

Conflicts of Interest in the Development of New Interventional Medical Devices

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Abbreviation: NIH = National Institutes of Health

INTRODUCTION

THE Standards Division of the Society of Interventional Radiology (SIR) recently created the Emerging Technologies Workgroup of the Technology Assessment Committee for the “dissemination of knowledge of groundbreaking information to potential researchers in interventional radiology.” Committee members are requested to determine new technologies and innovations that may become of particular importance to interventional radiologists. Many of these innovations are developed, supported, or promoted at least in part by the medical devices industry. Consequently, cooperation between physician researchers and in-

dustry will always have a vital role. However, there is increasingly vigorous debate concerning the role, ethics, and impact of medical industry in health care (1,2). One must therefore consider the implications for a relatively novel medical field such as interventional radiology that is characterized by brisk innovation and intimate collaboration with industry, else others outside of the specialty such as the media may take the lead.

In the present document, our goal is to further develop this discussion specific to interventional radiology. We will review some of the major data for and against increased physician–industry collaboration. Our goal is not to provide a set of guidelines for ethical collaboration; however, it is possible that guidelines could become warranted in the future. Finally, although most of this document will focus on physician–industry collaboration, readers should note that this discussion also applies to the independent physician–inventor who is not supported by industry. In fact, it applies to anyone in a patient-care position involved in a venture that may result in their personal gain. This personal gain may take obvious forms such as monetary gain or lavish entertainment, but can also be less tangible gains such as academic promotion or fame.

THE CASE AGAINST INCREASED COLLABORATION

The debate over conflict of interest has taken on an urgency within the past 15 years, as it has been brought to attention in the lay press and in medical

meetings around the globe. The debate has further changed from one based on opinion to one based on research.

A problem is realized when a conflict of interest leads to a loss of objectivity in patient care (eg, prescribing pattern or use of medical devices). This loss of objectivity has been demonstrated. Orłowski and Wateska (3) examined the impact of all-expenses-paid trips to popular sunbelt locations to attend symposia sponsored by pharmaceutical companies, and found that physician attendees’ prescribing patterns for the medications being promoted changed significantly after the symposia despite the attendees’ opinion that such symposia would not alter their prescribing behaviors. Lurie et al (4) found a similar effect of much less extravagant interactions: 25% and 32% of faculty and house staff, respectively, stated that they changed their prescribing practices at least once based on contact with pharmaceutical sales representatives. There are also published data demonstrating associations between requests made by physicians for additions to hospital drug formularies and their likelihood of having met with pharmaceutical sales representatives and/or accepting monies to attend or speak at educational symposia or to perform research (5). A systematic review of 538 studies published between 1994 and 2000 (6) reinforced the impact of contact with pharmaceutical sales representatives on practice behaviors.

The effect of collaboration on publication has also been shown. In a widely publicized paper in the *New England Journal of Medicine*, Stelfox and colleagues (7) examined the impact of physicians’ financial relationships with the

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pharmaceutical industry on their publication record with respect to calcium-channel blockers, which, at the time, were quite controversial. Published studies were categorized as supportive, neutral, or critical of calcium-channel blockers. Authors publishing supportive articles on calcium-channel blockers were significantly more likely to have financial relationships with manufacturers of calcium-channel blockers than authors publishing neutral or critical articles (96% vs 60% vs 37%, respectively; $P < .001$). Perhaps even more important than conflicts of interest among those publishing individual trials are conflicts of interest among those creating widely disseminated clinical practice guidelines, as these are intended to influence the practice of a large number of physicians. A cross-sectional survey of 192 authors of 44 clinical practice guidelines endorsed by European and North American societies on common adult diseases published between January 1991 and July 1999 (8) found that 87% of authors had some form of interaction with the pharmaceutical industry, 58% had received company financial support to perform research, and 38% had served as employees or consultants for a pharmaceutical company. Most clinical practice guidelines authors (59%) had relationships with companies that produced drugs considered in the guideline they authored, yet 55% indicated that the guideline process had no formal process for declaring these relationships. Specific statements regarding conflicted personal financial interactions were published within the print version of the clinical practice guidelines in only two cases, and 19% of respondents believed their coauthors' recommendations were influenced by their relationships (8). This discussion may then be extended to include session moderators at specialty societal meetings, societal representatives, and so forth.

The fact that the majority of influential manuscripts testing the impact of physician-industry collaboration on practice and publication patterns has involved the pharmaceutical industry should not belie the fact that such collaborations in the radiologic and medical devices industry occur and may be similarly problematic. There are indeed many examples of conflicts of interest involving the medical devices industry that have been followed by the media,

and we will briefly describe three of them. Given the controversial nature of this topic, we will attempt to avoid mentioning physicians by name as much as possible. If the reader is interested in additional details, we have included specific references where appropriate.

BusinessWeek recently reported a story about a large annual interventional cardiology meeting (9). A live demonstration was performed in which a cardiologist inserted an experimental device. Thousands in attendance watched as the procedure proved unsuccessful. The satellite link was cut before the patient died the same day. The founder of the annual meeting was also a cofounder of the company that invented the featured device, which was later sold to a biomedical company. This individual made a reported \$6 million from the sale, and would have earned an additional \$1.5 million if the product achieved established milestones (including an unspecified number of patients successfully treated). Some subsequently questioned if his financial stake played a role in the promotion of the product at the conference. One company CEO, wishing to remain anonymous, complained to the *BusinessWeek* reporters that the projects with which the individual was associated received "exaggerated attention."

A second example hits closer to home, and involved the first and corresponding author of a major trial published in the *New England Journal of Medicine* (10). At the time, the investigator worked at the Cleveland Clinic. The trial compared surgical endarterectomy with carotid artery stent placement with use of neuroprotective devices. As per his disclosure within the journal, the individual was the inventor of the device used and helped establish the company that developed it. The company was sold to a major biomedical company in 1999 for \$40 million. In his declared conflicts-of-interest byline at the bottom of the manuscript, the individual listed his conflicts as follows (10):

Dr. [XX] is the inventor of the [Company A] embolic-protection device used in the [XX] trial and was a shareholder in [Company A] at the time of its purchase by [Company B] in 1999; he does not now own any shares of stock in [Company B].

The individual's contract with the Cleveland Clinic was not renewed sub-

sequently in 2006 for failure to comply with the Clinic's conflicts-of-interest policy regarding his association with Company A (11). After several investigative reports, a detailed exposé by a reporter for the Cleveland *Plain Dealer* reported that the individual did not disclose that he continued to benefit from the sale of the device by a 1% royalty fee (11). The individual claimed that he did not realize he was still receiving these royalty payments, and would donate the proceeds to charity. He then sued the Cleveland Clinic, accusing the Clinic of discrimination and of damaging his reputation (12). He also accused other physicians (by name) at the Clinic of having unreported substantial conflicts of interest, brushed aside as "oversight" (11,13). There were other reported conflicts of interest and problems involving the individual's trials of the device involving patient enrollment, inclusion/exclusion criteria, patient follow-up, and timely adverse-event reporting; these led to warnings from the Food and Drug Administration in 2005 and, some believe, by former *New England Journal of Medicine* editor Jerome Kassirer (11) that investigators must be diligent about declaring apparent and real conflicts of interest. The individual was not the only one with a potential conflict of interest in the publication of the trial. This publicity came at a bad time for the Cleveland Clinic; its CEO at that time had to step down as a board member of AtriCure, Inc., as that company's devices were being used within Cleveland Clinic trials.

The third example demonstrates financial risk on the part of companies. In late 2007, United States federal prosecutors in New Jersey announced that they had reached a \$311 million settlement with several orthopedic medical device implant companies. Biomet, Johnson & Johnson unit DePuy Orthopedics, Smith & Nephew, Plc., and Zimmer Holdings, Inc., were to pay the funds as a result of a Department of Justice investigation into physician kickbacks (14). In some cases, surgeons were apparently paid up to \$200,000 per year for very little or no work; in other cases, lavish dinners or trips were apparently used to foster surgeon loyalty (15). An additional company, Stryker Corporation, was not required to pay a settlement, but agreed to certain reforms, including 18 months of monitoring in lieu of fines. The compa-

nies involved subsequently posted their payment rosters online, which included names of physicians and amounts received (16).

Despite numerous examples of conflicts of interest within the medical devices industries, there has been sparse actual research on these themes within radiology. Brown et al (17) demonstrated that those with financial relationships with industry presenting at the 2003 Radiological Society of North America (RSNA) meeting were more than twice as likely to be discussing non-FDA approved use of a commercial product than those without industry-relationships. However, this demonstrated that there was potential for hazardous influence, not that such influence in fact had occurred.

Regardless, the evidence would seem quite strong that physician–industry collaboration and related conflicts of interest have a very real potential to influence physicians’ practice patterns and their choice of devices, often without physicians themselves realizing their effect.

STIFLING PROGRESS? THE CASE AGAINST INCREASED REGULATION

The National Institutes of Health (NIH) is one of the world’s foremost biomedical institutions, with more than 18,000 employees and \$28 billion of funding to support approximately 325,000 outside researchers (18). Its approach to researcher–industry interaction has varied over the years. Before 1995, the NIH enforced rigid limitations on its employees (19). When Harold Varmus became the NIH director in 2005, he was charged with improving the recruitment and retention rate of the top scientists, and improving the quality of NIH’s in-house research. Most would agree that he successfully achieved both by easing restrictions on scientist–industry collaborations 2 years after taking office while helping to convince the United States Congress to double the NIH budget (19). For many, this was convincing evidence in favor of less stringent regulation.

The tables were then turned at the NIH. Following a series of articles in the *Los Angeles Times* beginning in December 2003 on consulting honoraria from pharmaceutical companies to prominent officers of the NIH (20,21), the

then- and current Director of the NIH, Elias Zerhouni (himself a radiologist by training and former chairman of the Department of Radiology at Johns Hopkins University [22]), made a series of sweeping reforms placing significant limitations on interactions between NIH scientists and industry (23). The resultant backlash was fierce (24–26), with many encountering difficulty in hiring new scientists.

Following this policy reversal at the NIH, Tom Stossel, a hematologist at Brigham and Women’s Hospital in Boston, wrote a passionate rebuttal against regulation of academic–industrial research (27). Stossel (27) noted that many of the major advances of 20th-century medicine, including development of the Hepatitis B vaccine (28), would not have occurred without partnership between academic research and industry. He hypothesized that, had such restrictive limitations on collaboration been in place during the 1970s and 1980s, the growth of the biotechnology industry may have been severely crippled. Stossel (27) believed that relatively rare scandals (eg, 29–33) more recently have driven much of the current regulation-heavy frenzy, and that proponents of increased regulation make three basic arguments:

1. Academic–industrial interactions promote research misconduct;
2. Commercial involvement results in bias in the interpretation of research data, limitation of academic freedoms, and violation of fundamental values accepted by researchers; and deterioration of the quality of research (34); and
3. Public trust in and support of research will erode (35).

As Stossel (27) points out, there are data or persuasive arguments in contradiction of each of these arguments. There are NIH-generated data demonstrating no increase in the rate of accusations of scientific misconduct by academic institutions (36), and the death rate within industry-sponsored phase I cancer trials has not changed within the past decade (37). One could argue that the highly cited report by Stelfox and colleagues (7) that showed that researchers publishing in favor of calcium-channel blockers were more likely to collaborate with pharmaceutical companies may be explained by these re-

searchers being simply more attuned to the truth, as subsequent work has demonstrated their opinion to be closer to the truth. Overly restrictive institutional policies may harm academic freedoms more than collaboration (and contractual agreements) with industry, and previous surveys have shown that the public believes there should be more collaboration, not less, and that the majority of the public believes that scientists should be able to benefit financially from their discoveries (27,38). In 2004, the *Canadian Medical Association Journal* instituted a new policy restricting submissions for certain types of manuscripts (reviews and commentaries) from authors with significant conflicts of interest (39). A subsequent letter to the editors from Steve Arshinoff (40), a well published ophthalmologist in Toronto, decried the new policy as essentially eliminating the potential contribution of many “experts.” This, of course, is a risk—those most knowledgeable and published within a particular field will have valuable contributions to make, but will also be the same experts sought after by industry for guidance and/or collaboration. Who has the right to decide if one is able to perform both functions?

Finally, where should the line be drawn? The approach of many journals, as well as that of the International Committee of Medical Journal Editors (41), is to simply list the potential or real conflicts of interest. A similar policy applies for accredited scientific meetings. This is often where it stops, ie, there are minimal consequences of conflicts of interest. A recent editorial in the *Canadian Medical Association Journal* listed many other types of conflicts of interest besides monetary, including an example of a radiologist who interprets positron emission tomography scans as having a conflict of interest when publishing positive positron emission tomography trials (42). If all researchers in such situations were to be restricted in chairing meetings, submitting manuscripts, and so forth, would any expert be left?

IN DEFENSE OF COMPANIES’ MOTIVATIONS

Numerous articles have been published on the potential risks of physician–industry collaboration. Numerous (albeit fewer) articles have been published defending such collaboration in

lieu of the medical advances enabled. Virtually no articles have been published defending the motivations and actions of companies in these collaborations. This is probably unfair.

Companies in any field have the primary objective of generating income and expanding. They must rely on and optimize product quality, supply and distribution, and product promotion. In medicine, it is generally the strategy of product promotion that comes under fire in these discussions. Medical companies will often be criticized by at least a significant minority for any form of direct promotion they attempt, be it to patients, physicians, or government/medical regulatory bodies or societies. Yet the popular media will soundly laud a resurgent computer company with a strong advertisement portfolio. The difference appears to lay only in the type of industry: because medical companies deal with the public's health, the prevailing view appears to be that physicians should be protected from any sort of outside industrial influence.

Medical companies and the physicians with whom they work should be proud of the many advances they have primarily developed, supported, or facilitated. They have provided crucial support for fledgling specialties, including those of interventional radiology. Some might argue that the reputation of medical companies is unduly tainted by a relatively low number of scandals and unfortunate events. There are examples in which medical industries have made their own attempt to self-regulate, and created their own sets of rules governing interaction with physicians (43). There are also surely peevish and complaints, which are common to many medical industry companies, that are rarely put into words publicly for fear of how their articulation would reflect on their companies. There are likely many company representatives who have had to deal with overbearing physicians—in some instances, it is the physician who is “pushing the envelope,” attempting to take advantage of their position as a consumer of a company's wares to obtain free gifts or some sort of support. Without complying with the physician's demands, the company may fear losing the patron's business to a competing company.

CONCLUSION

There is substantial evidence demonstrating the effect of physician–industry collaboration (and monetary rewards) on publication results in other fields. Conversely, without physician–industry collaboration, many technologies and devices currently in mainstream use would not have been developed. In addition, without industry support, interventional radiology as a medical specialty would probably be less advanced than it is today.

A clear balance is necessary. Physicians and industry must strive to clarify a working relationship that ensures that physician–industry collaboration and conflicts of interest do not (i) harm patients, (ii) cloud the judgment of the treating physician, and (iii) waste public funds by using drugs or devices that are no better than less expensive alternatives. However, the methods and standards by which these are measured, as well as the consequential formal regulations necessary, are not as clear.

Perhaps the stage of this debate within a medical field is a marker of its maturity: well developed fields such as internal medicine have well developed guidelines on physician–industry collaboration and support. Interventional radiology is still relatively young, and may therefore require more time to develop its own discussion and resultant approach. In the meantime, the field will be subject to formal governmental and granting agency regulations (most recently, the Physician Payments Sunshine Act [44]). This may or may not be sufficient. If nothing else, we must at least agree that physicians demonstrate a level of awareness of these issues and maintain ethical conduct that is independent of (or in addition to) any sort of outside regulation.

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