

# COOK®

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**Re: Comments on "Draft Guidance for Industry and FDA Staff: Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials"**

These comments are filed in behalf of the Cook Group Inc, and represent an expansion of our comments filed August 21, 2006. Cook is a holding company of international corporations engaged in the manufacture of diagnostic and interventional products for radiology, cardiology, urology, gynecology, gastroenterology, wound care, emergency medicine, and surgery. Cook pioneered the development of products used in the Seldinger technique of angiography, and in techniques for interventional radiology and cardiology. Cook products benefit patients by providing doctors with a means of diagnosis and intervention using minimally invasive techniques, as well as by providing innovative products for surgical applications. Cook sells over 15,000 different products which can be purchased in over 60,000 combinations.

On behalf of Cook, I would like to commend the FDA Center for Devices and Radiological Health for producing an outstanding and timely guidance document on this very important topic. Below are some brief comments regarding the document that may be pertinent to future discussion and revision.

It is well-known among statisticians that the use of Bayesian methods requires significant knowledge of the mathematics, model building, and model checking, as well as the programming skills required to perform these tasks. Although the document provides ample references, and recommends that consultation be made with the statistical experts, there is inadequate emphasis on the need for a statistical expert to perform the required study planning and data analysis.

Section 5.5 mentions that prior information may be "too informative." Suggested remedies for this include discounting the prior information and/or increasing the stringency of the decision rule to artificially reduce the power estimate. While statistical remedies may be possible, we believe it is necessary to step back from Bayesian statistics

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for a moment and reconsider what "too informative" may mean to the FDA determination of safety and effectiveness.

For decades scientists have been trained to utilize all available prior information, respecting the prior discoveries of colleagues, past and present. This is a fundamental principle of science; almost any peer-reviewed journal article contains references to prior studies as fact. If prior information is available and corroborated, then it is an adequate basis for scientific decisions. Potential study sponsors and investigators are interested in having informative prior information, as, *a priori*, this provides a scientific basis for determining if a study is needed and ethically justified, if it is reasonably designed and if it is likely to succeed. Strong prior information may be well-justified and reliable depending upon its origin and applicability to the study hypothesis (e.g. a GCP clinical study performed outside the United States).

If the prior information so strongly predicts success in a study of safety and effectiveness, then one must ask if the prior information is sufficient to make a determination of reasonable assurance of safety and effectiveness. With all due respect to the value of another study, if the prior information adequately supports an FDA determination, then the additional confirmatory study will unnecessarily delay potential access to needed devices. The additional study will also increase the cost of the device unnecessarily. Moreover, the additional study may lack ethical justification. Therefore, if the prior information is "too informative," the FDA should consider making the determination for approval based upon available information.

If the FDA could make the determination based upon the prior information that is "too informative," but decides confirmative data are needed, then performing the confirmatory study as a post market study should be considered. There are several benefits to post market studies over pre-market studies. Even though the potential for bias is recognized in retrospective analysis, if the prior information is "too informative," then a subsequent study is only confirmatory and often functions to address secondary issues such as to 1) confirm that biases did not substantially affect testing of the study hypothesis, 2) provide additional safety data for rare events, and 3) provide more information for secondary endpoints and subset analysis. Additionally, pre-market clinical studies have been repeatedly criticized for narrow patient selection and use of highly specialized investigators compared to expected post market clinical practice. Only in a post market study is the outcome optimally evaluated in the target population under more normal medical practice conditions. Therefore, the use of a post market study would achieve the objectives of 1) confirming the study hypothesis supporting safety and effectiveness, 2) providing additional safety information, 3) gathering more information for secondary and subset analysis, 4) evaluating outcome in the broader patient population, and 5) providing experience across a broader spectrum of clinicians. In

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summary, when the prior information is "too informative" for a Bayesian approach and yet the FDA decides confirmatory data are necessary, consideration should be given to a post market study approach.

Finally, with medical device trials it is often the case that numerous study centers are able to contribute only a small number of patients to the study. This creates problems with justification of pooling multi-center data. A Bayesian hierarchical model has a clear advantage over frequentist methods in this situation. This may be emphasized as an additional benefit of the methodology.

Again, on behalf of Cook Group Incorporated, I congratulate the Agency on producing outstanding draft guidance and I look forward to reviewing the final guidance when it becomes available.

Sincerely,

A handwritten signature in black ink, appearing to read "Scott Snyder". The signature is written in a cursive style with a large initial "S".

Scott Snyder, Ph.D.  
Manager, Biostatistics and Clinical Data Management  
Cook/Med Institute