Conflict of Interest, Disclosure, and Trial Reports

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When I was an assistant professor, my previous training had not prepared me for the unexpected attention that 2 articles, both from the same study, were to receive. One article provided evidence that abruptly stopping β-blockers might increase the risk of coronary events.[1] The other suggested that, compared with the use of high-dose diuretics, which is now no longer recommended, the use of β-blockers might be associated with a lower risk of coronary events in hypertensive patients.[2] While the news media's coverage of the risk study was transient, the pharmaceutical industry had a more sustained interest in the other publication.

My family and I were invited to a first-class resort, where I presented the results at a sponsored conference. Although I lacked both the golf skills and the sense of entitlement to make the most of the holiday, the effort did result in a publication in an industry-funded supplement.[3] With several other scientists, I was also invited to serve as a consultant to develop a slide set about β-blockers and to give a series of funded talks for the manufacturer. Young but knowledgeable, I was certain that I could help the sponsor fashion an unbiased presentation, but from the outset, I chose not to travel and give talks around the country. While scientific advice could be provided in a disinterested fashion, funded speaking engagements seemed to me to have the potential to cross the line into the arena of marketing.

At a meeting set up by a communications company to produce the slide set, I participated with representatives from the manufacturer and senior scientists whose work I knew well. Over lunch, we chatted about interests, projects, and families. The preliminary outline for the slide set contained a number of traditional topics, such as the effects of β-blockers on blood pressure or anginal symptoms. As we developed content, I soon found myself advocating the use of studies that featured the manufacturer's product as the best illustrations. My experiences at the pleasant luncheon and in the scientific discussions made me feel as if the other consultants and I had a kind of social duty to reciprocate both the kindness and the investment made by the sponsor in the slide set. Accordingly, I spoke out about the importance of using some of the sponsor's studies as examples. At the time, I failed to recognize that this sense of duty might be in conflict with an intention to create an unbiased presentation about the risks and benefits of β-blockers.

It turns out that I am not alone. In a study of medical residents, 61% were confident that drug company promotions did not influence their practice, but only 16% were equally confident that their colleagues were not influenced by those same drug company promotions.[4] How is this possible? Self-interest simply distorts the way we render judgments about ourselves. As Katz and colleagues[5] describe the problem, "When a gift or gesture of any size is bestowed, it imposes on the recipient a sense of indebtedness. The obligation to directly reciprocate, whether or not the recipient is directly conscious of it, tends to influence behavior. . . . Feelings of obligation are not related to the size of the gift." Precisely my experience.

Other interesting social science insights have emerged from the field of behavioral economics. For instance, Ariely[6] conducted a series of experiments in which study participants were rewarded financially for the number of correct answers on tests. The experiments were designed so that cheating was possible. On the basis of the results of these experiments, Ariely concluded that many individuals cheat when they have a chance, but only by a small amount; they know that they are overclaiming the number of correct answers; but this low-level cheating does not cause them to view themselves as dishonest. When I recently used a university envelope to mail a letter to my daughter, I too did not view myself as dishonest, perhaps because I used my own postage stamp.

These minor dilemmas fail to cross key moral boundaries with the result that they are not experienced as a conscious and deliberate choice between the size of the reward and the potential cost to credibility or reputation. The frequently expressed view that industry gifts or consulting fees are too small to influence behavior simply misses the point that, regardless of their size, they influence behavior,[5] and a self-serving bias distorts the way that individuals perceive themselves.[7] As a result, industry gifts, fees, or funding have become culturally acceptable even though service in a profession does not itself provide immunity from po-

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tential conflicts of interest or from the appearance of conflicts of interest.

Recent high-profile failures to disclose financial relationships with industry have been major embarrassments to the profession. Several professors who promoted the use of atypical antipsychotics for bipolar illness in children had received hundreds of thousands of dollars that went unreported to their institutions. The new guidelines from the Association of American Medical Colleges on the efforts to manage the relationships between academic scientists and industry sponsors emphasize transparency.[8] Senators Chuck Grassley (R, Iowa) and Herb Kohl (D, Wisconsin) have introduced the Sunshine Act,[9] which would require the public posting of information about all industry payments or transfers of value worth $100 or more. This act, if passed, will help ensure the transparency that the profession on its own has not yet been able to muster.

Although journals' disclosure forms have become increasingly complex in recent years, the benefits of transparency are nonetheless decidedly limited. It is not possible to look at a disclosure about industry funding of research, consulting, or speaking and know how to interpret the disclosure or its potential effect on a published clinical trial. Indeed, a funding disclosure does not necessarily mean that any bias is present. Even if the disclosures included exact dollar amounts, the interpretation would remain difficult.

Authors of sponsored studies do not regard themselves as biased. Empirical studies nonetheless suggest that the disclosure of a competing interest in an article affects readers' perceptions of its interest, importance, validity, relevance, and believability.[10] In short, the primary function of disclosure is prevention.[11] Full disclosure precludes the possibility that some competing interest may eventually come to light and discredit the authors, the journal, and the profession. If conflict-of-interest disclosures are not informative about bias in trial reports, what resources are available?

Under the assumption that the submitted or published article contains an accurate report of the study results,[12] an assessment of the quality of the article provides important information. The CONSORT recommendations for reporting the results of clinical trials provide an excellent checklist[13] that includes key elements of the aims, methods, results, and discussion. For instance, the methods should address approach to randomization, allocation concealment, and blinding. The results should include information on recruitment, baseline data, and loss to follow-up as well as the outcomes and adverse events. The CONSORT criteria incorporate the traditional views about high-quality reports of clinical trials.

Several other approaches, although more difficult to apply, may be useful as well. First, what is the quality and the scientific merit of the hypothesis addressed by an industry-funded trial? Answers to this question, which require an understanding of the current state of the science, are important because, with several notable exceptions, the various institutes of the National Institutes of Health have largely turned the evaluation of drug treatments over to industry. The expansion of the pharmaceutical industry in the second half of the 20th century has provided a large number of safe and effective medications for many conditions. At the same time, industry has a fiduciary duty to shareholders to provide a return on investment. On occasion, marketing interests have shaped or dominated short-term decision-making processes. Power resides in the ability not only to pose particular questions and shape trial designs but also to obtain results and disseminate findings.

In the genre of trial reports, the hypothesis for a completed trial often appears as a kind of invisible assumption, one that deserves active scientific discussion. Do the selected hypothesis and its associated outcome address an important public health question? What comparison group was selected for study? If the trial has an active-treatment comparison group, were the control agent and dose appropriate?

In addition, external sources can sometimes be used to assess the quality of the conduct of the trial. Many industry-funded trials are now conducted in part or in whole in other countries. If the case-fatality rate for an outcome is higher than expected in the United States, this disparity may arise from differences in health care systems, or more mild forms of the disease may not have come to the attention of the investigators. Similarly, if the event rate for the primary outcome is much lower than expected, incomplete ascertainment of events may have been a problem for the investigators. Insofar as incomplete ascertainment is nondifferential, the primary effect is loss of study power, which would be especially troubling for an equivalence trial. In other words, the observed incident rate can serve as a kind of quality metric.

Also, what is the relationship between the results and the discussion? The investigators, who know the strengths and weaknesses of their study as well as the literature, owe their readers an engaging, disinterested, and thoughtful accounting. What is the fit between the results and the discussion points? How do the investigators weigh the balance of risks and benefits? Indeed, high-quality discussions, which bring closure to the uncertainty embodied in the study hypothesis, provide readers with an aesthetically satisfying experience.

Is the discussion cautious, well-defended, and disinterested? Or are the data used to marshal an argument that has the look and feel of advocacy or promotion? In an effort to dismiss safety findings, do the investigators treat adverse effects and complications with the same intense skepticism that is usually reserved for findings of efficacy? The presence of an editorial accompanying the published trial, especially when the trial investigators and the editorialist disagree about the implications of the findings,[14,15] is one marker for a problematic discussion in the article. In major journals, the absence of an editorial is often correlated with a well-constructed discussion. Of course, a disparity between results and discussion may represent professional as

well as financial conflicts, and other sources such as the *ACP Journal Club* often help to situate the findings in evidence or practice.

The design and conduct of drug treatment trials remain primarily in the hands of industry. Public funding to prioritize, plan, and conduct major drug safety and efficacy studies of public health importance is not likely to replace the current system soon. In the meantime, the US Food and Drug Administration scientists who review and approve trial designs and the academic scientists who collaborate with industry in drug development can help shape the questions posed by industry-funded studies to the advantage of the health of the public.

While transparency is a critical preventive measure, bias is not identifiable by the fact that funding may have been received from a source with special interests. The bias of conflict of interest is a behavioral phenomenon. Under the assumption of an accurate report, the design of the trial, the conduct of the study, and the interpretation of the results are perhaps the best measures that clinicians, researchers, and other readers have to assess the possibility of such a bias among their scientific colleagues and themselves.

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Reducing Adolescents' Exposure to Alcohol Advertising and Promotion During Televised Sports

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According to the World Health Organization (WHO), "the global burden related to alcohol consumption, in terms of both morbidity and mortality, is considerable in most parts of the world."[1] Globally, alcohol consumption causes 1.8 million deaths (3.2%), results in 58.3 million disability-adjusted life-years (4.0%) lost, is the leading risk factor for disease burden in low-mortality developing countries, and is the third largest risk factor in developed countries.[1] Alcohol-related problems are most apparent among young persons, with Jernigan and Mosher[2] arguing that such problems have "reached crisis proportions around the globe." In the United States, a recent article[3] concluded that "the prevalence and toll of underage drinking in the United States remain high," and the US Federal Trade Commission[4] acknowledged that "underage drinking is a leading public health and social problem in the

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