DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

April 29, 2016

University Of Michigan
William Meurer, MD, MS
Taubman Center B1-354 Spc 5303
1500 E. Medical Center Drive
Ann Arbor, Michigan 48109

Re: G160072
Trade/Device Name: Influence Of Cooling Duration On Efficacy In Cardiac Arrest Patients (ICECAP) Trial
Dated: April 1, 2016
Received: April 1, 2016
CMS Category: B4
Annual Report Due: One Year from the Date of This Letter

Dear Dr. Meurer:

The Food and Drug Administration (FDA) has reviewed your Investigational Device Exemption (IDE) application regarding your pivotal study (ICECAP) for a significant risk device. While FDA identified some outstanding issues in your application, FDA has determined you have provided sufficient data to support initiation of a human clinical study; this means that there are no subject protection concerns that preclude initiation of the investigation. Your application is therefore approved with conditions, and you may begin your investigation using a revised informed consent document which corrects deficiency number 3 after you have obtained institutional review board (IRB) approval. Your investigation is limited to 50 US institutions and 1800 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.

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 issue(s):

Clinical

1. To make sure that subjects will not be delayed in receiving essential medical intervention, please describe the measures that will be taken to facilitate rapid triage of eligible STEMI

patients to the catheterization lab for possible PCI, including how and when therapeutic hypothermia will be initiated in these patients to ensure that they will meet the target of a core body temperature of < 34˚C within 240 minutes of cardiac arrest and also the STEMI/PCI guideline (90 minutes).

2. The ICECAP Study primary (powered) outcome measure is neurological function at 90 days post cardiac arrest. On page II-31, Section 6.2 Primary Safety Outcome defines a primary safety endpoint as all-cause mortality at 90 days. However, this outcome does not appear to be a powered endpoint, and it is not clear how this information will be reported, e.g., it does not appear on the list of serious adverse events that will be monitored/reviewed by the DSMB, Section 3.3.1. Please discuss how this primary safety outcome will be captured, analyzed and reported (to the DSMB) in the context of the current study design to ensure that the DSMB can appropriately consider mortality data in their periodic reviews and in their recommendations to continue or suspend enrollment in the trial.

<u>Informed Consent</u>

3. Please address the following issues related to your informed consent document:

    a. Please revise the section "Why is this study being done?" to clarify that hypothermia will be used irrespective of participation, and that the "study intervention" is modified durations of hypothermia.

    b. Under the section titled "What is involved in the study?" you state that the patient must have had a witnessed cardiac arrest within the past 10 hours. Please explain how you came up with 10 hours if enrollment into the study is within 6 hours of the initiation of cooling (which presumably happens upon arrival into the emergency department).

    c. In the section "What is involved in the study?" (p. 3), please reconcile the statement "intent to continue life-sustaining treatments for at least 5 days" with the protocol's analogous but seemingly inconsistent references to "3 days" and "96 hours" (i.e., 4 days).

    d. In the Section titled "How long does participation in the study last?" you state, "You (representing the patient) or the medical team may decide to stop the intervention if there are serious side effects, if you or the medical team decide that treatment is not in the patient's best interest, or if the study leadership decides to stop the study." Note that principal investigator (PI) termination and patient/legally authorized representative (LAR) withdrawal are treated differently with respect to data collection and follow-up. For example:

        i. If the PI terminates subject participation, it is for safety reasons (potential safety reasons should be identified). Treatment is discontinued, but follow-up is still required and the data remains in the study.

        ii. If the patient or LAR withdraws the subject from the study, it can be for any reason. No further follow-up is required (unless the patient agrees to it), data from that point

forward is not included in the study (unless the patient/LAR agrees to follow-up), but data up to the point of withdrawal is kept in the study.

Please make the necessary changes to your informed consent form to make these study choices clear.

In your submission that responds to the deficiencies listed above, please identify your response as an amendment to G160072. 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 reporting on http://www.clinicaltrials.gov. Please see "Guidance for Sponsors, Investigators, and Institutional Review Boards Questions and Answers on Informed Consent Elements, 21 CFR 50.25(c)" at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM291085.pdf for further information on this regulation.

FDA will waive those requirements regarding submission and prior FDA approval of a supplemental application and receipt of certification of institutional review board (IRB) approval 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. As a reminder, you must 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.

Your application includes only minimally acceptable monitoring procedures. The FDA guidance, which presents acceptable approaches to monitoring clinical investigations, is located at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf. Your procedures may vary but must be sufficient to assure the protection of the rights, safety, and welfare of the subjects involved in the clinical investigation and the integrity of the resulting data.

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: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf.

FDA encourages sponsors to collect clinical trial data in accordance with the Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126396.pdf) 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(d)(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 sex- and race-specific 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 and minorities, 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 G160072, and must be submitted in duplicate 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: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm049859.htm. Additionally, information which you should provide to participating investigators, titled, "Investigators' Responsibilities for a Significant Risk Device Investigation," is available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm049864.htm.

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 signed cover letter and the complete original paper submission. This authorization applies to the original, amendments, supplements, and reports, as applicable, for your submission type.

For more information about FDA's new eCopy program, including the new technical standards for an eCopy, refer to the guidance document, "eCopy Program for Medical Device Submissions" at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf. In addition, we strongly encourage you to visit FDA's eSubmitter

website at http://www.fda.gov/ForIndustry/FDAeSubmitter/ucm221506.htm in order to develop an eCopy in accordance with the new 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 the Submission Issue Q-Sub with valid eCopy to the address listed above. 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: The Pre-Submission Program and Meetings with FDA Staff at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf. 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 yours,

for Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
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 for your consideration:

Clinical

1. There were several monitoring entities that were mentioned within your protocol, but no specific information was provided regarding their role(s), membership, or Charter. We recommend that you address the following in order to provide clarification regarding your planned monitoring procedures:

    a. The role of the Medical Safety Monitors is unclear to FDA based on our review, including whether they will be tasked with the same role as a Clinical Events Committee (CEC), i.e., to adjudicate endpoints and adverse events. We suggest that you identify the group that will be adjudicating the endpoints and adverse events, and provide the membership of this group and the Charter when available.

    b. There were several monitoring entities mentioned (e.g., internal medical monitor, site monitors, study monitor from the clinical coordinating center, etc.); however, their identification and specific roles are not clear. We recommend that you identify all study monitors, their names, titles and affiliation, as well as their specific role(s) in the study, in addition to providing a detailed study monitoring plan.

2. You state (page II-10 of the protocol) that, "As part of routine medical care, cooling may be initiated by EMS…" In light of the new AHA recommendations for pre-hospital cooling with cold saline (Class III, No Benefit, LOE A), we recommend that you address the following:

    a. We suggest that you provide a discussion with scientific justification (literature, etc.) for including patients who received pre-hospital cooling in terms of the benefit presented to the subject.

    b. We suggest that you identify the number (or percentage) of sites that will be using pre-hospital cooling and the method(s) used.

    c. We suggest that you discuss whether inclusion of patients with pre-hospital cooling may confound your results.

3. You have identified two primary objectives (p. II-6), to determine:

   a. (Objective A) the shortest duration of cooling that provides the maximum treatment effect; and

   b. (Objective B) whether the duration-response implies efficacy versus no cooling.

   You have provided a statistical analysis plan for Objective A. Regarding Objective B, however, we find no specific analysis plan. Rather, you state (pp. II-10-11 and pp. II-47-48):

   > "Establishing a positive duration response implies confirmation that cooling is effective in improving outcome or recovery versus normothermia, when a normothermia control arm is not clinically acceptable…At each interim analysis, the trial may stop for futility if no cooling duration greater than 6 hours is found to be more effective than the 6-hour duration…a rhythm type will stop for futility if
   >
   > 1. At least 300 patients have been randomized to the 6-hour duration arm;
   >
   > 2. There is at least a 50% probability that the 6- hour duration is the target duration."

   Although we acknowledge your concern that prior research and lack of equipoise may render a normothermia control arm "not clinically acceptable," we do not believe your study design is sufficient to test the hypothesis underlying Primary Objective B. Specifically, we disagree with your *a priori* conclusion that the mere absence of treatment effect differences renders 6 hours of hypothermia a surrogate for normothermia. In this regard, we point you to your discussion (pp. II-18-19) of the ambiguity surrounding the results of the randomized, controlled Targeted Temperature Management (TTM) trial ("To many…interpreted as lack of overall benefit from cooling beyond using advanced temperature control devices to prevent hyperthermia…To many others…interpreted as showing that two doses of hypothermia are equally effective.") Accordingly, if you wish to maintain Primary Objective B, we request that you formulate an appropriately delineated and justified hypothesis and analysis plan. We suggest that you reconsider your interim analysis and randomization plans such that the currently proposed futility stopping rule be modified to instead allow for the opening of an additional normothermia control arm.

4. We recommend that you explicitly define the "treatment effect" which is to be evaluated within the Primary Analysis (Section 9.2) and to which you refer throughout the submission. We assume that "treatment effect" refers to survival with optimized neurological function. If so, it appears to us that your proposed metric of neurological function, a weighted modified Rankin Scale (mRS) score at 90 days post-arrest, equates the neurological and clinical significances of death (mRS 6) and strokes with mRS 4 and 5. We suggest that you justify your choice of weighting, and please clarify if your weighted mRS has been validated. Although we do not necessarily disagree with the rationale for a weighted mRS in your study, we believe it should be a secondary analysis, with a conventional mRS as the primary endpoint's metric. We also believe the addition of weighted "step-offs" between adjacent mRS scoring risks adding confounding bias to individual assessors' scoring, irrespective of planned assessor blinding.

5. You state that all analyses and stopping rules will be applied separately to two distinct rhythm type populations (shockable rhythm and pulseless electrical activity (PEA)/asystole). Essentially you are proposing two independent trials. In your discussion of trial power (Section 9.7, p. II-49), you assume identical treatment effects (16%) for both rhythm type populations and equal numbers of enrolled patients with each rhythm type ("1800 patients, assuming 50% are in each rhythm type"). We acknowledge your sample size simulations, but suggest that you clarify what steps, if any, you plan to take to assure such timely and balanced enrollment. Although we appreciate the known differences in outcomes with the two rhythm type populations, we do not fully understand your decision not to initially pool the rhythm type populations for analysis and then perform pre-specified sub-group analyses based upon rhythm type. We recommend that you justify your reasons for not adopting this approach, especially given your belief that the treatment effects will be the same in both populations.

6. With regard to temperature monitoring and the maintenance of the target core temperature (33˚ ± 1˚C), you indicate (p. II-157) that "Core temperature should be continuously measured at two sites. Esophageal, bladder, and blood (e.g., pulmonary artery catheter) are acceptable sites." We are concerned about the implications for effectiveness inferences given the varying accuracy and precision of the numerous temperature measurement strategies and cooling devices (5 device types) involved in the trial. Importantly, we believe the devices have different risk profiles (e.g., endovascular vs topical cooling) and may also have differences in effectiveness in achieving and maintaining designated temperature control. We suggest clarifying if you intend to test for interaction effects based upon device type. If not, please justify the poolability of the data from the different devices that will be used in the study.

7. Please consider pre-specifying sub-group analyses for key variables that may confound the results (e.g., cardiac interventions during hospitalization, arrest etiology, use of other adjunctive CPR devices in the field).

8. You state (Section 6.2, p. II-31) that "the primary safety outcome is all cause mortality at 90 days." Please consider pre-specifying a hypothesis-tested primary safety endpoint. For example, you may wish to consider a comparison to a justified performance goal of survival to hospital discharge with good neurological outcome (e.g., mRS < 4).

9. We acknowledge your efforts to prevent early withdrawal of enrolled subjects on the basis of anticipated neurological outcome (i.e., the "principle [of] no withdrawal for poor neurological prognosis is allowed within 3 days" (p. II-23)), and we agree that patient withdrawal could markedly affect interpretability of the primary endpoint. You have pre-specified an imputation model to account for missing data from withdrawn patients (Section 9.9). Nonetheless, we remain concerned that patient withdrawals will occur as a function of neurological status. Therefore, we recommend that you pre-specify appropriate sensitivity analyses for the primary endpoint and maintain a detailed log of all subject withdrawals. We also recommend that you pre-specify secondary analyses based upon as-treated and per-protocol analysis populations.

10. You plan to enroll up to 1800 patients at up to 50 sites over 4 years, with a target enrollment rate of 38 patients per month. Given locale-dependent variations in survival after out-of-hospital cardiac arrest (OHCA), we suggest you pre-specify a by-site

analysis, including an appropriate site poolability analysis.

11. Currently, subjects who are not cooled to < 34˚C within 4 hours of initiation of cooling are not enrolled into the study. However, this may be valuable information related to cooling methods and/or patients that may or may not be able to be cooled. As such, please consider capturing and analyzing these data as well.

12. Currently your Schedule of Assessments contains a "?" for the 6-month/180-day mRS score, as well as the 30-day and 180-day patient reported outcomes. We suggest clarifying why you currently have question marks at these assessment time points.

13. You have suggested that up to 50 sites may participate in this study. We suggest clarifying whether all of these sites are anticipated to be US sites, or whether any of the sites are expected to reside OUS.

14. You reference a Manual of Procedures (MoP) in several locations within your application. However, we could not locate the MoP in the submission. We recommend providing FDA with the MoP.

15. We note that you will include a DSMB for this trial. We recommend describing the membership of the DSMB and provide a copy of the Charter when it is available.

16. We note that you will include a Study and Data Management Center for this trial. We recommend providing FDA with information regarding the membership of the Study and Data Management Center.

Statistical

17. The current adaptive randomization utilizes treatment response observations at each interim analysis. Given the assumed 38 subjects per month accrual rate, covariate imbalance is likely to occur during such a randomization strategy. Such imbalance may be more pronounced at interim analysis per type if one rhythm type has a relatively low prevalence. This may affect the comparability across the treatment duration groups especially if other clinical and/or nonclinical variables are known to affect the treatment response. For example, your current study design assumes that hypothermic temperature duration is the only variable (or the variable with the greatest impact) affecting neurological outcome in survivors of cardiac arrest. Other parameters that may have an impact on the chain-of-survival, but do not appear to be captured in any analysis include: 1) the time from cardiac arrest to the initiation of CPR; 2) time from initiation of CPR to ROSC; 3) time from ROSC to initiation of cooling; and 4) the time from initiation of cooling to achievement of the target temperature (33ºC). In the event that an optimal duration is established, it would also be of great clinical interest to obtain data on the relative importance of these parameters (from cardiac arrest to target core body temperature, etc.). We recommend that you discuss whether there are any other important clinical and/or nonclinical variables that may also affect the neurological outcome for the survivor of an out-of-hospital cardiac arrest, and if so, please consider capturing and analyzing this data as well.

18. The protocol does not contain the mathematical formula for the posterior probability that the treatment arm h is the target duration for type r. We recommend that you clarify how this quantity is calculated. If explicit mathematical formulation is not possible, please consider providing the algorithm or section of the relevant program code used to calculate this posterior probability.

19. We recommend that you clarify whether the W_i is the observed value for $W(M_{90})$. If yes, then W_i takes one of the 5 discrete values. The statistical analysis assumes that W_i follows a normal distribution, which is not commonly used for discrete values. We recommend that you discuss why such a distribution is chosen for the observed weight for a patient.

20. On page II-82 (ICECAP study design simulation report), two distributions for μ are presented as well as the distribution of τ^2. We recommend that you clarify these parameters.

21. According to section 4.6, the transition matrix assumes an informative prior for all treatment arms and both rhythm types. Since there are potentially 10 treatment arms, 2 rhythm types, and 7 mRS states, it is not obvious what impact an informative prior will have on the final study result. We recommend that you clarify what impact an informative prior will have on the final study result and whether this informative prior is used in the interim analysis only or the final analysis (or both).

22. You indicate "it is sufficient to calculate only the posterior probability that a treatment arm is superior to the 6-hour duration arm" for the statistical analysis. According to the protocol, the 6-hour arm will open for rhythm type r if there are at least 300 subjects enrolled across all arms in that rhythm type and there is at least a 0.33 probability that 6 hours is the target duration for that rhythm type. We recommend that you discuss whether it is possible that the 6-hour arm does not open throughout the trial and how the posterior probability can be calculated if the 6-hour arm is never opened throughout the study.

23. According to the protocol, the posterior probability that a treatment arm is superior to the 6-hour duration arm is calculated using both independent priors and using the hierarchical priors. We note that distribution assumptions for several parameters have been removed in the current IDE assumption. We recommend that you discuss whether the posterior probability is still calculated using both independent priors and using the hierarchical priors as indicated in the current protocol. If yes, please consider providing the hierarchical priors and explain why two sets of priors are used and which prior is the final analysis.

24. You provide a longitudinal model that imputes the missing 90-day mRS based on the 30-day mRS score. We recommend that you specify a plan for patients whose 30-day mRS values are not available.

25. The process of simulating virtual subjects is not clearly described in the protocol. We recommend that you provide a detailed list of all input parameters required to simulate virtual subjects. In addition, there is one probability matrix in the simulation virtual subject section. We suggest that you clarify whether that is the only transition matrix used in all simulations or whether it is an example of one specific scenario.

26. The current simulation for the type I error rate control shows the probability of identifying one positive trend when both rhythm types have flat duration response curves. Because the two rhythm types are to be studied separately, we believe that the type I error should include the following situations:

    a. The probability of identifying a positive trend in at least one rhythm type when in fact both duration response curves should be flat; and

    b. The probability of identifying a positive trend in one rhythm type when in truth its duration response curve is flat while the duration response curve for the other rhythm type has a positive trend.

    The current simulation does not provide the probability of identifying **at least** one positive trend when in truth both duration response curves are flat. Given that most of the probability of identifying one positive trend is greater than 0.03, the probability of identifying **at least** one positive trend could be greater than 0.05. In addition, this simulation does not provide the probability of identifying a positive trend in one rhythm type when in truth the duration response curve is flat for this rhythm type but the duration response curve has a positive trend for the other rhythm type.

    Overall, the current simulation has not demonstrated adequate type I error control. We recommend that you provide a type I error simulation that takes into consideration the above two situations.

    The use of post-trial simulation type I error rate is not well understood in a regulatory setting. This post-trial simulation type I error rate will be reviewed to provide additional support for the ICECAP trial.

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.

Future Considerations

You should also give serious consideration to the following, which FDA considers important for the support of a future submission:

1. Your trial will allow for treatment (i.e., body cooling) to be effected by multiple devices that utilize disparate temperature management techniques, each with a different safety and effectiveness profile. Please understand that in the absence of pre-specifying appropriate sub-group analyses that account for the use of multiple cooling technologies, FDA believes it is highly unlikely that the trial's dataset would ultimately support labeling changes for any or all of the devices involved. Therefore, FDA recommends that if these data will be used to

support labeling changes to individual devices, that pre-specified sub-group analyses (by device type used) be incorporated into your statistical plan.

The Future Considerations listed above are intended to assist in your plans for a future marketing application only. No response is necessary under this IDE, unless you wish to modify your device or study to address these concerns, in which case approval of an IDE supplement may be needed.

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: The Pre-Submission Program and Meetings with FDA Staff at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf.