

CONFLICT-OF-INTEREST POLICIES FOR INVESTIGATORS IN CLINICAL TRIALS

BERNARD LO, M.D., LESLIE E. WOLF, J.D., M.P.H., AND ABIONA BERKELEY, J.D.

ABSTRACT

Background There is substantial concern that financial conflicts of interest on the part of investigators conducting clinical trials may compromise the well-being of research subjects.

Methods We analyzed policies governing conflicts of interest at the 10 medical schools in the United States that receive the largest amount of research funding from the National Institutes of Health. These institutions are Baylor College of Medicine, Columbia University College of Physicians and Surgeons, Harvard Medical School, Johns Hopkins University School of Medicine, the University of Pennsylvania School of Medicine, the University of California at Los Angeles School of Medicine, the University of California at San Francisco School of Medicine, the University of Washington School of Medicine, Washington University School of Medicine at St. Louis, and Yale University School of Medicine.

Results All 10 universities required that faculty members disclose financial interests to university officials. Only four required disclosure by all members of the research staff. Five universities required disclosure of all financial interests, even though federal regulations specify a threshold for disclosure. Six universities required disclosure to the institutional review board as well as to a committee on conflicts of interest or a university official. Four universities had stricter requirements for investigators conducting clinical trials than required by federal regulations. One university prohibited investigators from having stock, stock options, consulting agreements, or decision-making positions involving a company that sponsored the research. A second university prohibited researchers from trading stock or stock options in a company that sponsored the research or sold the product or device under study. Two universities ordinarily did not allow faculty members to participate in clinical research if they had what federal regulations refer to as a "significant" financial interest in the company owning the product or device being studied, but exceptions were allowed.

Conclusions Policies governing conflicts of interest at leading medical schools in the United States vary widely. We suggest that university-based investigators and research staff be prohibited from holding stock, stock options, or decision-making positions in a company that may reasonably appear to be affected by the results of their clinical research. Of the 10 medical schools we studied, only 1 had a policy that was close to this standard. (N Engl J Med 2000;343:1616-20.)

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PARTICIPANTS in clinical trials accept risks primarily to advance scientific knowledge. The recent death of a volunteer in a phase 1 trial of gene therapy has sparked concern that financial conflicts of interest on the part of investigators may compromise the well-being of research subjects.^{1,2} Furthermore, conflicts of interest may lead to bias in the conduct of clinical trials and may undermine trust in the results. We determined how 10 leading medical schools deal with potential conflicts of interest on the part of investigators conducting clinical trials. We paid particular attention to stock options, an increasingly common form of reimbursement by start-up companies.³⁻⁵

Federal regulations require investigators applying for funds from the U.S. Public Health Service to disclose "significant" financial interests in companies that might reasonably appear to be affected by the research.⁶ Such interests include stock and stock options totaling more than \$10,000, payments such as salary and consultation fees exceeding \$10,000 a year, and more than 5 percent ownership in any relevant company or other business entity. Investigators must also disclose the financial interests of spouses and dependent children. In addition, institutions must "manage, reduce or eliminate" any conflicts of interest, although they have considerable discretion in doing so.⁶

METHODS

We studied the conflict-of-interest policies of the 10 U.S. medical schools that receive the largest amount of research funding from the National Institutes of Health, according to a ranking by *U.S. News and World Report*.⁷ These institutions are (in alphabetical order) Baylor College of Medicine, Columbia University College of Physicians and Surgeons, Harvard Medical School, Johns Hopkins University School of Medicine, the University of California at Los Angeles School of Medicine, the University of California at San Francisco School of Medicine, the University of Pennsylvania School of Medicine, the University of Washington School of Medicine, Washington University School of Medicine at St. Louis, and Yale University School of Medicine.

In June and July 2000, we obtained information about policies on conflicts of interest in clinical research from the World Web sites of the 10 schools, because faculty members are likely to seek the information on the Web. To confirm that our data were

From the Program in Medical Ethics (B.L., L.E.W.), the Center for AIDS Prevention Studies (B.L., L.E.W.), the Division of General Internal Medicine (B.L., L.E.W.), and the Office of Student Affairs (A.B.), University of California at San Francisco, San Francisco. Address reprint requests to Dr. Lo at bernie@medicine.ucsf.edu.

complete and up to date, we contacted an official at each institution by telephone or e-mail. These officials were located in the offices for research affairs, research administration, contracts and grants, or compliance or in the institutional review board (IRB).

Because disclosure, regulation, and prohibition are the main policy options for dealing with possible conflicts of interest,^{8,9} we determined what disclosure was required, what financial arrangements required the university's approval, and what arrangements were prohibited. We analyzed the policies, in accordance with established legal principles for the interpretation of contracts and statutes.

RESULTS

The conflict-of-interest policies of the 10 institutions are summarized in Table 1.

Disclosure of Financial Arrangements

As required by the federal regulations, all 10 universities required disclosure of financial interests, including stock and stock options and income from salary, honorariums, and consulting fees. About half the universities did not require disclosure of equity or income below a certain threshold, usually \$10,000.

Five of the universities went beyond the federal regulations by requiring disclosure of all financial interests, regardless of their value.

All 10 university policies applied to full-time and part-time faculty. Reporting requirements for other investigators, such as research staff and trainees, varied considerably. Four policies applied to all research staff, and three other policies applied to selected research staff, generally those with "responsibility for the design, conduct, and reporting" of research. Only four policies applied to trainees.

All the institutions required disclosure of financial interests held by spouses and dependent children of investigators. One university extended disclosure to "de facto spouses," parents, siblings, and adult children. Two universities also required disclosure of any "trust, organization, or enterprise" over which the faculty member "exercises a controlling interest."

All 10 universities required disclosure to a university committee or official who would either approve the

TABLE 1. CONFLICT-OF-INTEREST POLICIES AT THE 10 MEDICAL SCHOOLS RECEIVING THE LARGEST AMOUNT OF FUNDING FROM THE NATIONAL INSTITUTES OF HEALTH.

| VARIABLE | MEDICAL SCHOOL | | | | | | | | | | TOTAL |
|---|----------------|-----|------|------|-----|------|-----|------|------|-------|-------|
| | A | B | C | D | E | F | G | H | I | J | |
| Interest that must be disclosed | | | | | | | | | | | |
| Stock | Yes | Yes | Yes* | Yes† | Yes | Yes† | Yes | Yes‡ | Yes† | Yes | 10 |
| Stock option | Yes | Yes | Yes | Yes† | Yes | Yes† | Yes | Yes‡ | Yes† | Yes | 10 |
| Income | Yes | Yes | Yes§ | Yes§ | Yes | Yes§ | Yes | Yes | Yes§ | Yes | 10 |
| Loan or gift | Yes | Yes | Yes | | Yes | Yes§ | | Yes | Yes§ | Yes | 8 |
| Decision-making position | Yes | Yes | Yes | | Yes | | | Yes | Yes | Yes | 7 |
| Person with interest requiring disclosure | | | | | | | | | | | |
| Faculty member | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Immediate family | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Selected research staff | | | | | Yes | | Yes | Yes | | | 3 |
| All research staff | | Yes | | | | Yes | | | Yes | Yes | 4 |
| Trainees | | | Yes¶ | Yes¶ | | | | | Yes | Yes** | 4 |
| Party to which disclosure must be made | | | | | | | | | | | |
| University official or committee | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Institutional review board | | | Yes | Yes | Yes | Yes | Yes | Yes | | | 6 |
| Research subjects | | | | | Yes | | | Yes | | | 2 |
| Professional community (in publications or presentations) | Yes | Yes | | | | | | | Yes | Yes | 4 |
| Prohibited interest | | | | | | | | | | | |
| Stock | Yes | Yes | Yes* | Yes† | | | | | | | 4 |
| Stock options | Yes | Yes | Yes | Yes† | | | | | | | 4 |
| Consulting fee | Yes | | Yes§ | Yes§ | | | | | | | 3 |
| Decision-making position | Yes | | | | | | | | | | 1 |

*Disclosure was required only if the financial interest exceeded \$10,000 per year for a publicly funded study, or \$20,000 for a privately funded study.

†Disclosure was required only if the financial interest exceeded \$10,000 per year or 5 percent ownership.

‡Disclosure was required only if the financial interest exceeded \$10,000 per year or 5 percent ownership for a federally funded study, or \$1,000 per year for a nonfederally funded study.

§Disclosure was required only if the financial interest exceeded \$10,000 per year.

¶The disclosure requirement applied only to research fellows.

||The disclosure requirement applied to research fellows and students.

**The disclosure requirement applied only to students.

disclosed financial arrangements or ensure that steps were taken to manage, reduce, or eliminate the conflict of interest. This requirement was consistent with the federal regulations. Six institutions also required investigators to disclose financial interests to the IRB, and two of the six required disclosure to research subjects. Four institutions required disclosure in presentations and published articles.

Prohibition of Certain Financial Arrangements

Four universities had additional requirements. University A prohibited faculty from having any financial interests, including stock options, consulting agreements, and decision-making positions, that involved a company sponsoring the study. However, such interests were permitted if they involved a company manufacturing the product or device being studied, as long as that company did not sponsor the trial. University B prohibited faculty and research staff from trading in stock or stock options in a company sponsoring the research or selling the product or device being investigated. This prohibition was to apply from the inception of the proposal or request to conduct research until a week after the results had been made public. However, researchers were permitted to own equity in such a company, as long as they did not trade it during the research period.

Universities C and D stopped short of prohibitions, but ordinarily did not allow faculty members to participate in clinical research if they had a "significant" financial interest in the company owning or licensing the product or device being studied. University C specified several exceptions to this presumptive ban. Investigators could hold stock or stock options valued at less than \$20,000 in a publicly traded company (or \$10,000 if the faculty member had a federal grant), provided that there was "complete independence" between the acquisition of the financial interest and the research. Cited examples of completely independent acquisition of an interest included a gift from a family member and an inheritance. In addition, exceptions to the presumptive ban were allowed for a newly recruited faculty member. At University D, although financial interests totaling less than \$10,000 were generally permitted, principal investigators were not allowed to hold any commercial interest in a company sponsoring their research.

Penalties for Noncompliance

The policies of seven universities specifically addressed violations of conflict-of-interest policies, such as failing to make a required disclosure or providing false, misleading, or incomplete information. The penalties included censure, suspension of grants and of IRB approval of studies, nonrenewal of appointment, and dismissal. The application of these penalties is discretionary; we did not collect data on actual penalties that have been imposed.

DISCUSSION

Research subjects, the medical profession, and the public rely on clinical investigators to act impartially and with integrity. In clinical trials, investigators make many judgments that may affect the safety of the subjects and the results of the trial, including whether a person is eligible to participate, whether a participant should receive a modified dose of a drug, whether an adverse event has occurred, whether an adverse event is related to the intervention, and whether an adverse event must be reported.¹⁰ These decisions are difficult to regulate or oversee, because they arise continually in all phases of a trial and require considerable discretion.

After a serious adverse event has occurred, such as the death of an asymptomatic volunteer, a research project is scrutinized. In retrospect, reasonable people may disagree with the investigators' design of the trial, interpretation of the data, or response to unexpected situations.^{2,11} Other scientists and the public must trust that investigators make such decisions solely on the basis of their professional judgment, without regard for personal gain.¹² Financial conflicts of interest may undermine that trust. Evidence of insider trading before the results of clinical trials are made public further compromises that trust.¹³ Thus, the policies that govern conflicts of interest in clinical trials may need to be stricter than those governing conflicts in laboratory research.

Conflicts of interest may occur whenever a person is entrusted with acting on behalf of others or in the public interest. In other professions, disclosure and regulation are regarded as inadequate in some situations, and sharply defined prohibitions are imposed.^{8,9} Judges may not hear cases in which they have a financial stake.¹⁴ Government officials may not participate in any matter in which they have a financial interest (e.g., stock ownership).¹⁵ Such prohibitions reflect the fact that in some situations, even the appearance of impropriety may damage public trust.

We found that current conflict-of-interest policies at medical schools vary widely and have substantial shortcomings in the context of clinical trials. University C allowed two problematic exceptions to its general stipulation that investigators not have a financial interest in the company developing the product being studied. These exceptions were for newly recruited faculty members and for family gifts or inheritances. There is no logical reason why a conflict of interest on the part of a new faculty member would be of less concern than a conflict of interest on the part of another faculty member. Any concern about recruiting faculty members would be better addressed by the adoption of uniform, strict conflict-of-interest policies by all medical schools.¹⁶ Regarding gifts and inheritances, the ethical issue is not how the stock was obtained but whether it may bias the investigator's role in the clinical trial. It is the financial interest it-

self that creates a conflict of interest, not the origin of the financial interest. University B prohibited investigators from trading stock or stock options during a clinical trial. However, investigators who hold but do not trade stock or stock options still have a serious conflict of interest, and they may profit after the trial has been completed.

Overall, we found that the conflict-of-interest policies at medical schools were substantially weaker than the policies that govern some industry-sponsored clinical trials. Some multicenter cardiology trials forbid investigators from owning stock or options in the company whose product is being studied¹⁷ or in the company sponsoring the study.¹⁸ The Global Use of Strategies to Open Occluded Coronary Arteries trial went beyond the prohibition of any financial equity, prohibiting in addition honorariums for speaking engagements, payments for consulting, and reimbursements of any kind from the corporate sponsors until one year after publication of the results.¹⁸ In the recent Heart and Estrogen/Progestin Replacement Study, the investigators (as well as members of their immediate families) could not have any financial interest in the sponsoring company, including ownership of stock or stock options (Hulley SB: personal communication). Similar prohibitions have been suggested by the American Federation for Clinical Research.¹⁹ Although such prohibitions may prevent researchers who have developed a product or technique from engaging in clinical trials to determine its efficacy and safety, they do not prevent the research from being conducted.

Our study had important limitations. Although we contacted officials at each university to check our data, it is possible that some of our information is inaccurate. Officials at five universities said they were in the process of revising their policies and, thus, may already be addressing some of the issues we discuss. In a particular case, an institution may impose stricter measures than those stated in the formal policy. Nonetheless, it is likely that the materials we found on the institutions' Web sites are similar to those that investigators at those institutions would obtain. In addition, we did not consider intellectual conflicts of interest, which are inherent in research and are not hidden.²⁰ We also did not consider clinical trials conducted without the involvement of a medical school. Conflicts of interest may be much more difficult to address in this context.²¹

Conflict-of-interest policies for federally sponsored researchers are currently being reconsidered.²² Universities have a special social role in training young scientists, providing care to patients recruited for clinical trials, making unbiased clinical recommendations, and developing social norms and professional values. Thus, we believe that university scientists who conduct clinical research should be held to a higher standard than researchers employed by commercial organizations.

On the basis of our findings, we suggest that university-based investigators and staff be prohibited from holding stock, stock options, or decision-making positions in a company that may reasonably appear to be affected by their clinical research. Of the 10 medical schools we studied, only 1 had a policy that was close to this standard. Three others went beyond the federal requirements, but in our view they did not go far enough. Rather than trying to manage or reduce these conflicts of interest, we suggest prohibiting them.

Operationally, this proposal would cover financial interests in the company sponsoring a clinical trial, the company that manufactures the product or device being tested, and the companies that manufacture competing products or devices. We believe these restrictions should apply to all members of a research team and to their immediate families, not just to investigators with responsibility for clinical decisions. These recommendations would not prevent investigators in clinical trials from having a grant or contract that supports their time or effort from the manufacturer of the product or device or from the sponsor of the trial.

We disagree with recent suggestions that prohibitions on stock, stock options, or decision-making positions be imposed only on investigators who are responsible for the selection of subjects, informed consent, or clinical management.^{2,23} Bias may also occur in the design of the study, the ascertainment of outcomes, or the interpretation of results.

Supported in part by grants from the Robert Wood Johnson Foundation and the National Institutes of Mental Health (MH42459) and by a Jane Shohl Colburn Student Research Fellowship.

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