The Legal and Ethical Issues Surrounding Financial Conflict of Interest in Orthopaedic Research

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Ethics in Practice

The Legal and Ethical Issues Surrounding Financial Conflict of Interest in Orthopaedic Research

By Kanu Okike, BA, and Mininder S. Kocher, MD, MPH

Case 1. An orthopaedic surgeon publishes a paper featuring a positive evaluation of a new medication to prevent deep venous thrombosis. The surgeon serves as a paid consultant to the drug manufacturer.

Case 2. An orthopaedic surgeon is asked by a medical device company to conduct a study evaluating a novel total hip prosthesis. The device manufacturer assumes responsibility for funding the study and publishing the results.

Case 3. An orthopaedic surgeon has developed a novel synthetic tendon graft, which she hopes to market after obtaining approval from the United States Food and Drug Administration (FDA). She seeks to enroll one of her patients in a clinical trial of the graft.

Conflict of interest has been defined as "a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)."[1] Within the field of medicine, financial conflict of interest may play a role in clinical practice, continuing medical education, or academic research. This article focuses on conflict of interest in orthopaedic research.

In the research setting, financial conflict of interest may occur when an investigator conducts research that is related to the interests of a company from which he or she receives funding, or a company in which he or she has stock or ownership interest. The subject has attracted substantial media attention in recent years, due in part to scandal[2-5] and tragedy[6].

Conflict of interest as it relates to medical research has also received considerable attention in the medical literature[7-15], and with good reason. Industry provides 60% of all funding for biomedical research[16] and 70% of the money required for clinical drug trials[8]. Furthermore, fully one-quarter of all biomedical investigators receive research funding from for-profit companies[17]. Among the orthopaedists who presented research at the 2002 Annual Meeting of the American Academy of Orthopaedic Surgeons (AAOS), 32% had a financial conflict of interest to report[18].

This high prevalence of corporate funding in orthopaedic research is not inconsequential. Studies have shown that industry-funded research is more likely to result in positive findings[17,19-23], more likely to restrict investigator behavior[17], and less likely to result in negative findings[20]. In addition to compromising the integrity of academic medicine, conflicts of interest may also threaten the welfare of clinical research subjects[24]. Government and professional organizations have responded with laws and guidelines to address conflict of interest in biomedical research.

Legal Implications

The government of the United States ushered in the current era of cooperation between academia and industry with the passage of the Bayh-Dole Act of 1980, which encourages academic partnership with industry and allows universities to patent innovations that have been developed with federal funds[25]. The first attempts to regulate the resultant conflicts of interest in academic medicine occurred close to a decade later when, in 1989, the United States Department of Health and Human Services (DHHS) proposed an extensive set of prescriptive guidelines[26]. However, widespread condemnation by the medical community of the intrusive nature of this policy led to its swift retraction[10].

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Beginning in 1995, all investigators applying for funding from the United States Public Health Service (PHS) agencies, including the National Institutes of Health (NIH) and the Centers for Disease Control (CDC), were required to disclose to an appointed university official all "significant" financial interests that would "reasonably appear to be affected by the research." In this case, "significant" was defined as more than $10,000 or 5% equity in a company[27]. Three years later, any investigators who were applying to the FDA for approval of a new drug or device were required to disclose "significant" financial interests in the sponsoring company; for this purpose, "significant" was defined as more than $50,000[28].

It was not until May 2004 that the federal government issued guidelines that specifically addressed conflict of interest in research involving human subjects. In *Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection,* the DHHS urged investigators to provide financial conflict-of-interest information when obtaining informed consent, and recommended that informed consent be obtained by someone without such a conflict[29]. However, that document emphasizes that these recommendations are "nonbinding" and, as such, amount to little more than a series of suggestions that institutions, institutional review boards, and investigators might consider. A leading health-policy expert has described the document as notable for the "qualified nature of its recommendations, which are not backed by any regulatory authority."[24]

To date, the government has yet to pass any law that regulates financial conflict of interest in biomedical research. The Fair Access to Clinical Trials Act, which was considered in the House and Senate in 2004 and again in 2005, focuses primarily on the mandatory registration of clinical trials[30-33]. However, the Senate version of the bill would also prohibit research contracts that give industry the ability to limit or unreasonably delay the presentation or publication of results[31,33]. The measures had not been passed at the time of this writing, however, and future prospects appear uncertain at best.

Thus, current federal guidelines require disclosure of competing interests to institutions and regulatory agencies, while the responsibility for managing financial conflicts of interest is left in the hands of individual universities. Unfortunately, university conflict-of-interest policies vary widely among institutions and have been found to lack specificity[34,35].

It should be noted that although federal guidelines do not require disclosure of financial interests to research subjects, at least one court has found a physician-researcher liable for not doing so. In *Moore v. Regents of the University of California* (1990), the court ruled that a physician has a fiduciary duty to disclose to his or her patients any relevant interests, including financial, that may affect the medical judgment of that physician[36]. More recently, Alan Milstein brought suit against the University of Pennsylvania on behalf of the parents of Jesse Gelsinger, an eighteen-year-old man who died during a gene-therapy experiment in 1999[37]. In his complaint, Milstein argued that the failure of the defendants to notify Gelsinger and his family that the researchers and the University stood to profit from the experiments represented a failure to obtain informed consent[38]. The University of Pennsylvania settled for an undisclosed amount one month after the complaint was filed[39]. Milstein has proceeded to file a number of other lawsuits against clinical researchers—at least two of which included charges of failure to disclose financial interests—but none have gone to trial, which has made it difficult to assess the validity of this approach.

Ethical Implications

Medical journals were perhaps the first to develop specific policies to address conflict of interest in medical research. The *New England Journal of Medicine* began requiring disclosure of funding sources in 1984[40], and *The Journal of Bone and Joint Surgery* followed one year later[41]. Recently, medical journals have also taken steps to address industry suppression of negative results. In particular, the International Committee of Medical Journal Editors has mandate that all clinical trials be registered with an approved entity (such as www.clinicaltrials.gov) at the time of study inception to be eligible for publication[42]. It is believed that prospective registration of clinical studies will make it more difficult for industry to suppress negative results.

Professional organizations have also sought to address financial conflict of interest in medical research. The AAOS, for example, promotes a policy that centers on disclosure:

> "An orthopaedic surgeon reporting on clinical research or experience with a given procedure or device must disclose any financial interest in that procedure or device if the orthopaedic surgeon or any institution with which that orthopaedic surgeon is connected has received anything of value from its inventor or manufacturer."[43]

The American Medical Association (AMA), in addition to requiring disclosure, prohibits remuneration not "commensurate with the efforts of the researcher" as well as the purchase or sale of stock belonging to the company for whom the investigator is performing research. The policy also recommends that individual medical centers take the initiative to develop "specific guidelines for their clinical staff."[44]

Guidelines for ethical conduct have also been proposed by representatives of the drug and device industries[45,46]. In 2004, for example, the Advanced Medical Technology Association (AdvaMed) issued a "Code of Ethics on Interaction with Health Care Professionals."[45] While the document focuses primarily on interactions between physicians and industry in the clinical realm, interactions in the research setting are considered as well. In particular, agreements with clinical investigators are described as being subject to guidelines governing arrange-

ments with consultants. The selection of research partners by industry should be on the basis of "qualifications and expertise," and not the volume of business that is generated. Also, contracts should include a written research protocol, and compensation should be "consistent with fair market value for the services provided."

Recognizing the heightened risk of harm in research dealing with human subjects, some organizations have also developed specific policies to address conflict of interest in clinical research. The AMA, for example, requires that investigators disclose all conflicts of interest to potential research subjects as part of the informed consent process. Furthermore, to properly differentiate between the role of a physician as a clinician and the role of a physician as an investigator, the informed consent of the subject is to be obtained by someone other than the treating physician. Physicians must ensure that the sponsoring company will not obstruct the presentation or publication of results, and that financial compensation is "commensurate" with research efforts. The policy also notes that it is "unethical for physicians to accept payment solely for referring patients to research studies."[47]

The most far-reaching guidelines published to date, however, have been those of the Association of American Medical Colleges (AAMC)[48]. The six main principles of this policy can be summarized as follows:

1. With regard to research done on human subjects, all significant financial interests are potentially problematic and require close scrutiny.

2. Researchers with significant financial interests may be permitted to conduct research on human subjects under "compelling circumstances," subject to conditions imposed by a conflict-of-interest committee.

3. Significant financial interests should be fully disclosed to the institutional conflict-of-interest committee and updated regularly.

4. Institutional policies should be "comprehensive, unambiguous, well-publicized, consistently applied, and enforced through effective sanctions."

5. When compelling circumstances permit a researcher with financial interests to conduct clinical research, "rigorous, effective and disinterested monitoring" is crucial.

6. Individuals conducting research on human subjects must know the conflict-of-interest guidelines of their institution and must "act diligently" to fulfill the requirements.

While the policy defines "significant financial interests" in a manner similar to the 1995 PHS guidelines (see above, under "Legal Implications"), what is meant by "compelling circumstances" is left to the interpretation of the individual university. It is worth noting that "full disclosure…to research subjects and others" is listed as a possible requirement to be imposed by the conflict of interest committee.

Conclusions

Conflict of interest is common in orthopaedic research. The prioritization of financial interests over patient welfare or scientific objectivity is clearly objectionable. Ethical considerations require full disclosure of financial conflict of interest to research subjects, journals, and others and also require appropriate management of such conflicts by the institution. However, only disclosure is required by law. No attempts have been made to restrict the type or amount of financial conflict of interest that an individual researcher may have.

With regard to Case 1, an investigator may publish a positive evaluation of a drug manufactured by a company for which he or she serves as a paid consultant. However, this financial conflict of interest, as well as any others, should be fully disclosed when submitting the research for publication or presentation. When reading the resultant article, orthopaedic surgeons should bear in mind that the results of such studies are more likely to be positive regarding the item being evaluated.

With regard to Case 2, an orthopaedic surgeon may contract with a medical device company to conduct a study evaluating a novel prosthesis. The device manufacturer may provide funding for the research as long as it is *consistent with fair market value* and *commensurate with the efforts of the researcher*. The study should be registered at the time of its inception at www.clinicaltrials.gov or another similar registry. Finally, the investigator should not allow the device manufacturer to assume responsibility for reporting the findings, as this may allow the company to obstruct or unreasonably delay the presentation or publication of results (especially if they are unfavorable).

With regard to Case 3, the orthopaedic surgeon will have a significant conflict of interest in a clinical trial of the synthetic tendon graft that she has developed. According to AAMC guidelines, individuals with significant financial interests should not conduct clinical research unless "compelling circumstances" prevail. While this approach certainly represents a laudable goal, it may not be feasible at the current time. As such, the situation should be regarded as potentially problematic and should be closely scrutinized by the surgeon's institution. When seeking institutional review board approval, the conflict should be disclosed fully. One or more of the surgeon's patients may be enrolled in the trial, but the conflict should be fully disclosed to them and informed consent should be obtained by someone other than the surgeon (to differentiate between her role as a clinician and her role as an investigator).

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