MAYO CLINIC

EDITORIAL

September 2009
Volume 84
Number 9

Mayo Clinic Proceedings

Bidirectional Conflicts of Interest Involving Industry and Medical Journals: Who Will Champion Integrity?

Conflict of interest: A set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest.
Institute of Medicine, 2009.[1]

Discussions of conflicts of interest (COIs) appear to be the latest rage in medical journals. A search of the term *conflict of interest* in PubMed (last performed August 17, 2009) reveals more than 7300 items, with approximately 70% of them published in the past decade. *British Medical Journal (BMJ)*, *Journal of the American Medical Association (JAMA)*, *The New England Journal of Medicine (NEJM)*, and *The Lancet* registered more than 195, 170, 160, and 125 COI items each. *Mayo Clinic Proceedings* has, for the most part, watched from the sidelines, accounting for only 8 items on PubMed. This position results from the *Proceedings* not recruiting articles on this topic, and most of the manuscripts on COI that were spontaneously submitted were rejected independent of their points of view because the editors and reviewers determined that they had no new or novel insights to share with journal readers. However, when new or novel views *were* presented to the reviewers of the *Proceedings*, those submissions were approved using the same standards that the journal uses for all manuscripts. As such, the journal has recently published an article on COI in clinical practice[2] and a spirited exchange of letters that followed,[3] and an exchange of letters[4] and editor's note[5] discussing the journal's position on reviewing industry-affiliated manuscripts.

Dr Lanier was a laboratory-based researcher at Mayo Clinic from 1983-2006 but currently focuses on clinical research. His research has been funded by multiple governmental, foundation, professional-association, and industry sources. Dr Lanier has not sought nor received industry funding for his research since becoming Editor-in-Chief of *Mayo Clinic Proceedings* in January 1999.

Address correspondence to William L. Lanier, MD, *Mayo Clinic Proceedings*, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (lanier.william@mayo.edu).

In the current issue of the *Proceedings*, the journal adds to its collection one more COI article that has passed the journal's stringent peer-review standards.[6] In his commentary, Dr Laurence Hirsch, a part-time practicing endocrinologist, former employee of Merck & Co and current employee of another biomedical company, contributor to the Pharmaceutical Manufacturers Association (P*h*RMA) guidelines on publication standards,[7,8] and former president of the International Society for Medical Publishing Professionals (ISMPP), argues that journals and journal editors have compromised their credibility as adjudicators of COI and, although likely unintentionally, have abetted plaintiffs' lawyers to the detriment of the pharmaceutical industry. Specifically, Hirsch argues that journal editors sometimes use one set of COI standards for accepting or rejecting manuscripts when it suits their purposes and another set of standards when it does not.

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Although not mentioned specifically by Hirsch, the downstream effect of such actions, if true, could be to stifle creativity and productivity in the United States and move industry research and development abroad. Also lost within this discussion is the fact that journals, clinicians, and patients benefit from high-quality industry-sponsored research related to the introduction and critique of therapeutics and devices, and industry benefits when it is able to publish high-quality information in credible journals. Actions on either side that inappropriately harm trust in the system, whether originating with industry sponsors, authors, journals, or editors, hurt patient care. In an ideal environment, journals should applaud strong drug and device companies that perform and publish high-quality research, and authors and industry should seek out journals and editors that demand high standards for publication but apply those standards equally to all parties.

The pharmaceutical industry has made itself an easy target for criticism by journals and journal editors in large

measure because, when new drugs are being introduced or evaluated, the pharmaceutical industry wants to have a say in how studies are designed, who conducts the research, how the data are analyzed, and how quickly a line of investigation moves from conceptualization to completion and publication. Actions that the pharmaceutical industry would characterize as appropriate and necessary (eg, direct participation in drug registration studies as legally required by the Food and Drug Administration) are sometimes viewed by journals and editors as excessive control and manipulation. When industry-associated seeding trials,[9] fragmentation of data, duplicate publication (often containing subtle changes in manuscript authorship, titles, figures, tables, and text to make the duplication difficult to track),[10] and other flaws[6] enter the picture, journals and editors typically think that these are simply more evidence of a pharmaceutical industry selling its long-term integrity for short-term financial gain.

In an effort to remediate some of the problems, P*h*RMA companies have collaborated to develop guidelines for proper conduct when pharmaceutical companies publish research findings and other information.[7,8] Unfortunately, compliance with the P*h*RMA guidelines is voluntary, even by the companies that were cosigners. Hence, whether these guidelines will serve as a basis of meaningful change remains to be determined.

Many pharmaceutical companies have contracts with groups of authors' editors to help with the copy editing and formatting of manuscripts. This, per se, is not a problem. However, problems arise when the pharmaceutical industry's authors' editors write the manuscripts themselves, as a part of a commercial campaign aimed at saturating the literature with "infomercial" articles.[11] This process is further harmed by commercial groups (ie "medical education and communication companies") that simultaneously help plan the publication campaigns *and* promotional campaigns outside the indexed medical literature.[11] Having heard the arguments of these company representatives (through my interactions with ISMPP), it appears that some have little appreciation that the indexed literature represents anything more than another opportunity to promote a product. This attitude has been confirmed by others.[12] Such attitudes invite duplicate publication, and, when caught, the offenders, like duplicate-publishing authors of all stripes, seem to reflexively respond with, "We were just trying to get our important message to a broader audience."

Drug companies understandably seek out (for their original research efforts) investigators who are well versed in conducting clinical studies of drugs. However, contemporary investigators who contribute to these studies are increasingly viewed by the public as biased or, worse yet, on the take.[6,13] In many cases, affiliation with a drug company alone, not proof of any wrongdoing per se, has become a reason for journals and editors to exclude investigators and authors from public discussions.[6,14] According to Rothman,[15] in taking this path, we have now entered into an era of scientific McCarthyism. This is a far cry from an earlier era when investigator participation in industry-financed drug evaluation trials was viewed as an asset. Given the downside risk for journals and journal editors who published flawed industry-funded research, is it possible that, in reactionary behavior based on saving their own personal brand integrity and that of their journal, the editors have sometimes gone too far? It is a concept that few have written about.

One wonders what the ghosts of Mayo Clinic greats Drs Edward Kendall and Philip Hench would think of the current situation in which industry affiliation in virtually any form places an investigator and his or her published material under suspicion. Working in concert with Merck & Co during World War II, Kendall and Hench's research eventually led to the discovery and clinical introduction of cortisone.[16,17] For this and related research, they, along with Tadeus Reichstein of Switzerland, won the 1950 Nobel Prize in Physiology or Medicine. Should our revisionist history view Kendall and Hench with suspicion because they were "tainted" by a drug company? And what about Drs Gertrude Elion and George Hitchings, both employees of Burroughs Wellcome Company, and Dr James Black, a former employee of the Pharmaceutical Division of Imperial Chemical Industries and later an employee of Smith, Kline, and French Company, all 3 of whom shared the 1988 Nobel Prize in Physiology or Medicine "for their discoveries of the important principles of drug treatment"[18]? Among their many accomplishments, Elion and Hitchings were responsible for the introduction of 6-mercaptopurine, trimethoprim, azathioprine, allopurinol, and acyclovir, and Black introduced propanolol and cimetidine.[18] The 3 scientists were celebrated at that time in *JAMA*,[19] *Science*,[20] and the *Journal of the National Cancer Institute*[21] and later in *The Lancet*,[18] with no mention of concern related to COI. Specifically, the 1988 Nobel Laureates were celebrated *because of* their accomplishments while working with industry, not *despite* their ties to industry. Using the standards of 2009 (ie, a mere 2 decades later), would we now view their research as tainted by industry influence and use that idea to bias journals' peer-review processes against them?

In his analysis of journal editors, Hirsch suggests that contemporary editors do not use a single standard for all authors but instead selectively and excessively condemn authors who have drug company affiliation. Furthermore, Hirsch contends that editors have sometimes abetted the financial and other interests of plaintiffs' lawyers to the detriment of the pharmaceutical companies. If true, editors, whether intentionally or not, are guilty of an ancient con-

cept: the enemy (lawyers) of my enemy (pharmaceutical companies) is my (the editors') friend. Is it possible that criticism of industry by journals and journal editors, which began as a highly focused and intellectual exercise, has in some instances lost its focus because of critics' political expediency and lack of discipline? If such a deterioration of standards and practices has occurred right before our eyes, why has there not been more of a public outcry? Is it possible that journal editors have been given a pass simply because they are editors?

The uninitiated may incorrectly assume that journals' positions are entrenched because only harm can come from publishing manuscripts that have industry-associated COIs. However, data show us that this is not at all the case. For example, *NEJM*'s controversial November 2000 article on the VIGOR (Vioxx Gastrointestinal Outcomes Research) trial that evaluated rofecoxib, authored by Bombardier et al[22] and often discussed as an example in which industry COI affected the message, has now been cited more than 1750 times (Thompson/ISI Web of Science, Thomson Reuters; last confirmed, August 17, 2009), and the media coverage has followed suit. By May 2006, *NEJM* acknowledged that it had sold more than 900,000 reprints of this article (most of them to Merck & Co), bringing in at least $697,000 in revenue.[23] As public scrutiny of the article intensified, *NEJM* published an "Expression of Concern" statement in December 2005[24] to apparently clarify the published record, reaffirm the journal's ethical standards, and (perhaps) immunize the journal from criticism of any wrongdoing at a time in which plaintiffs' lawyers continued to seek multiple, multimillion dollar settlements from Merck. In publishing this statement, the journal gained even more publicity (most of it positive) for itself. This is just one example in which it does not appear to matter what journals or editors do or say about COI involving pharmaceutical companies: they can benefit on multiple fronts. Yet, when it relates to the public criticism of pharmaceutical companies, few consider this angle: Journals can have financial and reputational COIs when dealing with COI issues.

A group of contemporary journal editors, joining forces as the International Committee of Medical Journal Editors (ICMJE), attempted to remediate some of the many ills affecting industry/journal relationships. The ICMJE formulated guidelines on registering and publishing results of prospective human trials, fueled by a perception that pharmaceutical companies were publishing their favorable results more often than their unfavorable results. Debate about the validity of this concept and who is at fault (whether pharmaceutical companies were failing to pursue publication of positive and negative trials with equal vigor or whether journals were selectively publishing positive trials in an effort to boost journal ratings) persists today. Despite this, the ICMJE guidelines have been well-received and highly regarded. To date, the ICMJE members have published 4 editorials, the content of each disseminated on the ICMJE's unrestricted Web site[25-28] and additionally print-published in multiple journals[29-78] for a total of 50 print publications. Ironically, in engaging in this pattern of repetitive publication, it appears that the ICMJE authors behaved in a manner they would not tolerate in industry-affiliated authors or organizations. Perhaps the ICMJE authors (like some of the authors they criticize) just wanted to make sure their important message reached a broader audience.

Despite the collective efforts of the ICMJE to systematically address industry/journal problems, some ICMJE component journals and other journals[6] have taken additional steps aimed at industry's interactions with journals. For example, in 2005, the editors at *JAMA* dictated, and in 2008 reaffirmed, that authors of industry-associated research now need to have their data analysis confirmed by an outside, independent source.[79,80] This requirement, as discussed by Hirsch[6] and by Rothman and Evans,[81] does not apply to investigators independent of "for-profit" companies. In 2008, *JAMA* editors added to this data-analysis regulation a list of 10 rules applicable to industry-related manuscripts submitted to the journal, introducing the list with the statement, "As a beginning, we propose the following."[80] One wonders what will come next.

It is curious that journal editors have acquired such a low threshold for publishing rules to address industry-related COI, yet have less interest in addressing other meaningful forms of COI that result in contamination of the medical literature.[6,29-40] The reason for this is unclear, but perhaps a self-promoting herd mentality is to blame: the professional and social actualization that editors gain by uncritically joining forces with other editors may represent an irresistible temptation. This possibility is intriguing, particularly when viewed in terms of the ICMJE members' own definition of COI: "…conflict of interest exists when an…editor ...has relationships with other persons or organizations that inappropriately influence [bias] his or her actions."[29-40]

Hirsch[6] suggests that, regardless of the origins, it is inappropriate for editors to apply one set of rules for one demographic group and another set of rules for others; instead, pharmaceutical companies, authors, journals, and editors should be held to the same standards. Specifically, we should not tolerate behaviors in one group that we would disapprove of in another. With this as background, it is noteworthy that, of more than 7300 indexed articles, editorials, commentaries, and letters on COI, we have heard little of the criticisms raised by Hirsch. Could this be because editors and journals have not allowed dissenting views to enter the pages of their journals, or do authors feel that irritating the editor during attempts to publish such views could

result in reprisals? Some evidence suggests that both these issues may be occurring. If allegations recently published in the media and blog reports[82-84] on the interactions of Dr Jonathan Leo of Lincoln Memorial University and *JAMA* editors are to be believed, editors' obstruction to criticism and authors' fear of reprisals may indeed have a bearing on the balance of critical comments in the indexed literature. These allegations were expounded on in a March 20, 2009, *JAMA* editorial, initially released as an e-publication before print, but subsequently withdrawn electronically and not yet printed[85] (last verified using Google, PubMed, The DOI System, and the *JAMA* Web site on August 17, 2009). The collective reports about Leo identify not only an alleged problem but also a solution: Investigators and authors who wish to bypass any obstructing and behaviorally inappropriate editors and journals can use Internet resources. The current information revolution has brought with it a host of methods that should prevent any individual or small group of individuals from controlling the dialogue on either side of the COI discussion.

It is in the spirit of opening doors to additional conversation on COI that *Mayo Clinic Proceedings* publishes the article by Hirsch.[6] The journal anticipates and encourages letters to the editor on this topic. A panel of reviewers, a technique we have used previously, will review all letters collectively, and the decision to publish a letter will be based on its insights and novelty, not its point of view. It is hoped that through these efforts some heretofore unheard souls will provide insights on how all parties can do a better job of managing COIs at biomedical journals and championing the integrity of journals' actions and content.

William L. Lanier, MD
Editor-in-Chief

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