FDA INSIGHTS

# Conflicts of Interest

What is their potential impact on device evaluation?

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*The views and opinions presented in this article are those of the author and do not necessarily reflect those of the US FDA, the US Department of Health and Human Services, or the Public Health Service.*

Bias is inherent in all aspects of device development, evaluation, and use. Inventors, manufacturers, and investors generally hope to profit from the sale of the device. Inventors may also be investigators who are likely to have a strong desire for the device to work as intended. Investigators would not agree to participate in a study if they did not believe that the new technology would likely benefit their patients. The FDA is responsible for protecting and promoting public health, so they are often conservative but equally interested in seeing results that demonstrate patient benefit.

In the October 2005 issue of *Endovascular Today*, FDA Insights described the responsibilities of IRBs, investigators, sponsors, and the FDA to minimize the effects of potential biases. This article will focus on the specific biases that can be associated with conflicts of interest.

## HOW ARE FINANCIAL CONFLICTS OF INTERESTS IDENTIFIED?

When a sponsor of an investigational study recruits investigators, they must obtain a disclosure statement that provides current and accurate financial information as it relates to the study or investigational device. Specific information regarding the requirements can be found on the FDA Web site at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=54&showFR=1. When sponsors submits a marketing application, they are required to submit disclosures for all investigators participating in any study regarding the investigational device. Therefore, potential financial conflicts of interest are known to the sponsor before the study is initiated and by the FDA before a determination is made regarding the approval of the device. If a PMA requires FDA advisory panel review, financial interests are also disclosed to the panel. In addition, financial interests generally are disclosed when presenting data at scientific meetings.

## HOW CAN CONFLICTS OF INTEREST AFFECT STUDY RESULTS AND CONCLUSIONS?

The most obvious and direct method of affecting study results is to falsify the results. This could be done at the investigator level or by the manufacturer. A less obvious approach would be through "cherry picking" patients—enrolling only those likely to have favorable outcomes. Even less direct is the design of a clinical study that lacks adequate definitions of hypotheses, endpoints, complications, follow-up measures, etc., or scientific rigor to provide meaningful data. Nonobjective endpoints, such as some imaging tests or questionnaires, are particularly susceptible to the influence of bias, whether intentional or unintentional.

Conclusions are more difficult to falsify; however, they may be presented in absence of full disclosure of the study design and conduct and thus could be imperceptibly erroneous. If not erroneous, they could be inappropriately presented to be universally applicable. Not uncommon is data manipulation or "data dredging" that can be done with prior knowledge of results and thus the power to prejudice conclusions.

## HOW CAN THE EFFECTS OF THE CONFLICT OF INTEREST BE DETECTED OR NULLIFIED?

Study data are monitored by the FDA during the review of the PMA application. This monitoring procedure includes comparing source documents to the study database, as well as assessing protocol compliance. Individual investigational sites and the manufacturer are audited. In addition, the FDA has the ability to ask for complete electronic data sets to independently verify all statistical calculations performed by the sponsor. With this level of scrutiny, it is difficult to falsify data and results, or even to cherry pick, if the protocol is appropriately defined.

Design of the study, again in the US, is prospectively addressed during our investigational device exemptions (IDE) reviews. Although the sponsor proposes the investigational plan, preferably with the help of the investigators, the FDA provides clinical and statistical input to help ensure the collection of valid scientific evidence. In addition, during the PMA process, the FDA revisits the clinical protocol to determine whether the study was adequately designed and conducted to support the presented conclusions from the study.

Problems with inappropriate conclusions are more prevalent in presentations at meetings rather than in documents reviewed by the FDA. Adequate descriptions of studies should be required by meeting organizers to allow attendees to decide whether the conclusions presented are valid.

## HOW ARE KNOWN FINANCIAL INTERESTS ADDRESSED BY THE FDA IN DEVICE EVALUATION?

The FDA requires the sponsor of a PMA to address any financial interest that may affect the analysis of the clinical trial results that is noted in the disclosures provided with the PMA application. The sponsor may be able to provide a rationale for why the study design or monitoring of the clinical trials mitigates perceived bias by any one investigator. Alternatively, the FDA may choose to conduct an analysis of the dataset without data collected by an investigator with a financial interest.

## IF CONFLICTS OF INTEREST CAN BE IDENTIFIED AND ADDRESSED, WHAT IS THE PROBLEM?

Although it may be possible to discern whether an individual investigator with an identified conflict of interest obtained results inconsistent with the rest of the investigators in the study, it is not possible to tease out the impact of all conflicts of interest. For example, an investigator could either intentionally or unintentionally influence the opinions of fellow investigators, exacerbating the effect of their own bias. In absence of randomization, which is often the case with medical device studies, such biases are not easily addressed.

Because entities with conflicts of interest can theoretically impact results and conclusions, the interests and possible bias themselves are problematic, regardless of whether the conflicts truly did affect the definition, conduct, or reporting of a study. The mere possibility of deceit leads to a lack of confidence by the US public in the safety and effectiveness of the devices prescribed by their doctors, which can lead to increases in regulatory controls for devices.

Whether financial interests and possible conflicts have become more common or are just receiving more attention, these interests have made the evaluation of new devices or technologies more challenging. The pool of qualified investigators to conduct studies, as well as independent experts to address concerns with the evaluations, is diminished.

## WHAT ARE SOME POSSIBLE SOLUTIONS?

In order to minimize the risk of personal influence on outcomes and to minimize the potential effects of other biases, all clinical study plans should have clear definitions for patient selection, treatment plans, follow-up requirements, adverse events, study success, etc. Randomization and blinding should be used whenever possible and appropriate. In addition, the FDA frequently recommends the use of independent core laboratories, where appropriate, to more objectively evaluate key results, and independent data safety monitoring committees, when appropriate, to monitor patient safety and consider early termination for poor safety results or futility. FDA guidance regarding the establishment and use of data monitoring committees can be found at fda.gov/OHRMS/DOCKETS/98fr/01d-0489-gdl0003.pdf and at fda.gov/cber/gdlns/clintrialdmc.htm.

The desire for personal gain should be balanced by good science. All potential conflicts of interest should be disclosed completely and often, with serious consideration as to the appropriateness of participating in a study in light of significant conflicts. Those free of conflicts relevant to the panel subject matter could help by offering to serve on FDA Advisory Panels.

All involved in device evaluation and use must acknowledge the potential effects of real and perceived biases and conflicts of interest. Equally important is the need to acknowledge that biases are unavoidable. As such, emphasis should be placed on designing and conducting studies with appropriate mechanisms to minimize bias, but also on the auditing of studies to identify or rule out the effects of bias. ■

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