BACKGROUND

Medical device manufacturers are increasingly using predictive computer models during the product development process. These models are created for a specific context of use in order to simulate the device and relevant anatomy and physiology associated with predicting safety and efficacy outcomes. Since these models are created to predict the same endpoints that would be observed in clinical practice with the same population variability, we use the term virtual patients to refer to these simulations. These virtual patients can be incorporated into a study in way that is analogous to how some Bayesian clinical trials incorporate historical data as prior information.

The Medical Device Innovation Consortium (MDIC) working group on Clinical Trials Informed by Bench and Simulation (the working group) is proposing a mock IDE submission as a means to demonstrate the statistical considerations and choices associated with using this framework for a clinical trial designed with virtual patients. It is expected that this mock submission will provide a mutually beneficial way for the medical device and regulatory community to identify the issues that should be addressed when designing this type of trial.

A one hour, face-to-face Q-sub informational meeting is requested to cover the following topics, discussed briefly below:

1. Virtual patient model
2. Clinical statistical framework
3. Mock submission process

As noted below, we expect to cover the virtual patient model and clinical statistical framework in more detail via additional future pre-sub communication. The purpose of this meeting is to establish general familiarity with the approach and plan of the working group.

VIRTUAL PATIENT MODEL

To properly inform clinical evaluation, the predictive model must:

1. Simulate the clinical outcome of interest
2. Represent patient-to-patient variability
3. Use confidence intervals in the model output to represent uncertainty due to input sample size, model bias, gage R&R, etc.

The construction of a virtual patient model will be different for each particular outcome, and may involve a variety of disciplines. Potential examples include MRI heating, Nitinol valve frame or stent fracture, orthopedic implant fracture, or cardiac lead failure.

The inputs for the model can come from a variety of sources including animal and human studies, finite element analysis, and bench testing. Regardless of the origin, each data set needs to be considered statistically in order to represent variability seen across devices and patients. Additionally, the model output needs to reflect a clinically measureable factor (e.g. pacing threshold, lead fracture) as opposed to a traditional engineering metric such as temperature, stress or strain.

Applications that lend themselves to Virtual Patient models will involve local mechanisms that are well understood, for example fatigue fracture. Accordingly, the working group has identified fatigue fracture in a hypothetical new ICD lead (Model 2014VP) as a vehicle to facilitate the specific example necessary for this submission. The Model 2014VP has design changes that are expected to improve the handling characteristics of the lead, but could also affect fatigue performance.

Fatigue performance in the Model 2014VP lead will be modeled by incorporating bench fatigue strength with predicate lead *in-vivo* use conditions, similar to [1,2]. For demonstration purposes, we consider the case of fatigue fracture inside the heart, where cycle accumulation is solely due to heart motion. An actual implementation of this approach would consider all failure modes that could contribute to clinical performance.

CLINICAL STATISTICAL FRAMEWORK

The virtual patients will be implemented as prior knowledge in a Bayesian clinical trial. The statistical framework leverages FDA guidance for the use of Bayesian statistics in medical device clinical trials [3]. This approach can have benefits of decreased sample size and trial length while minimizing impact to study endpoints, type I error, and type II error.

There are two elements that may be novel to the statistician implementing or reviewing this method, discussed briefly below.

1. Many cohorts of virtual patient outcomes will be incorporated via a modified version of the power prior method. Cohort differences represent model uncertainty.
2. The number of virtual patients will be controlled by a loss function, which bases the number of virtual patients on the agreement between real and simulated data.

To explain this framework, a publication is being written by some of the working group members [4]. A brief overview of the two potentially novel concepts is given below and will be discussed in the informational meeting.

Incorporation of each cohort of virtual patient data is based on the method of power priors [5]. In this method, a discount value between 0 and 1 is applied to prior data, where 0 indicates no borrowed information and 1 indicates full borrowing. Unlike historical data, there is not a finite limitation on the number of virtual patients that can be simulated. Therefore, in order to better express variability, it is desirable to simulate a large number. However, the number of virtual patients incorporated into the study is subject to constraints driven by desired power and type I error. The modification developed by the working group converts the potentially large number of virtual patients to an effective number for incorporating into the study data. Integration across the multiple virtual patient cohorts accounts for engineering model uncertainty.

A loss function controls the number of virtual patients incorporated into the study data. This approach utilizes a function that scales the virtual patient number based on the agreement with the study data. In the approach developed by the working group, a Weibull cumulative distribution function is constructed that uses a Bayesian p-value as an input. When the clinical and virtual data are highly similar, the p-value approaches 1 and the full amount of virtual patients can be incorporated. Likewise when the clinical data diverges from the virtual data, the p-value approaches zero and the number of virtual patients also approaches zero. The Weibull parameters control the relationship between p-value and fraction of virtual patients allowed.

The loss function parameters and the maximum number of virtual patients allowed in the study are items to be agreed upon prior to starting the study.

There are two ways in which this method is suitable for a Bayesian adaptive design with interim looks. First is the traditional case where we adapt the trial based on the clinical endpoint response variable. Second, we adapt the trial based on input data used in the engineering model, collected from the (real) enrolled patients. Both cases can be used for sample size re-estimation or stopping the trial early for success or futility.

MOCK SUBMISSION PROCESS

A mock submission is proposed as a means to demonstrate the engineering and statistical considerations associated with using this framework for a clinical trial that incorporates virtual patients. It is expected that this mock submission will provide a mutually beneficial way for the medical device and regulatory community to identify the issues that should be addressed when designing this type of trial.

The idea for using a mock submission as a means to clarify the criteria and studies needed for a new method came from two prior mock submissions facilitated by the NCI-FDA Interagency Oncology Task Force subcommittee and members of the Clinical Proteomic Technology Assessment for Cancer Program on Protein Based Multiplex Assays. In these prior mock submissions there were two teams of participants, the ‘sponsor’ team and the ‘review’ team. The sponsor team prepared a submission and the review team reviewed the submission. This effort resulted in (1)

a publication describing the activity, what was learned, and some perspectives, (2) a Mock 510(k) filing, (3) a Mock pre-IDE Review Memorandum. This prior mock submission content is available at: http://www.clinchem.org/content/56/2/165/suppl/DC1

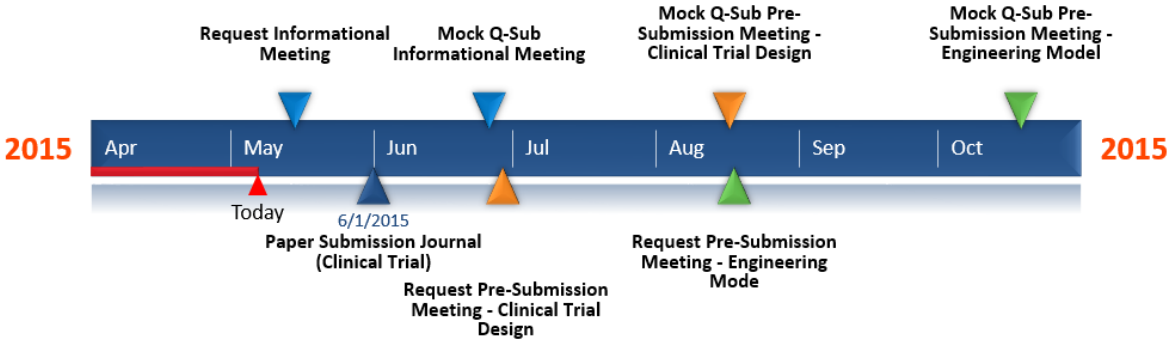
The MDIC working group plans to follow a very similar process for their mock submission. Specifically, the working group wishes to have two teams of participants, the 'sponsor' team and the 'review' team. The sponsor team will prepare the submission and the review team will review the submission. As much of the communication between the teams as is practical will be conducted as if this were a real submission, i.e. using the Q-sub process along with a modest amount of e-mail and telephone conversation, all of which will be documented.

The work of these teams will be published. At present it is expected that the following items will be the published content: (1) a journal publication with an overview of the process, learning and perspectives from the activity, (2) the mock IDE submission, (3) the mock pre-IDE document and review memorandum, (4) the slides and handouts from the informational meeting. Additionally, at the conclusion of these activities, the MDIC plans to hold a workshop to discuss the work.

It is expected that there will be three meetings, one information meeting and two pre-IDE meetings. The topic of the pre-IDE meetings will be the clinical trial design and the virtual patient model. This will result in two Mock pre-IDE Review Memorandums, one for each pre-IDE meeting.

It is expected that once the 'sponsor' team requests the informational meeting that the FDA will identify the 'review' team. The current 'sponsor' team members come from FDA, MDIC, and several device companies, listed at the end of this memo.

Below is a proposed target timeline:



Please note, this memo is intended to represent our current intent and understanding. We welcome suggested improvements to our proposal.

MOCK SUBMISSION WORKING GROUP PARTICIPANTS

The participants of the MDIC mock submission working group are a mix of engineers, regulatory affairs, and statisticians listed below, alphabetically by company.

Marc Horner, ANSYS
Valentin Parvu, BD
Laura Thompson, FDA
Rajesh Nair, FDA
Telba Irony, FDA

Tina Morrison, FDA
Dawn Bardot, MDIC
Adam Himes, Medtronic
Mike Johnson, Medtronic
Tarek Haddad, Medtronic
Lydia Telep, St. Jude Medical
Russ Klehn, St. Jude Medical

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[1] T. Haddad, A. Himes and M. Campbell, "Fracture prediction of cardiac lead medical devices using Bayesian networks," Reliability Engineering and System Safety, vol. 123, pp. 145-157, 2014.

[2] AAMI_PC_WG1_N169_E, Outline of Requirements for Fatigue Performance of Cardiac Rhythm Management Leads, draft standard under development by committee, available on request

[3] FDA, "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials," 5 February 2010. [Online]. Available: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071121.pdf. [Accessed 21 May 2015].

[4] T. Haddad, A. Himes, L. Thompson, T. Irony, R. Nair, " Incorporation of stochastic engineering models as prior information in Bayesian medical device trials and post-market surveillance", draft manuscript, available on request.

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