

Institutional Conflict of Interest

Financial conflicts of interest in a research setting can adversely affect patient care, teaching, and research. Discussions of these conflicts ordinarily focus on issues that arise when individual physicians and biomedical scientists conduct research in which they have a financial interest.^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18} Less attention has been paid to the conflicts of interest that arise when health care institutions have a financial stake in the research conducted in their laboratories and clinics.^{19,20} This relative inattention persists despite the increased pressure on health care institutions to seek new sources of revenue to fund their activities and the government's encouragement of the commercialization of federally financed discoveries.^{20,21,22,23}

In this article we analyze the ethical issues related to institutional conflicts of interest, focusing our analysis by presenting a case that arose at a Harvard-affiliated hospital. All the details provided are the actual facts of the case, although the names of the hospital, biotechnology company, drug, and diseases involved in the case are omitted. Our inquiry is limited to situations involving clinical research and a financial interest in the form of a licensing agreement, but the analysis can be extended to include institutional conflicts of interest that involve basic scientific research and situations in which an institution has equity in a company that is developing a compound, process, or therapy.¹⁹

A Case of Institutional Conflict of Interest

In collaboration with scientists at a biotechnology company, two employees in a division of a Harvard-affiliated hospital developed a new drug. The employees subsequently left the hospital. The hospital granted the biotechnology company exclusive worldwide rights to the hospital's portion of the drug patent in return for royalties on sales and other payments. If the drug is found to be clinically beneficial, annual sales could total millions of dollars, and the hospital could receive substantial royalties. According to an agreement between the hospital and the employees who developed the drug, each employee receives 12.5 percent of the hospital's proceeds, 50 percent is allocated to the hospital's general-research fund, 12.5 percent goes to the department in which the drug was developed, and 12.5 percent goes to the division.

Investigators at the hospital propose two phase 1–2 clinical trials of the drug. In one trial, the drug would be given to patients with an exceedingly rare, universally fatal disease in which certain normal biologic products are lacking. The hospital is a national referral center for the treatment of patients with this rare disease and for research on it. The second trial would be a multicenter study in which the drug would be used to treat patients with a more common medical disorder. The hospital would probably enroll 20 of the 150 patients in the study.

Neither the proposed principal investigator for both trials nor any of her nearest relatives have any financial interest in the biotechnology company or derive a personal financial benefit from the drug patent. The principal investigator's department and division at the hospital receive proceeds from the drug's royalties. Also, a senior physician at the

hospital is a member of the biotechnology company's scientific board and a consultant to the company. Payments for his services to the company go directly to his department, not to him personally.*

Distinguishing between Individual and Institutional Conflicts of Interest

An institutional conflict of interest arises principally when an institution has equity in a company and investigators employed by the institution conduct research that could affect the value of the equity interest, or when an institution holds a patent on a compound, process, or therapy that it licenses to companies and investigators employed by the institution conduct research on that compound, process, or therapy. Institutional and individual conflicts of interest differ in three ways. First, when an investigator at an institution has a financial stake in a company and is conducting research sponsored by that company, the institution receives the company's payment for the research and monitors the work, but the size of the payment is not linked to the success of the research. Thus, neither the short-term nor the long-term financial interests of the institution are linked to the outcome of the research.

Second, when the institution has a direct financial interest, the institutional conflict of interest is mediated through individual investigators employed by the institution. A physician, nurse, or biomedical researcher actually performs the patient care or research activities. Yet because of pressure or their institutional roles, such investigators may be unwilling to object to the institution's practices.

Finally, when individual investigators pursue their own financial gain, there is no doubt that this constitutes self-interested behavior, and their personal motives may undermine their patient care, teaching, or research activities. Conversely, society recognizes that health care institutions need to obtain funds to carry out their missions and sanctions institutional pursuit of such funding. Society may not view this as self-interested behavior and consequently may erroneously be more tolerant of circumstances in which an institution's financial interests may compromise the integrity of its missions than of similar situations involving individual conflict of interest.

A Framework for Analyzing Institutional Conflicts of Interest

Institutional conflicts of interest must be evaluated in the light of four factors: the relation between an institution's primary missions and its financial interest, the size of the financial interest, the degree of discretion involved in achieving the primary missions, and the seriousness of the harms that might result from the institutional conflict of interest.

Conflict of Interest and Primary Missions

Health care institutions have three primary missions that are pursued for the benefit of the public: patient care, teaching, and biomedical research.^{1,2,3,5,8,10,11,12,16,17,18,19,24} There can

be conflicts among these missions when one institution pursues them.^{8,10,11,12,24,25,26} It is well recognized, for example, that clinical research can conflict with patient care. Our society has developed procedures, such as reviews of clinical trials by institutional review boards, to prevent or mediate these conflicts.^{25,26}

Health care institutions also have other goals and interests, including raising funds to support their missions and gaining recognition for their accomplishments. Institutional conflicts of interest are conflicts between the primary missions of a health care institution and its other interests.^{1,2,8,10,11,12,16,17,18,19} Although securing financial resources is important, it is only a means — albeit a very important one — to support and further the institution's missions. Consequently, the institution's legitimate interest in obtaining funds to support its activities must be considered secondary to its primary missions. Any conflict between secondary interests and primary missions needs to be examined to ensure that the primary missions neither are compromised nor appear to be compromised.^{1,2,8,10,11,12,16,17,18,19}

The Size of the Financial Interest

In the case of individual conflicts of interest, the amount of the financial interest is an important factor in determining whether the conflict is prohibited. Financial interests that are small are unlikely to have, or to appear to have, an influence on decisions about patient care, teaching, or clinical research.^{1,8,10,11,12} A similar view should prevail with regard to institutional conflicts of interest.^{1,19} There is, however, no absolute standard for what constitutes a de minimis (minimal) financial interest. Factors that should be considered in establishing a dollar figure for a de minimis interest include the value of the present and potential payments to the institution, the nature of the events that trigger the payments, and the size of the institution's research, discretionary, and operating budgets.

Professional Discretion in Patient Care and Biomedical Research

Both patient care and biomedical research, the basic elements of clinical trials, entail a high degree of professional discretion — for example, in determining whether a symptom is an adverse reaction and whether an adverse reaction is severe enough to discontinue the therapy and in establishing relevant end points for a trial. We should try to minimize, if not eliminate, circumstances in which financial interests may influence or even distort any of these judgments.^{1,2,3,10,11,12,16,17,18,19} It is also inevitable that professional judgments will appear to be affected by institutional conflicts of interest. Because any discretionary decision can be influenced by many factors, it may be impossible for external observers to determine what factors influenced a particular decision. Indeed, it may even be difficult for decision makers to be certain about their own motives and what factors influenced a particular decision. Thus, reasonable people may wonder whether financial motives have influenced decisions.

Potential Harm from Conflicts of Interest

Patient Care

In the process of obtaining informed consent from patients for participation in a clinical trial, physicians might fail to provide information of interest to the patients, such as the nature or magnitude of the institution's financial interest in the results of the trial. If the patients gave consent without this information, their right to informed consent might be violated, and their consent might be invalid.^{25,26,27,28} An institutional conflict of interest could also influence the investigators to ignore or minimize symptoms indicating adverse reactions, which in turn might endanger the health of the patients in the trial. Furthermore, the positive results of a clinical trial in which adverse reactions were ignored or altered could lead to the approval of a therapy with unreported adverse effects that could endanger the health of patients throughout the United States.

Teaching

A student, postdoctoral fellow, or other trainee might be encouraged to conduct research in which the institution had a financial interest even if that research was not the most beneficial to the person's education or career development. However, teaching is not likely to be seriously threatened by institutional conflicts of interest involving clinical research.

Biomedical Research

Investigators conducting a clinical trial of a compound, process, or therapy in which the institution had a financial interest could compromise the trial by using a poor or biased study design or by introducing bias into the data-collection methods, statistical analyses, or reporting and interpretation of the data. In addition, the conflict of interest could distort research priorities by affecting the distribution of essential research-related resources, including space and discretionary funds. Subtle pressure might induce clinical staff to encourage patients to participate in a clinical trial in which the institution had a financial interest, reducing enrollment in other clinical trials with similar eligibility requirements. Finally, the appointment or promotion of faculty members associated with the clinical trial in which the institution had a financial interest could compromise the integrity of the appointment-and-promotion process. Even though particular decisions, such as those concerning space allocation or promotion, might not actually be influenced by financial motives, they might be perceived by other investigators in the institution as reflecting a bias in favor of the clinical trial in which the institution had a financial interest, thereby undermining morale.

Institutional conflicts of interest also threaten the overall biomedical-research enterprise in the United States. If the public becomes aware that a substantial proportion of clinical research is performed in institutions with conflicts of interest, its confidence in and support of biomedical research may be eroded. Although a financial conflict of interest on the part of one health care institution will not alter the public's perception of the integrity of biomedical research in general, there is a cumulative effect. Moreover, the nation's leading health care institutions have a critical role in defining the norms for appropriate practices. Public confidence is most likely to be maintained if it is the exception rather

than the rule for health care institutions to have financial interests in the clinical research conducted under their auspices.

These are not just potential threats. The primary missions of health care institutions have been compromised by individual investigators with conflicts of interest.^{3,13,29} The most notorious example may be the Tseng case, in which an ophthalmologist at Massachusetts Eye and Ear Infirmary conducted a study of an ointment for the treatment of "dry eyes" while he owned 530,000 shares in the company that would have marketed the medication if the trial had been successful. There were many irregularities in the clinical trial, as well as manipulation of the release of data.³⁰

Prima Facie Claim to Avoid Institutional Conflict of Interest

In the light of these considerations — the importance of preserving the integrity of the primary missions of health care institutions, the role of discretionary judgments in clinical trials, and the potential harms from conflicts of interest — there arises a prima facie claim that such a conflict should be avoided and that a clinical trial should not be conducted in an institution that has a financial interest in the outcome unless that interest is de minimis.

Some might argue that these ethical problems could be overcome by prohibiting commercial links between health care institutions and companies. This position ignores three points: federal encouragement of health care institutions to commercialize their discoveries,^{20,21,22} the lack of alternative avenues for developing biomedical advances into safe and effective products,²⁰ and the increasing financial pressures on health care institutions. Prohibiting commercial links between health care institutions and companies would require substantial changes in federal law and the economic system for supporting the development of biomedical products. The possibility of such extensive changes seems remote.

Others might argue for an absolute prohibition on conducting clinical research at institutions with a financial interest in a product under study. Just as no rights are absolute, no prohibitions should be absolute. The ultimate objective of health care institutions is to advance the primary missions of patient care, teaching, and biomedical research for the public good. The purpose of regulating institutional conflicts of interest is to protect the integrity of these missions. However, in the unusual circumstance that a primary mission could best be realized at an institution with a conflict of interest, the prohibition imposed by the prima facie claim could actually have the paradoxical effect of preventing the realization of the mission. In this case, the public interest would be better served if the prima facie claim were overcome. For example, an institution with a conflict of interest might be the only appropriate site for a clinical trial because of particular facilities or expertise that could not be found elsewhere. But even if the prima facie claim were overcome, the threat posed by the financial interest would remain and therefore necessitate appropriate safeguards.

Safeguards against Harm from Institutional Conflicts of Interest

Disclosure

Any patient considering whether to participate in a clinical trial should be told about the conflict of interest, and the conflict must be stated on the informed-consent form. In addition, the institutional conflict of interest should be disclosed to others, including the institutional review board, collaborators and coinvestigators at other institutions, other funders that have supported the clinical research, readers of articles and abstracts that report the research results, and audiences at oral presentations of the research results. Other safeguards adopted by the institution should also be disclosed to the patient.

In theory, disclosure to the patient might be unnecessary if the people involved in the care of the patient or the research were unaware of the institution's financial interest. Because it is both highly unlikely that these people would not know of the licensing arrangement and impossible to document who knows about the financial interest during the research, disclosure should be required in all cases. We recognize that disclosure of institutional conflicts of interest is not standard practice in informed-consent procedures and may be controversial,^{27,28} but it is consistent with the ruling in one well-publicized case.^{31,32} Moreover, disclosure of commercial relations is necessary for scientists to evaluate critically the merit of biomedical research.³³ Similarly, for patients to decide whether participation in a trial is in their interests, they must be able to evaluate the information they are provided, which necessitates the disclosure of institutional conflicts of interest.

Although disclosure has been the safeguard recommended most frequently, it is necessary but insufficient for several reasons.^{1,10,11,12,14} First, disclosure "only reveals a problem, without providing any guidance for resolving it."¹ Second, those who receive the information, especially patients, may not know how to evaluate it; in fact, the disclosure may only increase their anxiety during an already stressful period. Finally, health care institutions lack monitoring systems that can act on the basis of a disclosure of a conflict of interest. Universities, medical schools, and hospitals have begun to establish committees to monitor individual conflicts of interest,^{3,11,12} but there have been few efforts to establish similar committees for institutional conflicts of interest.¹⁹ Institutional review boards, collaborators, funding agencies, and journal readers are not organized to monitor or respond to disclosures of conflict of interest.

Internal Monitoring

Because internal reviews of patient care and research have been used to monitor individual conflicts of interest, a similar approach might seem appropriate for institutional conflicts of interest. Internal monitoring could be performed when an institutional review board, ad hoc committee, or chief of service reviewed the patient care and research data and analysis associated with a clinical trial.

Such an internal review seems insufficient. Because of their responsibility for the financial condition of the institution, officials may not be disinterested in their judgment. Furthermore, money is fungible; every administrator, chief of service, and investigator could therefore benefit from the institution's proceeds from a commercial license, even if

they or their departments did not receive the funds directly. To maintain public confidence, monitoring must operate independently of those who have responsibility for the institution's financial condition or who, in their professional roles, could benefit from increased revenues.

The institutional review board, which does not have primary responsibility for the financial condition of the hospital, has members from outside the institution, and has a mandate to review research protocols, might appear to be more independent. Yet, some members of the board might work for the department that stood to benefit financially from the clinical research, and others might benefit indirectly from the institution's royalties. Finally, the public perceives these boards as internal rather than external bodies. Just as citizens may be suspicious of the thoroughness of a government agency's review of its own behavior, there may be little confidence in an institutional review board's judgment when the institution has a financial interest in the research.

External Monitoring

External monitoring offers a final safeguard against the potential harm due to an institutional conflict of interest. If a trial is to be conducted at several centers, and none of the other institutions have a conflict of interest, then these institutions could provide a monitoring function that would be internal with respect to the trial but external to the institution with the financial interest. In one of the studies conducted by John Darsee, the multi-institutional aspect of the study resulted in the discovery of a fabrication of research results.^{34,35} However, the very possibility of a multicenter trial means that there are institutions qualified to perform the clinical research other than the institution with a financial interest, which in turn means that there is no compelling reason to overcome the prima facie claim and have the trial conducted at the institution with the conflict of interest.^{1,10,11,12}

Alternatively, a committee composed of people outside the institution could be formed to review the research design before the commencement of the trial and regularly review all data related to the research. This external committee should have the authority to require modifications of the research or even stop the trial. The chair and members of the committee should be sufficiently removed from the institution so as not to be subtly influenced by the interests of the institution or its members and yet sufficiently knowledgeable to review the research intelligently. To ensure that the committee members do not themselves have a conflict of interest, they should not hold stock in any company connected with the clinical trial and should receive no compensation for their monitoring activities (other than reimbursement for expenses). The membership of such a committee might include a biomedical researcher and an ethicist or lawyer, and the committee should have access to a statistician. Such an external monitoring committee, whose purpose would be analogous to that of peer review of articles submitted for publication and grant applications, would seem to provide the best safeguard.

External monitoring, however, has its own costs. For the committee members, the work would be time-consuming and professionally uncompensated, and it might put them in

the awkward position of criticizing colleagues. For the investigators at the institution itself, the external review could be quite time-consuming. The monitoring process might also create an adversarial relationship between the external reviewers and the institution's investigators. Nevertheless, in those few cases where the prima facie claim is overcome and a clinical trial proceeds despite an institutional conflict of interest, monitoring by an external committee would seem to provide the best safeguard.

Application of the Framework to the Case of the Harvard-Affiliated Hospital

The Harvard-affiliated hospital involved in this case has a substantial financial interest in the outcome of the clinical research, creating a prima facie claim that it should not conduct either of the clinical trials of the drug. In the trial involving the rare disease, however, researchers at the hospital claim that it may be the most appropriate site for the trial and perhaps the only institution capable of conducting the research. We are neither experts on this particular disease nor knowledgeable about all the special skills and facilities required to conduct such a phase 1–2 trial. However, a literature search seems to corroborate the researchers' claim. In the past 10 years, 19 original articles have been published on this disease, including 15 case reports and 4 reports on treatment. The hospital's research is the most recent, involves the largest number of patients, and constitutes the only therapeutic investigation of this disease conducted by a U.S. institution. Also, fewer than 50 cases of the disease have been reported, and the hospital may be one of the few referral centers that follows a sufficient number of patients to conduct a therapeutic trial. If the hospital does not conduct the trial, the public may be deprived of an effective treatment for this rare, fatal disease. To ensure that the public's interest in continued research on the disease is served, the hospital should probably perform the study, with appropriate safeguards.

Conversely, the prima facie claim should not be overcome for the multicenter trial involving a more common medical disorder. Hospitals other than the Harvard-affiliated hospital are well qualified to conduct the trial, and the number of patients that this hospital would contribute to the trial would be comparatively small. Although the multicenter nature of this trial does provide a safeguard against some of the threats posed by the institutional conflict of interest, it does not provide complete protection. The presence of safeguards does not mean that the public interest is better served by conducting the trial at the hospital that has a financial interest in the outcome.^{1,9,11}

Additional Regulation of Institutional Conflicts of Interest

Institutional conflicts of interest clearly exist. Public policies supporting technology transfer and the growing financial needs of health care institutions make it likely that these conflicts will become more frequent.²⁰ Yet we have no valid data on the dimensions of the problem or institutional responses to it. The paucity of data suggests the need for a study to document the frequency of institutional conflicts of interest and the existence and efficacy of institutional policies regulating them. If there are problems that institutions are not addressing properly, federal guidelines on institutional conflicts of interest might be

appropriate. Such conflicts arise almost exclusively in the development and clinical testing of compounds, processes, or therapies that require the approval of the Food and Drug Administration (FDA). Thus, an effective approach might be for the FDA to designate any data from clinical trials conducted at institutions with conflicts of interest as inadmissible evidence for the approval of a drug or device, unless there was sufficient reason to overcome the prima facie claim and appropriate safeguards had been implemented. Such a policy would result in uniform rules and interpretation of exceptions to those rules, with rigorous enforcement by a regulatory authority.

We recognize that this proposal would require more stringent regulation of institutional conflicts of interest than the recently proposed FDA regulations for individual conflicts of interest.³⁶ The stricter regulation is necessary because of the essential differences between institutional and individual conflicts. Before such federal guidelines were implemented, it would be important to evaluate their benefits as well as the burdens they would impose on health care institutions.

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