., no patient identifiers will be retained), the research is not likely to be determined exempt by an IRB under 45 CFR 46.104(d) 1-6). We also note that although FDA may not object to the IRB waiving informed consent for certain FDA-regulated minimal risk research as specified in 45 CFR 46.116(f)(3), P-ICECAP does not meet the requirements for this exception from informed consent. As such we

recommend describing all the data that will be collected in the ICDs and removing any reference to minimal risk research from the protocol.

7. The first paragraph in section 4.4 Consent Process, states the "LAR will be informed that the optimal duration of hypothermia has not yet been determined." This paragraph does not describe that the LAR will be informed that hypothermia has not been identified to be of greater benefit than normothermia. We recommend you include this information in this section of your protocol.

8. The modifications in the subsection 4.4.3 Assent for Minors, state that the trial does not require written documentation of the assent of the participating child. We defer to the Institutional Review Board (IRB), as the IRB is responsible for determining whether adequate provisions have been made for soliciting the assent of children and determining whether and how assent must be documented (21 CFR 50.55). Of note, this subsection is missing from the protocol's Table of Contents. We recommend you include this subsection in the protocol's Table of Contents.

9. You added a new subsection to the protocol, Subpart D determination (11.5) that states "Guideline concordant usual care of pediatric patients resuscitated from cardiac arrest already involves targeted temperature management inclusive of both the 33 degree and 36.5 degree target temperatures used in this trial." This statement is misleading, as it is possible that a "zero-cooling" arm will not be implemented. We recommend you specifically identify in this section that the trial's objective is to determine whether longer durations of cooling are associated with better outcomes and that your trial is not designed to identify whether hypothermic TTM is superior to normothermic TTM for management of OHCA.

   We note that this subsection does not provide a robust discussion of the risks and benefits of hypothermic TTM compared to normothermic TTM. You may wish to provide additional justification to support that the anticipated benefits of enrollment in your trial are justified by the risks of hypothermic TTM, including longer durations of hypothermic TTM, compared to normothermic TTM.

10. Study Design Consideration (SDC) #6 identified that language in multiple areas of the protocol (and ICD) suggest that subjects randomized to zero-hour cooling will have received therapeutic hypothermia as standard of care (SOC) at the time of randomization. You have adequately addressed this concern in the ICD (and resolved Approval Condition #7); however, this inaccurate language remains in multiple sections of the protocol including the "Study Enrollment Procedures" (i.e., the figure retains this language), "Change in guardianship," "Withdrawal from study," "Interventions, Administration, and Duration," "Adverse Event Recording," and Statistical Considerations. We recommend that you correct this language.

<u>Statistical</u>

11. 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.

12. 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.

13. 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.

14. 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.

15. 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.

16. 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.

17. 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.

18. 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.

19. 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 $PPPP(MMMMM)$. 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.

20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

25. 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.

26. 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

27. We recommend you provide FDA with the DSMB Charter and membership when available. We also recommend DSMB membership include a bioethicist and a pediatric intensivist.

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.