Managing Conflicts of Interest in the Conduct of Clinical Trials

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NEW TRENDS IN CLINICAL RESEARCH

The interaction between medical research and for-profit corporations is not new, but it has expanded considerably in recent years. Some of the recent trends may accelerate the research process, particularly when large clinical trials are required. However, a renewed commitment to the application of high ethical standards is essential to ensure that societal trust in research is not eroded, subjects enrolled in trials do not become merely a means to an end, and medical research is efficiently translated into clinical advances that will benefit future patients. This article focuses on the analysis of conflicts of interest in the conduct of clinical trials in both academic and community-based settings. Specifically, it discusses how the roles of research scientists and clinical practitioners differ and the importance of ensuring that participants’ consent to enroll in clinical trials is not the result of confusion about the goals of an experimental treatment that may resemble clinical care. The article also discusses the potential conflicts of interest that can arise when clinicians stand to gain from enrolling their own patients as subjects in clinical trials and examines various instances in which disclosure of information regarding funding and compensation may serve to minimize such conflicts. This article emphasizes that to preserve the integrity of research and to protect the welfare of human subjects who enroll in trials, physicians should have adequate training in the conduct of research and be familiar with the ethics of research. When a physician has treated or continues to treat a patient who is eligible to enroll as a subject in a clinical trial conducted by the same physician, someone other than the treating physician should obtain the participant’s informed consent. Finally, the article addresses disclosure of financial incentives and related funding issues.

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See also pp 72 and 85.
demic centers; conversely, 60% of industry funding is allocated to community-based trials, which represents a 3-fold increase in less than a decade.6

The role of contract research organizations varies, but they are essentially networks that provide trial sponsors with access to hospitals, physicians, and their patients. Many are involved in direct patient recruitment and patient screening, others create and design trials, and others conduct trials. In some instances, they subcontract with site management organizations, which assist community physicians in enrolling patients and in reporting back to the contract research organizations.6 These companies enroll physicians and patients through extensive advertisements, including billboards, newspapers, radio and television, health fairs, community seminars and lectures, and direct mail. These organizations might encounter considerable conflicts of interest because they are paid by pharmaceutical companies that ultimately depend on positive trial outcomes and, therefore, their financial viability may be pitted against research integrity and the safety of research subjects.

Much of the research conducted through contract research organizations and site management organizations involves new drugs or devices for which Food and Drug Administration (FDA) approval is necessary and, therefore, is subject to a federal regulation known as the Federal Common Rule,7 which governs research involving human subjects that falls under the purview of federal agencies. Consequently, many industry-sponsored trials that are conducted in community settings undergo a review process similar to the one required of federally funded research performed in academic centers. However, rather than relying on academic institutional review boards (IRBs), sponsoring companies often choose to have their research protocols reviewed by independent boards,8 which generally are for-profit entities that are not part of larger organizations and whose board members are paid for their work. Although some commentators have argued that independent boards conduct their review more efficiently than IRBs affiliated with academic centers, others have expressed concerns that independent boards face financial conflicts of interest since their very existence depends on the continuous flow of protocols to review, which may lead them to use less stringent review standards.9

This new environment in which clinical trials are conducted received considerable attention in the spring of 1999 in reaction to 2 news articles that exposed the conflicts of interest encountered by many community-based physicians.10,11 Patients were described as “commodities, bought and traded by testing companies and doctors.”12 It was stated that even if recruiting physicians were not involved in conducting the trials, they were offered financial incentives simply to refer patients to investigators. In some protocols, finder’s fees and additional bonuses for reaching certain quotas within deadlines amounted to several thousand dollars per patient. In addition to the financial conflict of interest that could lead some physicians to refer patients to trials inappropriately, the articles also questioned the competence of physicians, both in terms of their ability to conduct clinical trials and simply to care for a patient population that did not fall within their specialty.12

Overall, many of the concerns that were identified a decade ago in the Council’s report13 have persisted and may have increased, according to recent commentators.6,14 Physicians currently involved in biomedical research face an important challenge. High societal expectations that the burden of disease and disability can be reduced through research, combined with continued growth in the budget of the National Institutes of Health (NIH), as well as increased research and development funding by the private industry, create an atmosphere in which there are few forces that moderate the research imperative. Furthermore, the familiar federal safeguards established to ensure the respect and safety of research subjects might have lost their clout. Recent examples of clinical trials suspended for potential breaches of ethical standards abound, many of them involving prestigious academic centers.15-20

A renewed commitment to the application of high ethical standards is essential to ensure that societal trust in research is not eroded, and that subjects enrolled in trials do not become merely a means to an end,21 and medical research is efficiently translated into clinical advances that will benefit future patients. To that end, the Department of Health and Human Services announced in May 2000 that various measures would be taken to enhance the protection of research subjects.22 Specifically, the Department of Health and Human Services was to undertake efforts to improve the education and training of clinical investigators and IRB members who receive funding from the NIH to ensure that they are trained in bioethics and in research of human subjects.23 A related policy was issued in June 2000 that required investigators receiving funding from the NIH to be educated in the protection of human research participants.24 The NIH also oversaw the development of a Web-based course, “Human Participant Protections Education for Research Teams.”25 In August 2000, the Human Subject Protection and Financial Conflicts of Interest Conference was held; subsequently, the NIH issued an interim guidance draft on financial relationships in clinical research.26

Although many of these measures continue to be directed primarily at academic centers, it is clear that equivalent standards must be extended to all settings in which research is now conducted to maintain a consistent level of integrity across the spectrum of clinical research venues.

CONFLICTS OF INTEREST: NATURE AND SCOPE

In law, the term conflict of interest is used primarily in connection with fiducialies.27 A fiduciary holds some form of power that is to be used for the benefit of another, based on specialized knowledge or expertise. The fiduciary relationship involves dependence, reliance, and

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trust and is held to the highest legal standard of conduct.28 Many aspects of the fiduciary relationship exist in the patient-physician relationship, which explains why physicians also have an ethical duty to avoid conflicts between their commitment to heal patients and their economic self-interest.29 Physicians’ conflicts of interest are not a new phenomenon. As noted by one commentator:

The problem of conflicts of interest began to receive serious attention in the medical literature in the 1980s. . . . Among the areas of concern are self-referral by physicians, physicians’ risk sharing in health maintenance organizations (HMOs) and hospitals, gifts from drug companies to physicians, hospital purchasing and bonding practices, industry sponsored research, and research on patients.30

In each of these cases, a “professional judgment concerning a primary interest . . . tends to be unduly influenced by a secondary interest.”31 In the case of medical research, 2 sets of primary interests can be identified: the subjects’ welfare and the scientific integrity of the data. Both may be compromised by the dual roles of physician/investigator and by the influence of financial incentives or other forms of personal gain.

Conflicting Roles: Physicians as Investigators

The roles of research scientist and clinical practitioner are very different.31 Investigators act to generate scientific knowledge that potentially will result in future therapeutic benefits. Practitioners are focused on the present health and welfare of patients. Notwithstanding the distinction between researcher and clinical practitioner, research can be designed primarily to yield scientific knowledge, such as phase 1 clinical trials, or may offer some direct medical benefit to subjects, such as some phase 3 clinical trials. In each, risks and potential benefits must be weighed and informed consent obtained from prospective subjects, after disclosure of all material information. Since subjects might misconceive the nature of a research project, particular attention must be paid when researchers offer some medical benefit that can be integrated easily into a course of treatment. Although subjects in these trials are offered a treatment of unproven efficacy, many mistakenly believe that they are receiving cutting-edge treatment guaranteed to improve their condition. This “therapeutic misconception”32 may be reinforced when subjects receive the experimental treatment from the same physician who has administered all of their care in the past, in contrast to being referred to a clinical investigator located in an academic setting with a reputation for conducting research.

This conflict of roles has received increased attention recently.33 In one article,34 the authors identify academic medical centers as a source of the blurring roles between clinician and investigator because medical students and residents are educated in a setting in which both functions, care and research, coexist. The authors caution that investigators themselves may succumb to a form of cognitive dissonance in trying to reconcile the scientific goals of research with patient care, leading to the conflation of language of medical care with that of research. This ultimately undermines the informed consent process. It also may lead investigators to circumvent strict enrollment criteria,35 or to bypass established randomization processes.36

The concerns stemming from the blurred roles of physicians working in academic centers may be of equal or even greater concern in community-based or private clinics if care and research coexist in settings that traditionally have been treatment-oriented. Some conflicts may be unique to the academic setting, where investigators compete for grants, promotions, and prestige. Other pressures, however, may be unique to the private and community settings, such as competing demands on time from regular patients.

Safeguards Against Conflicting Roles

When the scientific alliance between investigators and their subjects appears to overlap with the therapeutic alliance that bonds physicians and their patients,37 trial participants may become confused about the goals of a treatment that is experimental but resembles the care they ordinarily received. This may hold true despite the fact that research subjects have provided their informed consent to participate in a trial. Extensive literature demonstrates the shortcomings of the current informed consent process in the experimental setting.38-41 The informed consent might be compromised even further when the physician/investigator who is responsible for enrolling participants in the trial and obtaining their consent stands to gain financially from each participant who is enrolled. The physician/investigator may be less inclined to emphasize how the experimental treatment differs from the care that is ordinarily provided, the additional risks involved, or lack of direct benefit to the participant. Therefore, safeguards should be put in place to ensure the integrity of the informed consent process. In particular, the nature and source of funding and financial incentives offered to physicians must be disclosed to a potential participant as part of the informed consent process.

Also, the physician who has treated a patient on an ongoing basis should not be responsible for obtaining that patient’s informed consent to participate in a trial to be conducted by the physician. Patients may feel indebted to their physician or may hesitate to challenge or reject their physician’s advice to participate in research. Instead, after the physician has identified that a patient meets a protocol’s eligibility and recommends that a patient consider enrolling in the trial, someone other than the treating physician should obtain the participant’s consent. The nontreating health care professional also could remain available to answer additional questions during the trial. With appropriate protections from the pressures of financial incentives, reliance on this nontreating professional to obtain consent may alleviate the pressure some pa-
tients may feel to enroll in a trial. Although this is likely to entail additional cost and may not be practical in all contexts, it would minimize the conflicting role of clinician and investigator.

Financial Conflicts

The stakes in clinical testing of new drugs and devices are high because for-profit corporations stand to gain large revenues from marketing new products before their competitors. Therefore, the rapid recruitment of sufficient numbers of patients has become paramount and may explain why manufacturers are willing to offer investigators $2000 to $5000 per patient in certain cases, in contrast to $1000 per subject enrolled in NIH-sponsored studies.42 Regardless of whether these payments, in fact, represent usual and customary or ordinary payments, they do represent reimbursements several-fold greater than those of Medicare or third-party carriers and explain why they are sought by both academic investigators and community-based practitioners.43 Drawing from the British experience, one article aptly points out, “Pharmaceutical companies offer general practitioners often quite substantial sums for each patient recruited in a trial, and it seems unlikely they would use such payments if they failed to work.”44 The Council has stated unequivocally that obtaining a fee simply for referral of a patient to a research study (and not for the performance of any medical service) is unethical.45

There are other instances in which physicians may face ethical tensions related to the financial support of clinical trials. More specifically, physicians may be presented with situations in which the interests of the trial sponsor and those of health care insurers are competing, for example, when more tests are performed than would be necessary for routine care or when participants experience complications that require interventions outside the research protocol. Some health plans will cover the expenses that arise from patients enrolling in clinical trials, most notably for cancer patients. Moreover, following a recent Institute of Medicine report on the extension of Medicare reimbursement in clinical trials,46 the Centers for Medicare and Medicaid Services (formerly, Health Care Financing Administration) has been ordered to cover “routine patient care” for seniors who are enrolled in trials.47 Notwithstanding this extension of coverage, proper billing for procedures performed during research is imperative, and physicians should not bill a third-party payer when they have received funds from a sponsor to cover the additional expenses related to conducting the trial.48 Although academic institutions should have in place compliance programs to detect such practices, physicians in private practice equally must ensure that research services are accurately recorded and billed. Physicians are responsible for ensuring that funds are spent according to the terms of the grant and for preventing any inappropriate charges to third-party payers.

Compensation from sponsors that is intended to induce physicians (or hospitals) to purchase drugs or services from the sponsors, which is ultimately paid for by Medicare or Medicaid, is prohibited under antikickback laws. This prohibition would encompass arrangements whereby physicians receive substantial payments characterized as research grants that actually represent compensation for performing minor tasks and therefore grossly exceed the fair market value of the services.49

Disclosure as a Safeguard Against Financial Conflicts

Consistent with the obligations inherent in professional self-regulation, physicians involved in clinical research have a responsibility to understand the impact of financial incentives and to recognize how they give rise to conflicts that affect the recruitment of subjects. Once potential conflicts are identified, they may be avoided, disclosed, or mitigated. Although the complete avoidance of conflicts may be the ideal situation, this is likely to be unrealistic in most circumstances. As a result, disclosure of the conflict may function as the primary mechanism to reduce the effect of the conflict.

One possibility is to disclose conflicts up front to oversight bodies. For example, IRBs, which have focused their attention on reviewing risks and benefits and the informed consent process, are entitled to review recruitment procedures, including the offer of financial incentives to investigators.49 In addition, IRBs could require that conflicts be disclosed as part of the informed consent process and in the accompanying consent form. Conflicts of interests would appear along with other information deemed as material from the perspective of potential subjects. Recently, however, many shortcomings of the IRB review process have been uncovered and their overall effectiveness put in doubt.50 One particular concern is that once a protocol and the informed consent form are approved, there is rarely any follow-up mechanism to verify how the informed consent process is performed.

In addition, disclosure to other parties can occur during or after the completion of a trial. The FDA requires sponsors of drugs, devices, or other biologics seeking to market their products to submit a disclosure statement on financial arrangements. The statement should include information regarding the following: (1) compensation made to clinical investigators, the value of which could be affected by the study outcome; (2) proprietary interests of investigators (eg, patents); (3) significant equity in the sponsoring company held by the investigators; or (4) other significant payment by the sponsor, such as a grant for ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria.51 However, the rule applies to investigators only, not subinvestigators. In the context of research conducted through multiple sites, each participating physician is more likely to be considered a subinvestigator rather than an investigator. This may leave a large gap in the reporting requirement. Moreover, although this re-
However, disclosure is an imperfect remedy, and it is unclear how patients would react and whether it would suffice to prevent improper enrollment. Regardless of the content of disclosure, many patients are likely to defer to their physician’s personal recommendation to enroll in a trial.\textsuperscript{34}

**Additional Safeguards to Counter Financial Conflicts**

In addition to the disclosure of financial interests that investigators have in conducting trials, conflicts could be counterbalanced by other mechanisms. Academic institutions and community-based hospitals often have extensive compliance programs, which help to minimize various types of reimbursement errors, and conflict-of-interest policies, which help to reduce reliance on industry. For example, some academic institutions place absolute caps on amounts that investigators may receive from industry.\textsuperscript{35}

Physicians who participate in trials, but who are not affiliated with institutions, should have mechanisms in place to ensure that funding received from research sponsors is accurately recorded in their accounting system. Other grant administration rules, which all physicians should follow, include the avoidance of cost shifting or transfers of funds among grants and transferring unspent funds into different accounts. Finally, a Fraud Alert issued in August 1994 by the Office of the Inspector General noted that an investigation could be warranted if physicians received grants from industry to perform studies that had no genuine scientific value and required no scientific research. However, arrangements between industry sponsors and physicians would not likely raise concerns if they are consistent with fair market value for the services rendered, are without variation based on volume so that compensation for the first and last enrollees are the same, and are meeting existing legal conditions.\textsuperscript{36}

**Other Material Incentives**

Nonmonetary incentives can also be used to encourage the timely recruitment of subjects, for example, an offer from the trial sponsor to provide laboratory equipment to the investigator or the investigator’s institution. Particularly troubling is the fact that issues related to authorship and the publication of study results have become negotiable elements of research projects. For individual physicians, publication in peer-reviewed journals is a mark of prestige in the medical community, whereas for sponsoring firms it is an important means of disseminating information. For example, publishing favorable results often translates in wider use of a new drug. However, of great significance to the sponsoring firm, positive results will help ensure that a new drug or device will be approved by the FDA. Unfavorable results, in contrast, can put an end to the development of a product or markedly reduce its penetration of the market. Therefore, sponsoring firms may seek to prevent or delay the publication of negative results. Overall, control over publication can lead to conflicts that affect both the protection of human subjects and the integrity of the research. Such control can be misused as an incentive that compromises a physician’s judgment for enrolling a subject in a trial.\textsuperscript{40} It can also compromise the integrity of the scientific enterprise when authorship is not determined according to an investigator’s scientific contribution or when important results are not published.\textsuperscript{4} Therefore, when entering into a contract to perform research, physicians should assure themselves that the presentation or publication of results will not be unduly delayed or otherwise obstructed by the sponsoring company.

**COUNTERING CONFLICTS OF INTERESTS**

Few physicians willfully would allow subject welfare to be compromised for the sake of financial gain or scientific integrity to yield to personal reputation. Yet, there are few mechanisms to ensure that the primary interests, patient welfare and scientific objectivity, are not unduly influenced by the sec-

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When physicians receive financial rewards for enrolling patients in trials or receive excessive compensation for conducting trials, their interests may conflict with those of subjects. Similarly, when physicians are at once investigators and clinicians, scientific advancement may conflict with the welfare of subjects. Fiduciary principles, which require physicians to refrain from placing their own interests above those of patients, should serve to guide ethical behavior whenever physicians engage in clinical trials. Moreover, whether potential subjects are healthy volunteers, long-time patients, or specially referred to a trial, they all should be provided with sufficient information to enable them to make true informed decisions about participation in research.

CONCLUSION

As the biotechnology and pharmaceutical industries continue to expand research activities and funding of clinical trials, and as increasing numbers of physicians both within and outside academic health centers become involved in partnerships with industry to perform these activities, greater safeguards against conflicts of interest are needed to ensure the integrity of research and to protect the welfare of human subjects. Physicians should be mindful of the conflicting roles of the investigator and clinician and of the financial conflicts of interest that can arise from incentives to conduct trials and to recruit subjects. In particular, physicians involved in clinical research should heed the following guidelines:

1. Physicians should agree to participate as investigators in clinical trials only when it relates to their scope of practice and area of medical expertise. They should have adequate training in the conduct of research and should participate only in protocols that they are satisfied are scientifically sound.

2. Physicians should be familiar with the ethics of research and should agree to participate in trials only if they are satisfied that an IRB has reviewed the protocol, the research does not impose undue risks on research subjects, and the research conforms to government regulations.

3. When a physician has treated or continues to treat a patient who is eligible to enroll as a subject in a clinical trial that the physician is conducting, the informed consent process must differentiate between the physician’s roles as clinician and investigator. This is best achieved when someone other than the treating physician obtains the participant’s informed consent to participate in the trial. This individual should be protected from the pressures of financial incentives, as described in the following section.

4. Any financial compensation received from trial sponsors must be commensurate with the efforts of the physician performing the research. Financial compensation should be at fair market value, and the rate of compensation per patient should not vary according to the volume of subjects enrolled by the physician, and should meet other existing legal requirements. Furthermore, it is unethical for physicians to accept payment solely for referring patients to research studies.

5. Physicians should ensure that protocols include provisions for the funding of subjects’ medical care in the event of complications associated with the research. Disclosure to participants also should include information on uncertainties that may exist regarding funding of treatment for possible complications that may arise during the trial. Physicians should ensure that such disclosure is included in any written informed consent.

6. The nature and source of funding and financial incentives offered to the investigators must be disclosed to a potential participant as part of the informed consent process. Also, a physician should not bill a third-party payer when he/she has received funds from a sponsor to cover the additional expenses related to conducting the trial.

7. When entering into a contract to perform research, physicians should assure themselves that the presentation...
or publication of results will not be un- dully delayed or otherwise obstructed by the sponsoring company.

This article is based on a Report of the Council on Ethical and Judicial Affairs that was adopted by the American Medical Association in December 2000.

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