

Impugning the Integrity of Medical Science

The Adverse Effects of Industry Influence

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THE PROFESSION OF MEDICINE, IN EVERY ASPECT—clinical, education, and research—has been inundated with profound influence from the pharmaceutical and medical device industries. This has occurred because physicians have allowed it to happen, and it is time to stop.

Two articles^{1,2} in this issue of *JAMA* provide a glimpse of one company's apparent misrepresentation of research data and its manipulation of clinical research articles and clinical reviews; such information and articles influence the education and clinical practice of physicians and other health professionals. The direct influence of for-profit companies on education³⁻⁶ and clinical practice^{7,8} has been well documented, so this Editorial deals primarily with clinical research.

The articles by Ross and colleagues¹ and by Psaty and Kronmal² document how one company, Merck & Co Inc, apparently manipulated dozens of publications to promote one of its products. But make no mistake—the manipulation of study results, authors, editors, and reviewers is not the sole purview of one company.⁹⁻¹² In this case, documents that provided evidence necessary to demonstrate the manipulation became public (and publishable) because of litigation involving one of that company's products, rofecoxib. As disclosed in the articles,^{1,2} all authors, except one, report having served as paid consultants for plaintiffs in litigation against Merck. However, at our insistence the authors of both studies have made all documents used in their articles available on the Internet and have provided the information necessary to access those documents (ie, Web site addresses) in the articles. Thus, anyone questioning the veracity or interpretation of the information in these 2 articles,^{1,2} or wishing to inspect the documents referenced in these 2 articles, will have ready access to the materials.

The study by Ross et al¹ illustrates that clinical trial articles and review articles related to rofecoxib frequently were written by unacknowledged authors who were employees of for-profit information industries, and often attributed first (or primary) authorship to academically affiliated investigators who either had little to do with the study or review or who did not disclose financial support from the company. It is important

to note that for some of the referenced publications listed in the Table of the article by Ross et al,¹ some of the authors either did not actually receive financial support from the company; were not required by the journal in which the study was published to disclose their financial support or relationship with the sponsor; did report their financial support or relationship with the sponsor, but the journal chose not to publish those author disclosures; or did disclose their financial support, and those disclosures were published.

However, it is clear that at least some of the authors played little direct roles in the study or review, yet still allowed themselves to be named as authors. Individuals, particularly physicians, who allow themselves to be used in this way, especially for financial gain, manifest a behavior that is unprofessional and demeaning to the medical profession and to scientific research.

The study by Psaty and Kronmal,² which is based on analysis of published articles, information provided by the company to the US Food and Drug Administration (FDA), and the company's own internal analysis, shows how Merck may have misrepresented the risk-benefit profile of rofecoxib in clinical trials involving patients with Alzheimer disease or dementia. The authors show that the company's report to the FDA appears to have attempted to minimize the mortality risk by using an "as-treated" analysis, whereas an internal analysis conducted by the company several months earlier and using the correct intention-to-treat analysis provided evidence of a significantly increased mortality risk among patients assigned to receive rofecoxib. The authors also report that, for at least 1 rofecoxib trial, company documents reveal that there had been no data and safety monitoring board in place, thereby potentially endangering patients who participated in this study. Moreover, as Ross et al¹ describe in their evaluation of this same trial (Figure 2 in their article), the data analysis for this study may have been completed before the academically affiliated authors were involved with the manuscript; this may not be surprising, given that 8 of the 11 authors named in the byline of the published article are identified as being Merck employees.

Journal editors also bear some of the responsibility for enabling companies to manipulate publications. Some editors may allow articles and supplements to be published without requiring complete disclosure of individual financial support, and without requiring clear and complete disclosure of industry support of and direct involvement with research ar-

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ticles or reviews. But even when disclosure is required and closely monitored, manipulation can still occur. For example, Figure 3 in Ross et al¹ includes a cover letter (dated October 2000) from Scientific Therapeutics Information Inc for the delivery of a manuscript “. . . to be submitted to *JAMA Express*.” The study was, indeed, published in *JAMA* (in January 2002),¹³ but not as an *Express* article. In that publication, it was disclosed that Merck sponsored the trial; that 3 of the 5 authors (including the first and corresponding author) were employees of Merck; and that the other 2 authors (who were identified as the coprincipal investigators) disclosed receiving funding from Merck. However, there was no disclosure that the manuscript had been written by Scientific Therapeutics Information Inc, a company specializing in the development of scientific literature,¹⁴ ie, writing papers for a price.

Perhaps some editors, investigators, reviewers, and readers would see little or no harm in this failed disclosure because all other disclosures were made. However, if there was nothing to hide, why were the names (and affiliations) of the individuals who actually wrote at least the first draft of the manuscript omitted? Experienced authors know that the initial draft (in this case paid for by Merck) sets the tone for the manuscript. Moreover, it is unfair to the authors of the first draft not to provide them with credit for their work.^{15,16} Another problem with failing to disclose “ghost writers” is that there is a reasonable assumption that the principal investigator was involved with writing the manuscript from the beginning. If a professional (ghost) writer is listed as an author, the issue becomes determining when the principal investigator became involved in the study. Even with the requirement for registering clinical trials,¹⁷ identifying the principal investigator is not one of the required elements in the registration information fields. It might be advantageous for including the names of the principal investigator(s) to become a requirement in trial registration, even though the vast majority of medical journals do not require registration of clinical trials.

It can be argued that merely disclosing relationships with for-profit companies and identifying who actually writes articles for publication does little to stop the practices for cases in which the relationships are unethical or in which the sponsor has inappropriate influence over the data or control over the manuscript. However, disclosure does provide readers with information that can be used in deciding about the credibility of the article—at least as interpreted by the reader. Full disclosure also might prove too embarrassing to authors who might reconsider lending their name and reputations to articles in which they did not meet requirements for authorship.

The article by Psaty and Kronmal² also represents another example of problems with data misrepresentation, data analysis, and selective reporting in industry-sponsored studies.^{9,18} In an effort to counteract such problems, in 2001 *JAMA* began to require that for all studies, an academic investigator who is not employed by the sponsor must attest that he or she “had full access to all of the data in the study and

takes responsibility for the integrity of the data and the accuracy of the data analysis.”¹⁹ In addition, for studies that are financially supported by for-profit companies, *JAMA* began to require that the data analysis must be conducted independently by an academic statistician who is not an employee of the sponsor and who is at an academic center, such as a medical school, or is an employee of a government research institute.¹⁹ This approach provides an additional layer of oversight for the integrity of the data analysis and reporting, such that if concerns about data manipulation or misrepresentation arise, a mechanism for investigation would be in place, such as by investigative committees appointed by the dean of the academic medical center at which the independent statistician is a faculty member. If all journals would have similar policies,²⁰ the likelihood of manipulation of data, inappropriate data analysis, and selective reporting of results could be substantially decreased.

Another source that may contribute to the manipulation of research studies involves peer reviewers who have relationships with industry. Such reviewers may provide biased reviews that favor products of companies with which they have strong financial relationships, may fail to disclose their conflicts of interest to journal editors, or may even provide for-profit companies with confidential information obtained during the peer review process. For example, it was recently reported that a peer reviewer for the *New England Journal of Medicine* sent a confidential manuscript that he was invited to review and that demonstrated an increased mortality risk associated with rosiglitazone to the manufacturer of this drug weeks ahead of the publication.²¹ Even though most journals require reviewers to disclose potential conflicts of interest, and editors must consider those disclosures in authorizing reviewers to complete reviews, actions such as this constitute a breach of trust and a violation of the ethical principles and confidentiality on which the peer review process is based.

What are the lessons from the 2 articles^{1,2} in this issue of *JAMA*, from other publications that have examined related issues,^{11,12} and from extensive experience with how clinical research has been manipulated by for-profit companies? First, manipulation of studies and misrepresentation of study results could not occur without the cooperation (active and tacit) of clinical researchers, other authors, journal editors, peer reviewers, and the FDA. Second, public trust for clinical research is in great jeopardy especially when the extent of how widespread such practices have become is unknown. Although we truly believe that the vast majority of researchers and other authors are honest and have the highest scientific integrity, manipulation of studies and publications by the pharmaceutical and medical device industries is either increasing or there has been more exposure of these practices. Third, in addition to clinical research, clinical practice and medical education also are greatly influenced by for-profit companies. Drastic action is essential, and cooperation of everyone involved in medical research, medical editing, medical education, and clinical practice is required for meaningful change to occur.

As a beginning, we propose the following:

1. All clinical trials must be prospectively listed in registries accepted by the International Committee of Medical Journal Editors (ICMJE) prior to patient enrollment, and the name(s) of the principal investigator(s) should be included as a required data element in the trial registration record.

2. All individuals named as authors on articles must fulfill authorship criteria. Journals should require each author to report his or her specific contributions to the article, and should consider publishing these contributions. All individuals who were involved with the manuscript or study but who do not qualify for authorship (such as those who provided writing assistance) must be named in the acknowledgment section of the article, with reporting of their specific affiliations and contributions and whether they were compensated for those contributions.

3. All journals must disclose all pertinent relationships of all authors with any for-profit companies, and must publish all funding sources for each article.

4. Journal editors must seriously consider funding sources and authors' disclosed financial conflicts of interest and financial relationships when deciding whether to publish a study or review.

5. For-profit companies that sponsor biomedical research studies should not be solely or primarily involved in collecting and monitoring of data, in conducting the data analysis, and in preparing the manuscript reporting study results. These responsibilities should primarily or solely be performed by academic investigators who are not employed by the company sponsoring the research.

6. All journals must require a statistical analysis of clinical trial data conducted by a statistician who is not an employee of a for-profit company.

7. Any author who fails to disclose financial relationships or other conflicts of interest, or who allows his or her name to be used for work that he or she did not actually perform, must be reported to the appropriate authority (ie, medical school dean or department chair) or appropriate oversight body. If an article in which this occurs is published, the offending author must then submit a letter to the editor, in which he or she provides full disclosure and apologies for the infraction to the readers of the journal. Depending on the nature and severity of the issue, the author may be banned from publishing articles in that journal.

8. Any peer reviewer who provides any confidential information, such as a manuscript under review, to any third parties, such as for-profit companies, or who engages in other similar unethical behavior, also should be reported to the appropriate authority (eg, medical school dean) or oversight body, and should be banned from reviewing and publishing articles in that journal.

9. Any editor who knowingly allows (or is party to allowing) for-profit companies to manipulate his or her journal must be relieved of the editorship.

10. To maintain a healthy distance from industry influence, professional organizations and providers of continu-

ing medical education courses should not condone or tolerate for-profit companies having any input into the content of educational materials or providing funding or sponsorship for medical education programs.

11. Individual physicians must be free of financial influences of pharmaceutical and medical device companies including serving on speaker's bureaus or accepting gifts.

Primum non nocere does not only hold true for physicians directly treating patients, but also holds true for all involved in medical research, biomedical publication, and medical education. When integrity in medical science or practice is impugned or threatened—such as by the influence of industry—patients, clinicians, and researchers are all at risk for harm, and public trust in research is jeopardized. Ensuring, maintaining, and strengthening the integrity of medical science must be a priority for everyone.

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