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"Conflict of Interest in Medical Research, Education and Practice"

Bernard Lo and Marilyn J. Field, editors, 2009, 414 pages, National Academies Press, $54.95

Review by Norman M. Goldfarb

"Conflict of Interest in Medical Research, Education and Practice" is a thorough review of conflict of interest in medicine. The book was authored by a committee appointed by the Institute of Medicine of the National Academies to study the problem and recommend solutions.

The book defines the purpose of conflict of interest policies as follows:

> The central goal of conflict of interest policies in medicine is to protect the integrity of professional judgment and to preserve public trust, rather than try to remediate bias or mistrust after it occurs

Of the committee's 16 recommendations, only one (#4.1) is specific to medical research:

> Academic medical centers and other research institutions should establish a policy that individuals generally may not conduct research with human participants if they have a significant financial interest in an existing or potential product or a company that could be affected by the outcome of the research. Exceptions to the policy should be made public and should be permitted only if the conflict of interest committee (a) determines that an individual's participation is essential for the conduct of the research and (b) establishes an effective mechanism for managing the conflict and protecting the integrity of the research.

The following extracts from the text explain why conflict of interest is an issue:

> Several systematic reviews and other studies provide substantial evidence that clinical trials with industry ties are more likely to have results that favor industry. One meta-analysis found that clinical trials in which a manufacturer sponsors clinical trials or the investigators have financial relationships with manufacturers are 3.6 times more likely to find that the drug tested was effective compared to studies without such ties (Bekelman et al., 2003). Another meta-analysis that included non-English-language studies found that studies that favored a drug were four times more likely to be funded by the maker of the drug than any other sponsor (Lexchin et al., 2003). A more recent literature review found that 17 of 19 studies published since the preceding two meta-analyses reported "an association, typically a strong one, between industry support and published pro-industry results" (Sismondo, 2008, p. 112). Similarly, another review found that industry-funded studies were more likely than other studies to conclude that a drug was safe, even for studies that found a statistically significant increase in adverse events for the experimental drug (Golder and Loke, 2008).
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> In addition, a study of materials submitted to the FDA in support of successful new drug applications found that clinical trials with statistically favorable results were almost twice as likely to be published as industry-funded studies that did not have favorable results (Lee et al., 2008). Overall, the results of more than half of clinical trials submitted to the FDA support of a new drug application remained unpublished more than five years after approval of the drug…

Several possible explanations can be offered for the association between industry support and results that are favorable to the sponsor. First, pharmaceutical and biotechnology companies seek to invest in products that will be shown to be effective and safe; hence, compounds that enter clinical trials have been selected as being likely to succeed. (That is, for-profit companies may be more risk adverse than nonprofit sponsors and fund mostly studies that seem likely to produce favorable results.) Second, investigators might have become persuaded by their own research that a drug is efficacious and, as a result, develop financial relationships with trial sponsors to help promote the future clinical development or use of the drug. Third, industry studies might be less rigorously designed or designed in a way that will bias the findings in favor of a drug, leading to false-positive conclusions that an intervention is effective, or they might be well designed but not actually conducted according to the protocol (Bero and Rennie, 1996; Steinman et al., 2006). Fourth, sponsors may be more likely to fully publish the results of studies with favorable findings (Rising et al., 2008)…

In addition, systematic reviews that look at meta-analyses rather than individual clinical trials as the unit of analysis also find an association between industry funding and conclusions that favor the sponsor's product. One study found that industry-supported reviews had more favorable conclusions, noted fewer reservations about the methodological limitations of the trials included, and were less transparent than reviews conducted by the Cochrane Collaboration. All seven industry-sponsored reviews recommended the experimental drug without reservation, whereas none of the Cochrane Collaboration reviews did (Jorgensen et al., 2006)…

Examples of Biased Reporting in Clinical Research

In a pivotal trial of celecoxib for treatment of arthritis, only data on outcomes at 6 months were presented, even though the original protocol called for the trial to be of a longer duration and the outcomes at 12 months were available when the manuscript was submitted, (Hrachovec and Mora, 2001). The outcomes at 6 months showed an advantage for the study drug, but the outcomes at 12 months showed no advantage compared with the use of the control drugs (Wright et al., 2001).

Published clinical trials suggest that selective serotonin reuptake inhibitors have a favorable benefit-risk profile in children with depression. When unpublished data were considered, the evidence indicated that the risks appeared to outweigh the benefits for all but one drug in this class (Whittington et al., 2004).

The results of trials of paroxetine that demonstrated an increased risk of teenage suicide or a lack of efficacy were not published. The data were revealed only after a lawsuit was brought against the manufacturer (Gibson, 2004).

The manufacturer of aprotinin, an antifibrinolytic drug used in cardiac surgery to decrease bleeding, withheld data that use of the drug increased the risk of renal failure, heart attack, and congestive heart failure (Avorn, 2006).

The results of a clinical trial that compared the use of ezetimibe plus a statin with the use of a statin alone in individuals with elevated cholesterol levels were not published until 2 years after the conclusion of the trial. The results showed no difference in carotid artery wall thickness in the two groups (Kastelein et al., 2008).

The results of a pivotal clinical trial of a blood substitute (PolyHeme) in patients undergoing elective vascular surgery were not released for 5 years after the trial was stopped by the sponsor. The trial showed significant increases in the rates of

mortality and heart attacks in the group receiving the experimental intervention (Burton, 2006; Northfield Laboratories, 2006):

The manufacturer of an implantable cardioverter-defibrillator allegedly failed to report critical, potentially fatal design defects for more than 3 years (Hauser and baron, 2005).

The manufacturer of a novel immune modulator for the treatment of HIV infection refused to provide a complete set of data to the investigators in a randomized clinical trial that showed that the investigational agent was ineffective (Kahn et al., 2000).

The manufacturer of a brand-name thyroid hormone attempted to block the publication of an article showing that a generic thyroid replacement therapy had bioavailability similar to that of the brand-name preparation (Rennie, 1997).

The book includes nine chapters:

- Introduction
- Principles for Identifying and Assessing Conflicts of Interest
- Policies on Conflict of Interest: Overview and Evidence
- Conflicts of Interest in Biomedical Research
- Conflicts of Interest in Medical Education
- Conflicts of Interest and Medical Practice
- Conflicts of Interest and Development of Clinical Practice Guidelines
- Institutional Conflicts of Interest
- Role of Supporting Organizations

The book is available in bookstores.

Reviewer

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