Managing Conflicts of Interest in the Conduct of Clinical Trials

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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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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, but caution is essential.

Investment in research and development by the top 20 pharmaceutical companies has more than doubled in the past 7 years.[1] In contrast, revenues are expected to grow only by 7% per annum for the coming years. Therefore, companies will need to generate more than $25 billion in sales to maintain current levels of profitability, which will require industry leaders to launch between 24 and 34 new drugs per year.[1] Furthermore, new drugs will have to cost less to develop or else be sold at higher prices to maintain current profit levels. To achieve this, the pharmaceutical industry will need to pursue more cost-efficient means of developing products.

One way this can be achieved is by turning away from academic health centers, which often are slowed by lengthy review processes and have large overhead expenses. Instead, industry increasingly relies on for-profit intermediary companies to seek less costly venues for the conduct of trials.[2] These organizations—contract research organizations and site management organizations —enable physicians in the private sector to be involved in trials outside academic settings.[3,4] Parallel to the proliferation of these organizations, the overall number of physicians involved in clinical research has increased 600% in 10 years, reaching more than 30 000 by 1998.[5] Investigators based in academic medical centers now represent only 46% of those conducting research, a decrease from 80% 10 years ago.[5] Also, only 40% of industry research funding is allocated to clinical trials performed in aca-

See also pp 72 and 85.

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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."[10] 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 report[13] 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 fiduciaries.[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

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."[30] 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.[48]

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-

quirement may help the FDA make final determinations about the validity of data obtained from trials, it does not offer any protection to subjects who were enrolled in the trials.

Another protection that can influence physician conduct stems from the disclosure requirements of peer-reviewed medical journals, which require authors to disclose financial information related to the conduct of their research. Currently, journals help ensure that ethical requirements pertaining to subjects have been complied with by requesting information on IRB review and informed consent. This mechanism, although important, may be insufficient since it is not likely to pertain to each physician who has participated in the trial by enrolling patients and collecting data. Only if the disclosure requirement were extended to include information on the financial compensation received by all participating investigators, and not just the authors, would it serve to alleviate the potential conflict of interests.

Regardless of whether disclosure is required by an IRB, the FDA, or a medical journal, direct disclosure to potential subjects holds value. This general proposition received legal attention in the case of *Moore v Regents of the University of California*,[52] in which a physician began conducting research during the treatment of a patient that resulted in the development of a cell line from which the physician derived considerable profits. The California Supreme Court found that the patient had a cause of action based on a breach of the physician's fiduciary duty to disclose material facts, such as economic interests, that may affect medical judgment.

Likewise, in the context of managed care reimbursement, courts have begun to examine incentives as constituting material information that should be disclosed as part of the informed consent process.[53] Omitting such disclosure of financial incentives when making a recommendation to a patient to enroll in a trial could be viewed as equally depriving the individual of material information.

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.[54]

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.[55]

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.[56]

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.[49] 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.[6] 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-

ondary interests, such as financial or personal gains. Judgment may not always be tainted, but distinguishing between cases may prove to be an impossible task.[30] Outcome data of a study will not show whether a physician was influenced by financial gain and inappropriately persuaded patients to volunteer in a trial. Only in the most egregious cases could it become apparent that a conflict of interest led to a breach of the physician's fiduciary duty. For example, if a subject experiences harm from a treatment received during a trial for which he/she did not qualify but for which records were falsified, the physician's conduct is likely to be questioned. However, if a physician who is influenced by incentives inappropriately persuades patients to enroll in a trial but none experience harm, it is less likely that the conflict of interest will be discovered. Nevertheless, each of these instances equally represents a breach of the physician's fiduciary duty and ethical responsibilities.

If a commitment on the part of the medical profession to preserve the ethical integrity of research on human subjects did not exist, even the most stringent safeguards to eliminate the effects of conflicts would be insufficient. Individual physicians, therefore, must remain personally accountable for the recommendations they make to patients regarding enrollment in clinical trials. The medical profession can instill the value of ethical research by emphasizing the need for investigators to be trained in the conduct of clinical trials, as well as in the ethics of research. Physicians who conduct clinical trials and enroll subjects should be familiar with relevant federal regulations pertaining to IRBs' review and informed consent requirements. They also should be mindful of the differences between the roles of clinician and investigator and be cognizant of potential financial conflicts that may affect their conduct.

Overall, the research enterprise relies on the integrity of investigators and depends on the cooperation of subjects. Preserving the public's trust is therefore of utmost importance. Yet, 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 unduly delayed or otherwise obstructed by the sponsoring company.

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REFERENCES

1. *Pharma2005: An Industrial Revolution in R&D*. New York, NY: PriceWaterhouseCoopers; 1998. Available at: http://www.pwcglobal.com/gx/eng/about/ind/pharm/phpubl_pharma2005.html. Accessibility verified November 26, 2001.
2. Rettig RA. Drug research and development. *Health Aff (Millwood)*. 2000;19:129-146.
3. Blumenstyk G, Wheeler DL. Academic medical centers race to compete in the $3.2 billion drug-testing market. *Chronicle of Higher Education*. March 20, 1998:A39.
4. Miller A. Trial run: small practices can participate in clinical trials: here's how [business and technology section]. *American Medical News*. September 27, 1999:21-22.
5. Lightfoot GD, Sanford SM, Shefrin AP. Can investigator certification improve the quality of clinical research? *ACPR Monitor*. Fall 1999:17.
6. Bodenheimer T. Uneasy alliance. *N Engl J Med*. 2000;342:1539-1544.
7. Protection of Human Subjects, 45 CFR §46 (October 2000).
8. Office of Inspector General, Department of Human and Health Services. *Institutional Review Boards: The Emergence of Independent Boards*. Washington, DC: Office of Inspector General, Department of Human and Health Services; June 1998. Publication OEI-01-97-00192.
9. Lemmens T, Freedman B. Ethics review for sale? *Milbank Q*. 2000;78:547-584.
10. Eichenwald K, Kolata G. Drug trials hide conflicts for doctors. *New York Times*. May 16, 1999:A1.
11. Eichenwald K, Kolata G. A doctor's drug trial turns into fraud. *New York Times*. May 17, 1999:A1.
12. Larkin M. Clinical trials: what price progress? *Lancet*. 1999;354:1534.
13. Council on Ethical and Judicial Affairs, American Medical Association. Conflicts of interest in biomedical research. *JAMA*. 1992;267:2366-2369.
14. Angell M. Is academic medicine for sale? *N Engl J Med*. 2000;342:1516.
15. Nelson D. More gene therapy experiments are suspended. *Washington Post*. February 8, 2000:A2.
16. Brainard J. Spate of suspensions of academic research spurs questions about federal strategy. *Chronicle of Higher Education*. February 4, 2000:A2.
17. Hubler E. FDA move halts local research. *Denver Post*. September 24, 1999:A1.
18. Manier J. UIC suspended from doing most human research. *Chicago Tribune*. August 28, 1999:A1.
19. Shamp J. Agency halts federally funded Duke research on new patients. *Herald-Sun (Durham, NC)*. May 12, 1999:A1.
20. Monmaney T. US suspends research at VA hospital in LA. *Los Angeles Times*. March 24, 1999:A1.
21. Jonas H. Philosophical reflections on experimenting with human subjects. In: Freund P, ed. *Experimentation With Human Beings*. New York, NY: George Braziller; 1970:1-31.
22. Kaufman M. Clinical trials sanctions urged. *Washington Post*. May 24, 2000:A2.
23. Seto B. Required education on the protection of human subjects: an NIH initiative. *Kennedy Inst Ethics J*. 2001;11:87-89.
24. National Institutes of Health. Required education in the protection of human research participants. Available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html. Accessed July 19, 2001.
25. Human Participant Protections Education for Research Teams. Available at: http://cme.nci.nih.gov. Accessed July 5, 2001.
26. US Department of Human Health and Services, Office of Human Research Protection. Financial relationships in clinical research. Available at: http://ohrp.osophs.dhhs.gov/humansubjects/finreltn/finguid.htm. Accessed July 5, 2001.
27. *Black's Law Dictionary*. 6th ed. St Paul, Minn: West Publishing; 1990.
28. Rodwin MA. Strains in the fiduciary metaphor. *Am J Law Med*. 1995;21:241-257.
29. Rodwin MA. *Medicine, Money, and Morals: Physicians' Conflicts of Interest*. New York, NY: Oxford University Press; 1993.
30. Thompson DF. Understanding financial conflicts of interest. *N Engl J Med*. 1993;329:573-576.
31. Beauchamp TL, Childress JF. *Principles of Biomedical Ethics*. 4th ed. New York, NY: Oxford University Press; 1994:441.
32. Appelbaum PS, Roth LH, Lidz CW, Benson P, Winslade W. False hopes and best data. *Hastings Cent Rep*. 1987;17:20-24.
33. Katz J. Human experimentation and human rights. *St Louis Univ Law J*. 1993;38:7-54.
34. Miller FG, Rosenstein DL, DeRenzo EG. Professional integrity in clinical research. *JAMA*. 1998;280:1449-1454.
35. Fisher B, Redmond CK, Poisson R, et al. Fraud in breast-cancer trials. *N Engl J Med*. 1994;330:1458.
36. Schulz KF. Subverting randomization in controlled trials. *JAMA*. 1995;274:1456-1458.
37. Blumgart HL. The medical framework for viewing the problem of human experimentation. In: Freund PA, ed. *Experimentation With Human Subjects*. New York, NY: George Braziller; 1970:39-65.
38. Levine RJ. Informed consent. In: *Ethics and Regulation of Clinical Research*. 2nd ed. New Haven, Conn: Yale University Press; 1988:95-153.
39. Daugherty C, Ratain MJ, Grochowski E, et al. Perceptions of cancer patients and their physicians involved in phase I trials. *J Clin Oncol*. 1995;13:1062-1072.
40. Olver IN, Buchanan L, Laidlaw C, et al. The adequacy of consent forms for informing patients entering oncological clinical trials. *Ann Oncol*. 1995;6:867-870.
41. Searight HR, Miller CK. Remembering and interpreting informed consent. *J Am Board Fam Pract*. 1996;9:14-22.
42. Shimm DS, Spece RG, DiGregorio MB. Conflicts of interests in relationships between physicians and the pharmaceutical industry. In: Spece RG, Shimm DS, Buchanan AE, eds. *Conflicts of Interest in Clinical Practice and Research*. New York, NY: Oxford University Press; 1996:321-357.
43. Lind S. Financial issues and incentives related to clinical research and innovative therapies. In: Vanderpool HY. *The Ethics of Research Involving Human Subjects: Facing the 21st Century*. Frederick, Md: University Publishing Group; 1996:185-202.
44. Foy R, Parry J, McAvoy B. Clinical trials in primary care. *BMJ*. 1998;317:1168-1169.
45. Council on Ethical and Judicial Affairs, American Medical Association. Fee-splitting: referrals to health care facilities [opinion 6.03]. In: Council on Ethical and Judicial Affairs, American Medical Association. *Code of Medical Ethics: Current Opinions*. Chicago, Ill: American Medical Association; 2000:59-60.
46. Committee on Routine Patient Care Costs in Clinical Trials for Medicare Beneficiaries. Aaron HJ, Gelband H, eds. *Extending Medicare Reimbursement in Clinical Trials*. Washington, DC: National Academy Press; 2000. Available at: http://www.nap.edu/books/0309068806/html. Accessibility verified November 26, 2001.
47. Cys J. Plan for Medicare coverage of clinical trials hailed. *American Medical News*. 2000;43:7.
48. Barnes M, Krauss S. Research issues take center stage in compliance process. *BNA Health Law Rep*. 1999;8:1344.
49. Office of Inspector General, Department of Health and Human Services. *Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research*. Washington, DC: Office of Inspector General, Dept of Health and Human Services; June 2000. Publication OEI-01-97-00195.
50. Office of Inspector General, Department of Health and Human Services. *Institutional Review Boards: A Time for Reform*. Washington, DC: Office of Inspector General, Dept of Health and Human Services; June 1998. Publication OEI-01-97-000193.
51. Financial Disclosure by Clinical Investigators, 21 CFR §54 (April 2001).
52. *Moore v Regents of the University of California*, 793 P2d 479 (Calif 1990).
53. *Neade v Portes*, 303 Ill App 3d 799 (1999).
54. Katz J. Informed consent to medical entrepreneurialism. In: Spece, RG, Shimm DS, Buchanan AE, eds. *Conflicts of Interest in Clinical Practice and Research*. New York, NY: Oxford University Press; 1996:286-299.
55. Knox RA. Harvard won't ease research standards. *Boston Globe*. May 26, 2000:A1.
56. Barnes M, Krauss S. Research issues take center stage in compliance process. *BNA Health Law Rep*. 1999;8:1344-1350.