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PUBLIC HEALTH SERVICE
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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
Office of Biostatistics and Epidemiology
Division of Biostatistics (HFM-219)

Memorandum

Docket #:	2006D-0191
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Title:	**Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials**
From:	Chinying Wang, Ph. D. (HFM-219) C. J. Wang 8/16/2006
To:	Division of Docket Management (HFA-305) Food and Drug Administration, 5630 Fishers Lane, Rockville, MD 20852

The draft guidance entitled "Guidance for the use of Bayesian Statistics in Medical Device Clinical Trials" provides FDA's recommendations on the use of Bayesian statistical methods in the design and analysis of medical device clinical trials.

Comments

1. The review of this draft guidance raises concerns on the misleading statements. The following are the examples:

> *When good prior information on clinical use of a device exists, the Bayesian approach may enable FDA to reach the same decision on a device with a smaller sized or shorter-duration pivotal trial.*
>
> *The Bayesian approach may also be useful in the absence of informative prior information. Bayesian approach can be useful in complex modeling where a frequentist analysis is difficult to implement or does not exist.*
>
> *Since sample size are typically small for device trials, good prior information can have greater impact on the analysis of the trial and thus on the FDA decision process.*
>
> *The Bayesian approach can sometime be used to obtain an exact analysis when the corresponding frequentist analysis only approximate or is too difficult to implement.*

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Planning the design, conduct, and analysis of any trial are always important form a regulatory perspective, but they are crucial for the Bayesian approach. For formal agreement meeting may be appropriate when using a Bayesian approach.

As more data are obtained, more updating can be performed. Consequently, the posterior distribution that has been obtained today may serve as a prior distribution later, when more data are gathered.

If absolutely nothing is know about that quantity, something called a non-informative prior distribution may be specified.

Exchangeability may depend on the statistical model use. The concept of a representative sample can be expressed in terms of exchangeability. (Actually, Exchangeability is expressed as the distribution of any set of interested outcome is unaffected by all permutations of the individual variables.)

2. For the statement of "*The Bayesian approach, when correctly employed, may be less burdensome than a frequentist approach*", two examples of use of Bayesian method in device trial (TRAMSCAN and INTERFIX) are included in the document. However, as stated in the document, no prior information was used in the study of INTERFIX. It is not clear how Bayesian approach was applied without prior information for the device clinical trial. Subsquently, questions for the appropriateness of less burdensome in the review using Bayesian method for the example are raised.

3. Most of Bayesian analysis is model-base approach. The review for the approval of device seems based on the results of simulations. The validity of results also relies on the appropriateness of model incorporated in the simulations. Therefore, validation of model is one of key factor for the acceptance of clinical trial results. The guidance should take model validation into account for the review process.

4. The sample size determination is a curtail factor for conducting clinical trial to obtain sufficient results to reflect the product's efficacy and safety. This concept should remain the same for all clinical trials either using traditional frequentist analysis or using Bayesian analysis. However, in the guidance, it states: "*When sizing a Bayesian trial, FDA recommends you decide in advance on the minimum sample size according to safety and effectiveness because safety endpoint may lead to a larger sample size. When hierarchical models are used, we recommend you provide a minimum sample size for determining the amount of information that will be "borrowed" form other studies. We recommend the maximum sample size be defined according to economical, ethical and regulatory considerations.*" The confusing statements regarding to the sample size for Bayesian analysis in this guidance raise serious concerns.

5. Likelihood function is a form of data and is used to formulate the posterior distribution in Bayesian analysis. The statement of "*A trial can be altered in many ways without changing the likelihood function*" raises questions. It is known that when trial is

altered the data collected should be changed. Consequently, it would change the likelihood function. It is not clear what the statement above implies. In addition, the guidance reveals that the device approval is based on the simulation method using Bayesian MCMC method to update the results. However, there is no clear statement to address how the real data collected from the clinical trial would be used into the formulation of Bayesian probability structure.

6. Missing data has a great impact on the results and should be take great effort to avoid. For CBER's regulatory, the worst-case sensitivity analysis for missing data is the standard requirement for approval. However, in this CDRH guidance, it suggests that "*you may use predictive probabilities to predict (or impute) missing data and trial results can be adjusted accordingly.*" The scientific base for the approval process should not be different to ensure the quality of results when the Bayesian analysis is applied in the clinical trials.

7. The main reasons for conducting interim analyses are ethical and economic considerations. In clinical trials, a concern of stopping trial early to ensure that individuals are not exposed to unsafe, inferior or ineffective treatment or device would motivate to design a clinical trial with sequential analysis even that the penalty of early looks for in the statistical analysis must be paid. On the other hand, for economic reason, the benefit of a design with sequential tests on the interim analysis is to reduce sample size for the situation that the treatment effect is highly expected. The clinical trial would stop early because the superiority test of treatment is achieved at an early look. However, the rationale for interim analysis for device approval is not clear stated in the guidance. There is lack of justification of using Bayesian method for interim analysis in the document.

8. The interim analysis should be carefully planned and described to incorporate assumptions, hypotheses, expected sample size, and stopping rules in the protocol. It also includes the role of independent data and safety monitoring board (DSMB) described clearly in the protocol. It is believed that the clinical trial using Bayesian analysis for the approval of medical devices should also follow the concerns stated in the following FDA Guideline ICH E9. It states: *"The execution of an interim analysis should be a completely confidential process because unblinded data and results are potentially involved. All staff involved in the conduct of the trial should remain blind to the results of such analyses, because of the possibility that their attitudes to the trial will be modified and cause changes in the characteristics of patients to be recruited or biases in treatment comparisons. This principle may be applied to all investigator staff and to staff employed by the sponsor except for those who are directly involved in the execution of the interim analysis. Investigators should be informed only about the decision to continue or to discontinue the trial, or to implement modifications to trial procedures."*

9. It should be stated with caution in the guidance regarding to use predictive distribution for the decision to stop trails by predicting the clinical outcome, or by predicting a clinical outcome from a validated surrogate. It also raises concern to use predictive distribution for adjusting trial results due to missing data.

10. For informative priors, it states that "*To avoid bias, we recommend you avoid using studies that are not representative (e. g., if non-favorable systematically excluded).*" Why the non-favorable study can not be used for the consideration of prior information. In the CDRH recommendation, the approval process put a havey weight on the prior selected from the favorable study for proved product. Consequently, using the favorable prior, it would lead favorably for the approval of new product.

11. As stated in the guidance, outcomes for devices can vary substantially by site due to such differences as physician training, technique, experience with the device, patient management, and patient population, CDRH suggests a Bayesian analysis with hierarchical model be used for the adjustment. This raises the concern for the regulatory review on the quality control of the usage of proved device. Instead of using statistical analysis such as Bayesian method to adjust the results, CDRH should advice the sponsor to develop the effort for the quality control.

12. In the guidance, it is called "Bayesian clinical trial". The appropriateness of the name of Bayesian clinical trials because of the application of Bayesian statistical method for data analysis is questioned. Should a clinical trial using Cox's regression analysis or Non-parametric analysis be called as a Cox Regression clinical trail or a Non-parametric clinical trial?

13. The statement "*Irony & Pennello(2001) discuss prior distributions for trails under regulatory review*" should not be part of recommendation, and only be included as a reference. The presentation in American Statistical Association proceeding reflects solely personal views. It should not be considered as regulatory recommendations.

14. The post-market surveillance should be based on the complete review on safety results from collected data of current approved product. This is public health issue and should not be based on the updated results from Bayesian analysis as stated in this guidance: "*FDA believes the Bayesian approach is well suited for surveillance purposes. ... You may readily update information provided by a pre-market clinical trial with post-post market data via Bayes's theorem if you can justify exchangeability between pre-and post-market data.*" The key concept stated in this guidance "*Today's posterior is tomorrow's prior*" should not be considered as a fundamental concept of Bayesian analysis. The recommendation of post-market surveillance by the statement of " *....use the posterior distribution from a pre-market study to serve as a prior distribution for surveillance purpose, to the extent that data from the clinical study reflect how the device is used after approval*" raises concern for the regulatory post-marketing approval process .