Garris, Cynthia

From: Zuckerman, Bram
Sent: Tuesday, June 06, 2006 12:17 PM
To: Stein, Bridgette R.; Garris, Cynthia
Cc: Campbell, Gregory; Zuckerman, Bram
Subject: Comments on Draft FDA Guidance on use of Bayesian Statistics in Medical D evice Trials from Dr. Stuart Pocock

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Cynthia and Bridgette,

Enclosed are comments from Dr. Stuart Pocock on the FDA draft guidance on Bayesian Device Studies. Dr. Pocock is from London, England and will not be able to attend on July 27. Are you the appropriate folks to send his comments to for inclusion in the official record?

Thanks,

Bram Zuckerman

From: Stuart Pocock [mailto:Stuart.Pocock@lshtm.ac.uk]
Sent: Tuesday, June 06, 2006 10:01 AM
To: Zuckerman, Bram
Cc: Campbell, Gregory; 'Richard E. Kuntz (richard.kuntz@medtronic.com)'
Subject: Re: FW: Draft FDA Guidance on use of Bayesian Statistics in Medical D evice Trials

Dear Bram

Thank you for forwarding me this draft FDA Guidance on Bayesian statistics in device trials. I am pleased to feedback my comments, and would be grateful if you and Greg could make sure they get into the system properly.

Since many statisticians and other trialists are somewhat mystified by Bayesian methods, any document that elucidates their practical use in a real-world setting is a valuable step forward. As such this FDA Guidance is important.

However, I do have my reservations as to how useful Bayesian methods are in most clinical trial settings. In my opinion, the more familiar frequentist statistical approach to trial design and data analysis serves trialists, science and regulators well. It has the advantages of being more widely understood and hence more readily communicated to clinicians and others not specialised in statistical methods. Frequentist methods are also easier to use, and to have a rigorous pre-defined analysis plan so that any two statisticians can reproduce any given result with reliability and without undue fuss. I also think that there is an increasing trend towards undue complexity in the biostatistical community, which is counter-productive when it comes to effective communication with other clinical scientists. In this respect, I fear that some computer intensive Bayesian methods eg MCMC techniques such as Gibbs sampling will inevi tably remain a mystery "black box" to many clinical trialists.

Thus, I think Bayesian statistics have a rather limited role in medical device (and other) clinical trials. Hence, I

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think it would be helpful to elucidate more specifically those trial circumstances in which Bayesian methods are truly needed, preferably with worked examples to illustrate the point to non-specialists.

Some feedback I get from the device industry and their collaborators is a concern that they are getting drawn into Bayesian designs and analyses when they do not really understand what it is all about. Thus I think CDRH need to be sensitive to the fact that many trial sponsors are comfortable and experienced in frequentist statistics, but bewildered by all but the most basic Bayesian concepts.

Having made that general plea for statistical realism, simplicity and communication let me comment on specific sections of the Draft Guidance:

Sections 1-3
Nicely set the scene on the context for using Bayesian methods.

Section 3.3
I think Bayesian methods are rarely used in practice, so they may be more common but the absolute use must be in less than 1% of all trials.

Section 3.5
WinBUGS is a great package, but any statistician needs a firm grounding in Bayesian methods before attempting to use it. One needs to guard against premature mis-use.

Section 3.8
I am not sure sample size reduction depends on being a Bayesian. It rests more on accepting prior data (wisely) to be combined appropriately with data from a new trial.

Exact analyses are rarely needed unless there is very little data.

Section 3.9
I would summarise the difficulties as being ignorance, undue complexity, inadequately imprecise pre-definition of intent and subjectivity.

Section 4.1
If one chooses a non-informative prior the Bayesian analysis is liable to agree with a more straightforward frequentist approach.

Section 4
Is well-written but probably assumes too much prior knowledge to be understood by many readers. This document needs to be written at a level that most applied statisticians and statistically-informed clinicians (eg Bram Zuckerman!) can follow. For instance, the subtle point in section 4.8 will be lost on most readers.

Section 5.1
Some trials would benefit from a mix of both Bayesian and frequentist methods. For instance, a frequentist analysis may be appropriate for most results, but be supplemented by a Bayesian methods for a specific issue eg interpretation of post trial data.

Section 5.3
Data on covariates, ie potential confounders, is especially important for non-randomised trials. Even so one needs to make clear that adjustment for them may help but not totally remove important biases.

Section 5.4
I would emphasise that selection bias is the key problem in historical controls ie you can't eliminate the prognosis - related reasons as to why who got what. The same problem concerns all non-randomised comparisons, whether they be historical or prospective.

Section 5.5

The use of informative priors is interesting: assuming prior data are "positive" it amounts to giving a trial an optimistic head-start. It has a certain analogy with combining a new trial's results with past data in a frequentist meta-analysis. That is, to use past data you may not need to be Bayesian.

Section 5.6
Hierarchical models are complex, and hence a mystery to most readrs of this Guidance. A specific real example of their use would help considerably.

Section 5.7
Determining trial size, whether it be fixed, based on interim analyses or in an adaptive design framework can be done with frequentist methods. It's not clear what extra usefulness a Bayesian paradigm adds. The same point applies to sections 6.4 and 6.5.

Appendix Section 9.3
Illustrates my concerns about complexity. If MCMC techniques require intensive computations and still may not converge, is it really wise to recommend such techniques in a practical regulatory setting where straightforward, robust, reproducible readily communicable methods should predominate?

I hope these comments help in getting our collective convergence to what is the appropriate role of Bayesian methods in medical device trials. I look forward to a continuing dialogue.

Kind regards

Stuart

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>>> "Zuckerman, Bram" <bram.zuckerman@fda.hhs.gov> 05/23/06 4:43 pm >>>

Greetings!

You may be interested in commenting on this draft FDA Guidance on use of Bayesian Statistics in Medical Device Trials.

Thanks,

Bram Zuckerman

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