

7.1.4 Conflicts of Interest in Research

Increasing numbers of physicians, both within and outside academic health centers, are becoming involved in partnerships with industry to conduct biomedical and health research. As they do so, physicians must be mindful of the conflicts such engagement poses to the integrity of the research and the welfare of human participants. In addition to financial conflicts of interest created by incentives to conduct trials and recruit subjects, physicians must be sensitive to the differing roles of clinician and investigator, which may require them to balance dual commitments to participants and science. This conflict of commitment is particularly acute when a physician-investigator has treated or continues to treat a patient who is eligible to enroll as a participant in a clinical trial the physician is conducting.

Minimizing and mitigating conflicts of interest in clinical research is imperative if the medical community is to justify and maintain trust in the medical research community.

Physicians who engage in research should:

- (a) Decline financial compensation that awards in excess of the physician's research efforts and does not reflect fair market value. Physicians should not accept payment solely for referring patients to research studies.
- (b) Ensure that the research protocol includes provision for funding participants' medical care in the event of complications associated with the research. A physician should not double-bill a third-party payer for additional expenses related to conducting the trial if he or she has already received funds from a sponsor for those expenses.
- (c) As part of the informed consent process, disclose to prospective participants the nature and source of funding and financial incentives offered to the investigators. This disclosure should be included in any written consent materials.
- (d) Avoid engaging in any research where there is an understanding that limitations can be placed on the presentation or publication of results by the research sponsor.
- (e) Refrain from knowingly participating in a financial relationship with a commercial entity with whom they have a research relationship until the research relationship ends and the research results have been published or otherwise disseminated to the public.
- (f) Disclose material ties to companies whose products they are investigating or other ties that create real or perceived conflicts of interest to:
 - (i) institutions where the research will be carried out;
 - (ii) organizations that are funding the research;
 - (iii) any journal or publication where the research results are being submitted.

- (g) Physicians who have leadership roles in institutions that conduct biomedical and health research as well as the entities that fund research with human participants should promote the development of guidelines on conflicts of interest that clarify physician-investigators responsibilities.

AMA Principles of Medical Ethics: II,IV,V

Opinion 7.1.4 Conflicts of Interest in Research re-organizes content from previous guidance and associated background report(s):

CEJA Report 3-I-00 Managing Conflicts of Interest in the Conduct of Clinical Trials

CEJA Report 3-I-98 Conflicts of interest—biomedical research

REPORT 3 OF THE COUNCIL ON ETHICAL AND JUDICIAL AFFAIRS (I-00)*
Managing Conflicts of Interest in the Conduct of Clinical Trials
(Reference Committee on Amendments to Constitution and Bylaws)

EXECUTIVE SUMMARY

This CEJA Report 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 scientist and clinical practitioner 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 resembles ordinary care. The report 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 where disclosure of information regarding funding and compensation may serve to minimize such conflicts.

To preserve the integrity of research and to protect the welfare of human subjects who enroll in trials, the report recommends that 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, the report recommends that someone other than the treating physician obtain the participant's informed consent.

Based on current CEJA Opinion 8.031, "Conflicts of Interest: Biomedical Research," the report reasserts that it is unethical for physicians to accept payment solely for referring patients to research studies. Any compensation received for conducting trials should be at fair market value and the rate of compensation should not vary according to the volume of subjects enrolled by the physician.

In addition, the report emphasizes that information regarding funding must be disclosed to a potential subject as part of the informed consent process. Disclosure should also include information on uncertainties that may exist regarding compensation to subjects for complications that may arise during the course of the trial. Finally, the report recommends that physicians should conform with journals' criteria for authorship and should ensure that sponsors will not unduly delay the publication of results.

* Reports of the Council on Ethical and Judicial Affairs are assigned to the Reference Committee on Constitution and Bylaws. They may be adopted, not adopted, or referred. A report may not be amended, except to clarify the meaning of the report and only with the concurrence of the Council.

REPORT OF THE COUNCIL ON ETHICAL AND JUDICIAL AFFAIRS*

CEJA Report 3-I-00

Subject: Managing Conflicts of Interest in the Conduct of Clinical Trials¹

Presented by: Herbert Rakatansky, MD, Chair

Presented to: Reference Committee on Amendments to Constitution and Bylaws
(Nelson G. Richards, Jr., MD, Chair)

1
2 Introduction
3

4 In December 1989, the AMA House of Delegates adopted a joint report of the Council on Ethical
5 and Judicial Affairs and the Council on Scientific Affairs entitled “Conflicts of Interest in
6 Biomedical Research.”² It outlined how conflicts of interests could be alleviated in the context of
7 research stemming from collaborations between academic health centers (AHC) and industry.
8 The report relied on a broad definition of conflicts of interest, including in its scope any “conflict
9 between the private interests and official responsibilities of a person in a position of trust.” In the
10 context of biomedical research, this was understood to arise primarily in cases where a researcher
11 enters into a financial arrangement with a profit-making corporation. The report noted that in
12 such circumstances, the researcher’s dedication to the advancement of medical knowledge could
13 conflict with his or her desire to increase income.
14

15 In addition to providing guidelines for mitigating conflicts, the report highlighted the growing
16 role of non-government funding in university-based biotechnological research. In the early 1990s
17 non-government funding was found to represent approximately 25% of all external support in the
18 top 100 academic research centers. At the same time, it had become increasingly common for
19 faculty researchers to serve as consultants to industry. The report carefully identified the benefits
20 and drawbacks of these relationships from the perspectives of clinical investigators, medical
21 centers and corporations. For instance, investigators benefit from additional funding for research
22 facilities, supplies and technical support. Medical centers often gain in reputation, and
23 corporations are viewed as making important contributions to society. However, such
24 relationships also can result in restrictions on the use and publication of research data or diminish
25 the emphasis AHCs traditionally place on patient care. Moreover, despite the fact that such a
26 partnership required corporate sponsors to relinquish some control over the research, a great deal
27 of suspicion remained regarding the objectivity of results.
28

29 In conclusion, the report emphasized the need to minimize potential sources of bias, particularly
30 where there is a direct relationship between a researcher’s personal financial interests and the
31 potential outcome of the research. These recommendations are now included in Opinion 8.031,
32 “Conflicts of Interest: Biomedical Research,” which advises AHCs to adopt guidelines that would
33 prevent investigators from engaging in insider trading and ensure that remuneration received
34 would be commensurate with the efforts of the researcher. Guidelines also should require the
35 disclosure and review of material ties to the corporations providing research funds. Whereas

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1 Opinion 8.031 primarily addresses conflicts of interest in academic centers, this report focuses on
2 the analysis of conflicts of interest in the conduct of clinical trials in both academic and
3 community-based settings.

4 5 New trends in clinical research

6
7 Analysts anticipate that the pharmaceutical industry will find considerable challenges in the years
8 to come. A recent industry report states that the investment in research and development by the
9 top 20 companies has more than doubled in the past seven years.³ In contrast, revenues are
10 expected to grow only by 7% per annum for the coming years. Companies will need to generate
11 more than \$25 billion in sales to maintain current levels of profitability, which will require
12 industry leaders to launch between 24 and 34 new drugs per year.³ Furthermore, new drugs will
13 have to cost less to develop, or else be sold at higher prices, to maintain current profit levels.
14 These are some of the reasons the pharmaceutical industry needs to pursue more cost-efficient
15 means of developing products.

16
17 One way this can be achieved is by turning away from AHCs, which often are slowed by a
18 lengthy review process and have large overhead expenses. Instead, industry increasingly relies
19 on for-profit intermediary companies to seek less costly venues for the conduct of trials.⁴ These
20 organizations—contract-research organizations (CROs) and site-management organizations
21 (SMOs)—enable physicians in the private sector to conduct trials outside of an academic
22 setting.^{5,6} Parallel to the proliferation of these organizations, the overall number of physicians
23 involved in clinical research has increased 600% in ten years, reaching more than 30,000 by
24 1998.⁷ Investigators based in academic medical centers now represent only 46% of those
25 conducting research, a drop from 80% ten years ago.⁷ Also, only 40% of industry research
26 funding is allocated to clinical trials performed in academic centers; conversely, 60% of industry
27 funding is allocated to community-based trials, which represents a threefold increase in less than
28 a decade.⁸

29
30 The role of CROs varies, but they are essentially networks, providing trial sponsors access to
31 hospitals and physicians, and their patients. Some are involved in direct patient recruitment and
32 patient screening, others create and design trials, and others conduct trials. In some instances,
33 they subcontract with SMOs, which assist community physicians to enroll patients and report
34 back to the CRO.⁸ These companies conduct extensive advertisements, through billboards,
35 newspapers, radio and television, health fairs, community seminars and lectures, and direct mail.
36 When targeting potential subjects, their message usually emphasizes the benefits of participating
37 in trials rather than the risks,⁹ and may be contributing to the overall favorable perception many
38 patients have of participating in trials, even those that offer no therapeutic advantage. When trials
39 are promoted to physicians, the advertising turns to financial incentives, promising generous
40 compensation, which may be unethical for physicians to accept. There are concerns that these
41 organizations face considerable conflicts of interest because they are paid by pharmaceutical
42 companies that ultimately depend on positive trial outcomes and, therefore, that their financial
43 viability may be pitted against research integrity and the safety of research subjects.

44
45 Much of the research conducted through CROs and SMOs involves new drugs or devices for
46 which FDA approval is necessary and, therefore, is subject to federal regulations generally known
47 as the Federal Common Rule.¹⁰ Consequently, many industry-sponsored trials that are conducted
48 in community settings undergo a review process similar to the one required of federally-funded
49 research performed in academic centers. However, rather than relying on academic Institutional
50 Review Boards (IRBs), sponsoring companies have their research protocols reviewed either by
51 their own boards or by independent boards.¹¹ Some commentators have expressed concerns that

1 independent IRBs face financial conflicts of interest since their very existence depends on the
 2 continued flow of protocols to review, which may lead them to use less stringent review
 3 standards. Such pressure may be compounded by “IRB shopping” whereby sponsors whose
 4 protocols are not approved by one IRB resubmit the same protocol to a different board hoping for
 5 a favorable result.¹¹

6
 7 This new environment in which clinical trials are conducted received considerable attention in the
 8 spring of 1999 in reaction to two articles that appeared in the *New York Times* exposing the
 9 conflicts of interest many community-based physicians face.^{12, 13} Patients were described as
 10 “commodities, bought and traded by testing companies and doctors.”¹² It was stated that even if
 11 recruiters were not involved in conducting the trials, they were offered financial incentives simply
 12 to refer patients to investigators. In some protocols, finder’s fees and additional bonuses for
 13 reaching certain quotas within deadlines amounted to several thousand dollars per patient. In
 14 addition to the financial conflict of interest that could lead some physicians to refer patients to
 15 trials inappropriately, the articles also questioned the competence of physicians, both in terms of
 16 their ability to conduct clinical trials, and simply to care for a patient population that did not fall
 17 within their specialty.¹⁴

18
 19 Overall, many of the concerns that were identified a decade ago in the Council’s report have
 20 persisted, and may have increased, according to recent commentators.^{8,15} Physicians currently
 21 involved in biomedical research face an important challenge. High societal expectations that the
 22 burden of disease and disability can be reduced through research, combined with continued
 23 growth in the budget of the NIH, as well as increased R&D funding by the private industry create
 24 an atmosphere where there are few forces moderating the research imperative. Furthermore,
 25 complacency may have grown toward the now familiar federal safeguards that were established
 26 to ensure the respect and safety of research subjects. Recent examples of clinical trials suspended
 27 for potential breaches of ethical standards abound, many of them involving prestigious academic
 28 centers.^{16,17,18,19,20,21}

29
 30 In order to ensure that societal trust in the research endeavor is not eroded, that subjects enrolled
 31 in trials do not become merely a means to an end,²² and that medical research is efficiently
 32 translated into clinical advances that will benefit future patients, there must be a renewed
 33 commitment to the application of high ethical standards. To that effect, the Department of Health
 34 and Human Services (HHS) announced in May 2000 that various measures would be taken to
 35 enhance the protection of research subjects.²³ Specifically, HHS will undertake efforts to
 36 improve the education and training of clinical investigators and IRB members who receive
 37 funding from the National Institutes of Health (NIH) to ensure that they are trained in bioethics
 38 and in human subjects research. Furthermore, the NIH will issue additional guidelines regarding
 39 conflicts of interest and will work with the FDA to develop policies for the broader biomedical
 40 research community, so that every researcher would be required to disclose to potential research
 41 subjects any financial interest in the clinical trial being conducted.²⁴

42
 43 While many of these measures continue to be directed primarily at academic centers, it is clear
 44 that equivalent standards must be extended to all settings in which research is now conducted in
 45 order to maintain a consistent level of integrity across the spectrum of clinical research venues.

46 Conflicts of interest: nature and scope

47
 48
 49 In law, the term conflict of interest is used primarily in connection with fiduciaries.²⁵ A fiduciary
 50 holds some form of power that is to be used for the benefit of another, based on specialized
 51 knowledge or expertise. The fiduciary relationship involves dependence, reliance, and trust and

1 legally is held to the highest standard of conduct.²⁶ Many aspect of the fiduciary relationship
 2 exist in the patient-physician relationship, which explains why physicians also have an ethical
 3 duty to avoid conflicts between their commitment to heal patients and their economic self-
 4 interest.²⁷

5
 6 Physicians' conflicts of interest are not a new phenomenon. As noted by one commentator:

7
 8 The problem of conflicts of interest began to receive serious attention in the
 9 medical literature in the 1980s... Among the areas of concern are self-referral by
 10 physicians, physicians' risk sharing in health maintenance organizations (HMOs)
 11 and hospitals, gifts from drug companies to physicians, hospital purchasing and
 12 bonding practices, industry sponsored research, and research on patients.²⁸

13
 14 In each of these cases, a “professional judgment concerning a primary interest (...) tends to be
 15 unduly influenced by a secondary interest (...).”²⁸ In the case of medical research, two sets of
 16 primary interests can be identified, namely the subjects' welfare and the scientific integrity of the
 17 data, which may be compromised by the dual roles of physician and investigator and by the
 18 influence of financial incentives or other forms of personal gain.

19
 20 *Conflicting roles: physicians as investigators*

21
 22 Ethicists have noted that the roles of research scientist and clinical practitioner deeply differ.²⁹
 23 Investigators act to generate scientific knowledge, which potentially will result in future
 24 therapeutic benefits. Practitioners are focused on the present health and welfare of patients.
 25 Notwithstanding the distinction between researcher and clinical practitioner, research can be
 26 designed primarily to yield scientific knowledge, such as Phase I clinical trials, or may offer some
 27 medical benefit to subjects, such as Phase III clinical trials. In each, risks and potential benefits
 28 must be weighed and informed consent obtained from prospective subjects, after disclosure of all
 29 material information. However, particular attention must be paid in the case where research
 30 offers some medical benefit and easily can be integrated in the course of clinical care, since
 31 subjects are prone to misconceive the nature of the project. Although subjects in these trials are
 32 offered a treatment of unproven efficacy, many mistakenly believe that they are receiving cutting-
 33 edge treatment guaranteed to improve their condition. This “therapeutic misconception,” a term
 34 coined in the mid 1980s,³⁰ may be reinforced when subjects receive the experimental treatment
 35 from the same physician who has administered all of their care in the past, in contrast to being
 36 referred to a clinical investigator located in an academic setting with a reputation of conducting
 37 research.

38
 39 This conflict of roles, or conflicting loyalties, has received increased attention recently.³¹ In one
 40 article,³² the authors identify academic medical centers as a source of the blurring of roles
 41 between clinician and investigator because medical students and residents are educated in a
 42 setting where both functions, care and research, co-exist. The authors caution that investigators
 43 themselves may succumb to a form of “cognitive dissonance” in trying to reconcile the scientific
 44 goals of research with patient care, leading to the conflation of language of medical care with that
 45 of research. This ultimately undermines the informed consent process. It also may lead
 46 investigators to circumvent strict enrollment criteria³³ or random assignments,³⁴ or to interfere
 47 with outcome assessments.

48
 49 There are reasons to believe that the concerns stemming from the blurred roles of physicians
 50 working in academic center may be of equal or even greater concern in community-based or
 51 private clinics if care and research come to co-exist in settings that traditionally have been

1 treatment-oriented. It is worth noting that some conflicts may be unique to the academic setting,
 2 where investigators compete for grants, promotions, and prestige. Other pressures, however, may
 3 be unique to the private and community settings, such as competing demands on time from
 4 regular patients.

6 *Safeguards against conflicting roles*

8 When the “scientific alliance” between investigators and their subjects appears to overlap with
 9 the “therapeutic alliance” that bonds physicians and their patients,³⁵ trial participants may
 10 become confused about the goals of a treatment that is experimental but resembles the care they
 11 ordinarily received. This may hold true despite research subjects providing their informed
 12 consent to participate in a trial. Indeed, there is extensive literature that demonstrates the
 13 shortcomings of the current informed consent process in the experimental setting.^{36,37,38,39} There
 14 may be cause to believe that the informed consent is compromised even further when the
 15 physician-investigator who is responsible for enrolling participants in the trial and obtaining their
 16 consent stands to gain financially from each participant who enrolls. The physician-investigator
 17 may be less inclined to emphasize how the experimental treatment differs from the care that is
 18 ordinarily provided, the additional risks involved, or lack of direct benefit to the participant.
 19 Therefore, safeguards should be put in place to ensure the integrity of the informed consent
 20 process. In particular, the nature and source of funding, and financial incentives offered to
 21 physicians, must be disclosed to a potential participant as part of the informed consent process.

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

35 *Financial Conflicts*

37 The stakes in clinical testing of new drugs and devices are high, as for-profit corporations stand to
 38 gain large revenues from marketing new products ahead of their competitors. Therefore, the
 39 rapid recruitment of sufficient numbers of patients has become paramount and may explain why
 40 manufacturers are willing to offer investigators \$2,000 to \$5,000 per patient in certain cases, in
 41 contrast to \$1,000 per subject enrolled in an NIH-sponsored study. Regardless of whether these
 42 payments, in fact, represent usual and customary or ordinary payments, they do represent
 43 reimbursements several-fold greater than those of Medicare or third-party carriers, and explain
 44 why they are sought by academic investigators and community-based practitioners alike.^{40,41}

46 In the context of general medical care, it has been noted that fee-for-service reimbursement
 47 systems may represent an incentive to provide more care than necessary to patients. Similarly,
 48 when physicians stand to gain from referrals in facilities in which they have invested, it has been
 49 demonstrated that the rate of referrals increases.⁴² Therefore, when clinicians stand to gain from
 50 enrolling their own patients as subjects in clinical trials, there is reason to believe that the rate of
 51 referral may increase. Drawing from the British experience, one author aptly points out

1 “pharmaceutical companies offer general practitioners often quite substantial sums for each
2 patient recruited in a trial, and it seems unlikely they would use such payments if they failed to
3 work.”⁴³

4
5 In addition to conflicts that pit the interests of physicians against those of patients, there are other
6 instances where physicians may face ethical tensions related to the financial support of clinical
7 trials. More specifically, physicians may be presented with situations where the interests of the
8 trial sponsor and other health care insurers are competing and where proper billing of procedures
9 in the course of research therefore is imperative. This concern arises from recent announcements
10 that some health plans will cover the expenses that arise from patients enrolling in clinical trials,
11 most notably for cancer patients. Moreover, following a recent Institute of Medicine report on
12 the extension of Medicare reimbursement in clinical trials,⁴⁴ the Health Care Financing
13 Administration (HCFA) has been ordered to cover “routine patient care” for seniors who are
14 enrolled in trials.⁴⁵ Notwithstanding this extension of coverage, physicians should not bill a third-
15 party payor when they have received funds from a sponsor to cover the additional expenses
16 related to conducting the trial.⁴⁶ While academic institutions should have in place compliance
17 programs to detect such practices, physicians in private practice equally must ensure that research
18 services are accurately recorded and billed. Physicians are responsible for ensuring that funds are
19 spent according to the terms of the grant and for preventing any inappropriate charges to third-
20 party payors.

21
22 In a similar vein, compensation from sponsors that is intended to induce physicians (or hospitals)
23 to purchase drugs or services from the sponsors that ultimately are paid for by Medicare or
24 Medicaid is prohibited under anti-kickback laws. This prohibition would encompass
25 arrangements whereby physicians receive substantial payments characterized as research grants
26 that actually represent compensation for performing minor tasks and therefore grossly exceed the
27 fair market value of the services.⁴⁶ Likewise, the Council has stated that obtaining a fee simply
28 for referral of a patient to a research study (and not for the performance of any medical service) is
29 unethical.⁴⁷

30 *Disclosure as a safeguard against financial conflicts*

31
32
33 Consistent with the obligations inherent in professional self-regulation, physicians involved in
34 clinical research have a responsibility to understand the impact of financial incentives and to
35 recognize how they give rise to conflicts that affect the recruitment of subjects. Once potential
36 conflicts are identified, they may be avoided, disclosed, or mitigated. Although the complete
37 avoidance of conflicts may be the ideal situation, this is likely to be unrealistic in most
38 circumstances. As a result, disclosure of the conflict may function as the primary mechanism to
39 reduce the effect of the conflict.

40
41 One possibility is to disclose conflicts up-front to oversight bodies. For example, IRBs, which
42 have focused their attention on reviewing risks and benefits and the informed consent process, are
43 entitled to review recruitment procedures, including the offer of financial incentives to
44 investigators.⁴⁸ IRBs also could require that conflicts be disclosed as part of the informed
45 consent process, and in the accompanying consent form. Conflicts of interests would appear
46 along with other information that is deemed material from the perspective of potential subjects.
47 Recently, however, many shortcomings of the IRB review process have been uncovered, and their
48 overall effectiveness put in doubt.⁴⁹ One particular concern is that once a protocol and the
49 informed consent form are approved, there is rarely any follow-up mechanism to verify how the
50 informed consent process is performed.

51

1 In addition, disclosure to other parties can occur during or after the completion of a trial. The
2 Food and Drug Administration requires sponsors of drugs, devices or other biologics seeking to
3 market their products to submit a disclosure statement on financial arrangements. The statement
4 should include information regarding: 1) compensation made to clinical investigators, the value
5 of which could be affected by the study outcome, 2) proprietary interests of investigators (e.g.
6 patents), 3) significant equity in the sponsoring company held by the investigators, or 4) other
7 significant payment by the sponsor, such as a grant for ongoing research, compensation in the
8 form of equipment, or retainers for ongoing consultation or honoraria.⁵⁰ However, the rule
9 applies to investigators only, not sub-investigators. In the context of research conducted through
10 multiple sites, each participating physician is more likely to be considered a sub-investigator,
11 rather than an investigator. This may leave a large gap in the reporting requirement. Moreover,
12 although this requirement may help the FDA make final determinations about the validity of data
13 obtained from trials, it does not offer any protection to subjects who were enrolled in the trials.

14
15 Another “back-end” protection that can influence physician conduct stems from the disclosure
16 requirements of peer-reviewed medical journals, which require authors to disclose financial
17 information related to the conduct of their research. Presently, journals help ensure that ethical
18 requirements pertaining to subjects have been complied with by requesting information on IRB
19 review and informed consent. This mechanism, although important, may be insufficient since it
20 is not likely to pertain to each physician who has participated in the trial by enrolling patients and
21 collecting data. Only if the disclosure requirement were extended to include information on the
22 financial compensation received by all participating investigators, and not just the authors, would
23 it serve to alleviate the potential conflict of interests.

24
25 Irrespective of whether disclosure is required by an IRB, the FDA, or a journal, direct disclosure
26 to potential subjects holds value. This general proposition received legal attention in the case of
27 *Moore v. Regents of the University of California*,⁵¹ where in the course of treatment, a physician
28 began conducting research that resulted in the development of a cell line from which the
29 physician derived considerable profits. The California Supreme Court found that the patient had
30 a cause of action based on a breach of the physician’s fiduciary duty to disclose material facts,
31 such as economic interests, that may affect medical judgment.

32
33 Likewise, in the context of managed care reimbursement, courts have begun to examine
34 incentives as constituting material information that should be disclosed as part of the informed
35 consent process.⁵² Omitting such disclosure of financial incentives when making a
36 recommendation to a patient to enroll in a trial could be viewed as equally depriving the
37 individual of material information.

38
39 However, disclosure is an imperfect remedy and it is unclear how patients would react and
40 whether it would suffice to prevent improper enrollment. Regardless of the content of disclosure,
41 many patients are likely to defer to their physician’s personal recommendation to enroll in a
42 trial.⁵³

43 44 *Other safeguards to counter financial conflicts*

45
46 In addition to the disclosure of financial interests that investigators have in conducting trials,
47 conflicts could be counter-balanced by other mechanisms. Academic institutions, as well as
48 community-based hospitals, often have in place extensive compliance programs that help
49 minimize various types of reimbursement errors, as well as conflict of interest policies that help
50 reduce reliance on industry. For example, some academic institutions place absolute caps on
51 amounts that investigators may receive from industry.⁵⁴

1
2 In addition, physicians who participate in trials but who are not affiliated with institutions should
3 have mechanisms in place to ensure that funding received from research sponsors is accurately
4 recorded in their accounting system. Other grant administration rules that all physicians should
5 follow include the avoidance of cost shifting or transfers of funds among grants, and of dumping
6 or transfers of unspent funds into different accounts. Finally, a Fraud Alert issued in August 1994
7 by the Office of the Inspector General (OIG) noted that an investigation could be warranted if
8 physicians received grants from industry to perform studies that had no genuine scientific value
9 and required no scientific research. However, arrangements between industry sponsors and
10 physicians that are consistent with fair market value for the services rendered, without variation
11 based upon volume, and that otherwise meet existing legal conditions, would not likely raise such
12 concerns.⁵⁵

13 *Non-financial incentives*

14
15
16 In addition to financial incentives, non-financial incentives can also be used to encourage the
17 timely recruitment of subjects, for example an offer from the trial sponsor to provide laboratory
18 equipment to the investigator or the investigator's institution. Particularly troubling is the fact
19 that issues related to authorship as well as the publication of study results have become negotiable
20 elements of research projects. For individual physicians, publication in peer-reviewed journals is
21 a mark of prestige in the medical community, whereas for sponsoring firms it is an important
22 means of disseminating information. For example, publishing favorable results often translates in
23 wider use of a new drug. However, of greater significance to the sponsoring firm, positive results
24 will help ensure that a new drug or device will be approved by the FDA. Unfavorable results, in
25 contrast, can put an end to the development of a product, or markedly reduce its penetration of the
26 market. Therefore, sponsoring firms may seek to prevent or delay the publication of negative
27 results. Overall, control over publication can lead to conflicts that affect both the protection of
28 human subjects and the integrity of the research. Such control can be misused as an incentive that
29 compromises a physician's judgement for enrolling a subject in a trial.⁴⁸ It can also compromise
30 the integrity of the scientific enterprise, when authorship is not determined according to an
31 investigator's scientific contribution, or when important results are not published.⁸ Therefore,
32 when entering into a contract to perform research, physicians should ensure themselves that the
33 presentation or publication of results will not be unduly delayed or otherwise obstructed by the
34 sponsoring company.

35 36 Countering conflicts of interests

37
38 Few physicians willfully would allow subject welfare to be compromised for the sake of financial
39 gain, or scientific integrity to yield to personal reputation. Yet, there are few mechanisms to
40 ensure that the primary interests, patient welfare and scientific objectivity, are not unduly
41 influenced by the secondary interests, such as financial or personal gains. Judgment may not
42 always be tainted, but distinguishing those cases where it has been from those where it has not
43 often may prove to be an impossible task.²⁸ Outcome data of a study will not show whether a
44 physician was influenced by financial gain and inappropriately persuaded patients to volunteer in
45 a trial. Only in the most egregious cases could it become apparent that a conflict of interest led to
46 a breach of the physician's fiduciary duty. For example, if a subject suffers harm from a
47 treatment received during a trial for which he or she did not qualify but for which records were
48 falsified, then the physician's conduct is likely to be questioned. However, if a physician who is
49 influenced by incentives inappropriately persuades patients to enroll in a trial but none suffer
50 more than minor side effects related to the experimental drug, it is less likely that the conflict of

1 interests will be discovered. Nevertheless, each of these instances equally represents a breach of
2 the physician's fiduciary duty and ethical responsibilities.

3
4 If there were not a commitment on the part of the medical profession to preserve the ethical
5 integrity of research on human subjects, even the most stringent safeguards to eliminate the
6 effects of conflicts would be insufficient. Individual physicians, therefore, must remain
7 personally accountable for the recommendations they make to patients regarding enrollment in
8 clinical trials.

9
10 Through education, the medical profession can instill the value of ethical research by
11 emphasizing the need for investigators to be trained in the conduct of clinical trials, as well as in
12 the ethics of research. Physicians who conduct clinical trials and enroll subjects should be
13 familiar with relevant federal regulations pertaining to IRBs review and informed consent
14 requirements. They also should be mindful of the differences between the roles of clinician and
15 investigator, as well as be cognizant of potential financial conflicts that may affect their conduct.

16 17 Conclusion

18
19 The research enterprise relies on the integrity of investigators and depends on the cooperation of
20 subjects. Preserving the public's trust is therefore of utmost importance. Yet, when physicians
21 receive financial rewards for enrolling patients in trials or receive excessive compensation for
22 conducting trials, their interests may conflict with those of subjects. Similarly, when physicians
23 are at once investigators and clinicians, scientific advancement may conflict with the welfare of
24 subjects. Fiduciary principles, which require physicians to refrain from placing their own
25 interests above those of patients, should serve to guide ethical behavior whenever physicians
26 engage in clinical trials. Moreover, whether potential subjects are healthy volunteers, long-time
27 patients, or specially-referred to a trial, they all should be provided with sufficient information to
28 enable them to make true informed decisions about participation in research.

29 30 Recommendations

31
32 The Council recommends that the following be adopted and the remainder of the report be filed:

33
34 As the biotechnology and pharmaceutical industries continue to expand research activities
35 and funding of clinical trials, and as increasing numbers of physicians both within and outside
36 academic health centers become involved in partnerships with industry to perform these
37 activities, greater safeguards against conflicts of interest are needed to ensure the integrity of
38 the research and to protect the welfare of human subjects. Physicians should be mindful of
39 the conflicting roles of investigator and clinician and of the financial conflicts of interest that
40 arise from incentives to conduct trials and to recruit subjects. In particular, physicians
41 involved in clinical research should heed the following guidelines:

- 42
43 1. Physicians should agree to participate as investigators in clinical trials only when it
44 relates to their scope of practice and area of medical expertise. They should have
45 adequate training in the conduct of research and should participate only in protocols
46 which they are satisfied are scientifically sound.
- 47
48 2. Physicians should be familiar with the ethics of research, and should agree to participate
49 in trials only if they are satisfied that an Institutional Review Board has reviewed the
50 protocol, that the research does not impose undue risks upon research subjects, and that
51 the research conforms to government regulations.

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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, as well as meet other existing legal requirements. Furthermore, according to Opinion 6.03, “Fee Splitting: Referral to Health Care Facilities,” 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. Also, a physician should not bill a third-party payor when he or she has received funds from a sponsor to cover the additional expenses related to conducting the trial.
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. Disclosure to participants also should include information on uncertainties that may exist regarding funding of treatment for possible complications that may arise during the course of the trial. Physicians should ensure that such disclosure is included in any written informed consent.
7. When entering into a contract to perform research, physicians should ensure themselves that the presentation or publication of results will not be unduly delayed or otherwise obstructed by the sponsoring company.

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CEJA Report 3 – I-98
Conflicts of Interest: Biomedical Research

INTRODUCTION

In December 1989 the Council on Scientific Affairs and the Council on Ethical and Judicial Affairs issued their joint report “Conflicts of Interest in Medical Center/Industry Research Relationships.” In regards to disclosure, the guidelines state

(c) clinical investigators should disclose any material ties to companies whose products they are investigating. They should disclose their financial ties, participation in educational activities supported by the companies, participation in other research projects funded by the companies, consulting arrangements, and any other ties. The disclosure should be made to the medical center where the research is conducted, organizations that are funding the research, and journals that publish the results of the research.¹

Revitalized discussions about full disclosure of any financial interest by those who conduct biomedical research have encouraged the Council to reconsider these minimum requirements.

DISCUSSION

It is difficult to deny that research-related gifts, either financial or material, play an important role in supporting research and increasing productivity. A study which examined academic scientists' experience with research-related gifts from industries revealed that 75% of those who received biomaterials, 66% of those who received discretionary funds, and 67% of those who received research equipment rated these gifts as “essential,” “very important,” or “important” to the progress of their research. Correspondingly, the data suggested that such gifts were associated with a variety of restrictions and expectations of returns, including the expectation of prepublication review of articles or reports.² The debate over calcium-channel antagonists has exemplified the need for complete disclosure of relationships with pharmaceutical companies for researchers who publish articles examining pharmaceutical products. A recent study of physicians' financial relationships with the pharmaceutical industry demonstrated that supportive authors were much more likely than critical authors to have financial associations with manufacturers of calcium-channel antagonists, as well as with manufacturers of other products.³ In addition, it has been reported that the tobacco industry paid several scientists over \$156,000 to write letters to the editors of health and industry related journals, as well as newspapers such as the Wall Street Journal, discrediting a 1993 Environmental Protection Agency report that linked secondhand smoke to lung cancer.⁴ For example, one biostatistician received \$10,000 to write a letter to the Journal of the American Medical Association.⁵ Letter campaigns such as this may mislead the public and the medical profession by presenting biased opinions that distort serious health-related controversies.

Conflicts of interest vary and can be interpreted differently. Many researchers and authors may feel that they can remain objective in areas of their expertise regardless of financial associations or research-related gifts. Critics view this claim skeptically. The integrity of the medical community and the research done within depends on the avoidance of real or perceived conflicts of interests and the accompanying biases. Of utmost concern is protecting the public from a researcher's or author's opinion that is tilted due to personal interests.

RECOMMENDATION

Many medical journals have adopted policies that require conflicts of interest to be disclosed to readers.^{6, 7} For the following reasons, the Council on Ethical and Judicial Affairs recommends that the following statement be adopted and that the remainder of this report be filed:

1. An explanatory statement that discloses conflicts of interest to readers should accompany published research. Other types of publications, such as a letters to the editor, should also include an explanatory statement that discloses any potential conflict of interest.

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Joint Report of the Council on Ethical and Judicial Affairs
and the Council on Scientific Affairs, I-89
Conflicts of Interest in Biomedical Research

Avoidance of real or perceived conflicts of interest in clinical research wherever possible is imperative if the medical community is to ensure objectivity, maintain individual and institutional integrity and present an image of objectivity and integrity to the outside world. This task is complex in part because of the paucity of objective information that has been disseminated to the medical community about what constitutes ethical behavior in the research setting. The culture of medicine has not sensitized individual investigators to appreciate how their actions might be viewed by those outside of the medical community. This communication is designed to present the first in a series of reports by the Council on Scientific Affairs and the Council on Ethical and Judicial Affairs about conflicts of interest in clinical research. The reports are not designed to promote rigid behavioral guidelines; rather, they explore key facets of the background and discuss ethical decisions related to the conduct of research. This report deals with economic conflicts of interest in relation to medical center-industry research collaborations.

WHAT IS CONFLICT OF INTEREST?

Conflict of interest in clinical research defies simple definition: one researcher's conflict of interest may be another's mutually beneficial working relationship.¹ Conflict of interest must be clearly distinguished from scientific misconduct. The generally recognized patterns that constitute misconduct in science include plagiarism, deception, falsification and/ or fabrication of scientific data. Scientific misconduct compromises the integrity of the biomedical research process. On the other hand, conflict of interest involves a distinct subset of issues. Conflict of interest is defined by Webster's Third New International Dictionary as "a conflict between the private interests and official responsibilities of a person in a position of trust." Although conflicts of interest are inherent in any research relationship, perhaps the most important area in which a conflict of interest may arise is the case of a researcher entering into a financial arrangement with a profit-making corporation. In that situation, the researcher's dedication to the advancement of medical knowledge may collide with the researcher's desire to increase his or her income.

The general norms of scientific behavior (including intellectual honesty and objectivity, reasonable doubt, etc.) are not necessarily compromised when a potential conflict of interest arises. The researcher's economic interests may coincide with his or her obligation of intellectual objectivity. Even in such a situation, however, the mere perception of a conflict of interest may be detrimental to scientific progress since a "shadow of doubt" may be cast on research that is conducted in an appropriate manner.

There has been some confusion in the literature on conflicts of interest as a result of differences in definition. Some commentators refer to potential and actual conflicts of interest; others speak about potential and actual harm from conflicts of interest. In this report, a potential conflict of interest will mean a situation in which a researcher has separate interests that might come into conflict. An actual conflict of interest will mean a situation in which the researcher cannot advance one interest without impairing another interest.

MEDICAL CENTER-INDUSTRY RESEARCH RELATIONSHIPS

Although clinical trials involving specific products typically are funded by industry, researchers pursuing questions that deal with basic biologic processes having limited direct clinical applicability traditionally have not had much access to research support from sources other than federal government. The majority of financial support for such research continues to come from the federal government. Although support

by industry for biomedical research has risen sharply in recent years, it still represents only about 5% of the total external funding received by research universities.³ The extent of industry support for clinical research in medical centers has not been specifically determined. However, industry support for biotechnology research, which perhaps is more likely than most research to be based in medical centers, is becoming quite substantial. For example, funds from industry account for 16% to 24% of all external support for university-based research in biotechnology.⁴ Estimates also indicate that nearly half of all biotechnology firms support research in universities, and that 90 of the top 100 universities that conduct biotechnology research receive financial support from industrial sources.⁵ Moreover, university faculty are employed as consultants by 90% of biotechnology companies and nearly 50% of faculty researchers in biotechnology serve as consultants to industry.⁵ Although these types of arrangements are relatively new, they are fast becoming important to the survival of both industry and academia as the research environment becomes increasingly competitive.

There are many perceived advantages to corporate funding of clinical research that is conducted in medical centers. These benefits accrue to the individual researcher, the institution, and to industry. Although some of these advantages may be similar, there are distinct differences.

BENEFITS TO CLINICAL INVESTIGATORS

Investigators who participate in clinical research in a medical center setting may benefit in important ways from corporate funding of their research endeavors. Potential benefits for investigators include:

- the identification of critical areas where research efforts are likely to result in useful information or products;
- an enhanced funding base for clinical supplies and research facilities;
- cost-effective allocation of available research dollars;
- the availability of funds for ancillary expenses related to research, including travel; and
- funds for additional technical support.

These benefits not only enable investigators to conduct research more efficiently, but also tend to increase the utility of the data that is collected.

BENEFITS TO MEDICAL CENTERS

Medical centers, as well as individual clinical investigators, tend to derive a number of benefits from corporate funding of biomedical research. Medical centers are likely to benefit from:

- research efforts that are focused in critical areas due to corporate sponsorship;
- outside sources of funding that help to offset indirect cost of research;
- cost-effective allocation of available research dollars;
- increased employment opportunities; and
- an enhanced reputation for the center among individuals in the medical community.

These benefits, like those that accrue to individual clinical investigators, contribute to the overall efficiency with which biomedical research is conducted.

BENEFITS TO CORPORATIONS

Corporations that provide research funds to clinical investigators in medical centers obviously hope to derive substantial benefits from their economic investment. Potential benefits for the corporation include:

- an increased ability to focus research in areas of potential profit; the opportunity for immediate product development based upon experimental results;
- direct access to medical center talent and facilities without need to duplicate on an ongoing basis;
- increased opportunities to achieve corporate goals while also making notable contributions to society;
- cost-effective allocation of available research dollars; and

- reductions in the corporation's taxable holdings.

Many of these benefits enhance corporate profits and thereby facilitate additional funding of other crucial research projects. However, research relationships between corporations and clinical investigators also may present disadvantages or risks not only to the investigator, but also to the medical center and the corporation.

RISKS TO CLINICAL INVESTIGATORS

Corporate funding of clinical research that is conducted in a medical center may present individual investigators with a number of disadvantages. Potential risks to the investigator include:

- restrictions imposed by the corporate sponsor on the publication or use of research results;
- pressures to emphasize commercial ventures at the expense of patient care;
- reductions in the amount of time available for other clinical responsibilities;
- increased pressures to produce or disseminate only those results that are of benefit to the corporation;
- forfeiture of the investigator's right to patent the results of his or her research; and
- cost-shifting to patients, especially for laboratory tests related to investigational new drugs.

The intensity of these risks may vary with the contractual limitations agreed to by the investigator and the corporation.

RISKS TO MEDICAL CENTERS

Medical centers also may be exposed to a number of disadvantages as a result of corporate funding of clinical research. Potential risks for the medical center include:

- a decreased emphasis on standard modes of patient care;
- a reluctance among investigators to exchange scientific information or to pursue cooperative activities;
- tension between clinical staff who support medical center-industry relationships and those who oppose commercial research in patient care settings
- pressure to modify standards of care;
- forfeiture by the medical center of the patent rights to research results;
- the loss of clinical staff to corporations; and
- inappropriate and/ or uncompensated use of medical center facilities.

The extent to which these disadvantages are realized by the medical center again may vary with the specific contractual provisions agreed to by the parties.

RISKS TO CORPORATIONS

Corporations that fund clinical research also are exposed to a variety of risks or disadvantages as a result of these research relationships. Potential risks to the corporation include:

- biased or fraudulent research results because of the pressure on individual investigators to produce data favorable to the commercial objectives of the corporation;
- a propensity on the part of the medical community to question the quality and objectivity of research funded by corporate entities; and
- lack of direct control over the course of research that is funded by the corporation.

In the current political climate, many of the direct benefits for investigators, institutions, and corporations have also been viewed by those critical of such collaborative arrangements as potential conflicts of interest. Although unfortunate, whenever money is involved, the possibility of conflict of interest or perception of conflict of interest seems to be omnipresent. The iconoclastic attitudes present in society may have heightened this perception. However, it is important to distinguish the appearance of conflict of interest from an actual conflict of interest. Differences in the types of collaborative arrangements between medical centers and industry may raise different kinds of issues. At least three different forms of

relationships between medical centers and industry have been described and similar ties between federal laboratories and industry have also become commonplace.

In the most frequent type of medical center-industry relationship, a company presents a research protocol to a clinical investigator and funds the investigator for carrying out the protocol-essentially a fee-for-service arrangement.⁶ This type of arrangement can certainly have salutary effects for both industry and medicine. This arrangement benefits health care institutions by providing supplemental financial revenue. In addition, students and fellows are introduced to the clinical research process. This partnership is in the best interest of the investigator, the center, and the company. Assuming that basic rules for scientific propriety are followed, this certainly constitutes an appropriate remunerative relationship. Although the perception of bias may always be present, to preclude such a relationship because of perception alone would be counter productive.⁶ It is incumbent upon both parties, however, to completely disclose the nature of this arrangement in all publications, presentations and applications.

A second, although less frequent type of medical center-industry relationship involves the submission of an unsolicited proposal by an individual investigator directly to a commercial company. The investigator often benefits by obtaining funds for needed equipment and supplies and the company benefits by the possibility of expanding its market potential for a given product. This arrangement also may be viewed as appropriate and mutually beneficial, assuming the proper conduct of science ensues and full disclosure is maintained.

The third and most innovative type of medical center-industry research relationship involves truly cooperative projects. Often, these types of relationships are enacted in the setting of a clinical trial. Numerous advantages exist for the individual investigator, the medical center, and industry for the development of cooperative programs between medicine and industry. The transformation of technology from basic into clinical laboratories and finally, into useful products with commercial value is an accepted and laudable practice that provides a sound basis for social, economic, and scientific policy.⁶ Full disclosure, however, is an essential ingredient to the success of this type of venture.

In 1986, Congress passed the Federal Technology Transfer Act that helped to foster closer ties between individual researchers within the government and industry. The act provided a new mechanism for government researchers to collaborate with industry, whereby government laboratories can negotiate with outside companies for exclusive licenses for products of research with a share of the royalty going to the inventor. A new program was created at the National Institutes of Health in response to the Technology Transfer Act (Collaborative Development Research and Agreement Program; CRADA). The NIH maintains a patent on new drugs or other products but grants the cooperating company a manufacturing license. Although this program has already spawned nearly 200 industry-sponsored research projects, critics have argued that the arrangement may compromise the independence of federal research efforts.⁷ Many believe this program will ultimately benefit society by accelerating the development of new products. Investigators at the National Cancer Institute have already signed 33 CRADA agreements and 24 are currently pending - far more than in any other division of NIH.^{7,8} Clearly, the CRADA program does have considerable impact upon the way researchers view themselves in relation to the profit sector.⁸ Perhaps most importantly, the program gives government researchers the opportunity to take advantage of private resources at a time when NIH funding is limited and when NIH salaries are not commensurate with private industry. This arrangement may also help to keep talented researchers working within the government sector. The predominant concerns expressed about the CRADA program have centered around potential compromise in the objectivity of participating investigators and the possibility for enhanced secrecy among researchers. These same themes are also evident in relationships between clinical investigators in medical centers and industry.

POTENTIAL PROBLEMS AND SOLUTIONS

Problems may arise when the clinical investigator and/ or medical center has a direct financial interest in the research program. This is especially true in situations in which drugs, devices, or other similar products are being examined. Researchers may hold stock or stock options in a company that manufactures the product or they may have other profit-sharing arrangements with the company. These financial interests may compromise, or give the impression of compromising, the objectivity of researchers and cause them to downplay or suppress negative data while exaggerating favorable data. As has been observed, even the most conscientious researchers have difficulty remaining totally unbiased about their work. For the clinical investigator who has an economic interest in the outcome of his or her research, objectivity is especially difficult. Economic incentives may introduce subtle biases into the way research is conducted, analyzed or reported, and these biases can escape detection by even careful peer review.

There are no data on the extent to which financial interests have influenced research projects. Nevertheless, it is clear that abuses have occurred. In perhaps the most prominent case, an ophthalmologist studied an experimental eye ointment while owning 530,000 shares of stock in the pharmaceutical company that was formed to market the product.⁹ Investigations revealed that the ophthalmologist made unauthorized modifications in the study design and minimized negative findings before selling his stock for a significant profit.¹⁰

It is extremely important that separation be made between real problems and the perception of conflict of interest. Medical centers must be involved in helping their clinical staff to avoid real conflicts and the appearance of conflicts of interest. This can only be accomplished if appropriate guidance is provided to clinical investigators on interacting with industry. Although it may be impossible to determine whether money subverts the actual obligations of individual researchers, each investigator must be aware of the perception of his/her activities.

Critics of medical center-industry research relationships have argued that such close ties alter the direction of basic research. Similar concerns have been expressed about impairing the free flow of medical information and about money subverting institutional obligations. Medical centers and individual researchers have recognized the economic necessity of pursuing new and innovative approaches to enhance their research programs. However, they have been somewhat reticent to acknowledge the countervailing need for accountability. The mere perception of conflict of interest may be enough to cast significant doubt upon an exemplary research program. Ethical standards in the conduct of clinical research are essential. It is the responsibility of each investigator to be cognizant of, and accountable for, his or her actions.

DEVELOPING ETHICAL GUIDELINES

Ethical guidelines for circumstances in which clinical researchers face economic conflicts of interest ultimately turn on two principles. First, the researcher may ethically share in the economic rewards of his or her efforts. If a drug, device, or other product becomes financially remunerative, the researcher should not be required to surrender the portion of the profit that reasonably resulted from his or her contribution. This principle underlies the Council on Ethical and Judicial Affairs' opinion on patents:

A physician may patent a surgical or diagnostic instrument he has discovered or developed. The laws governing patents are based on the sound doctrine that one is entitled to protect his discovery. (Section 9.09, *Current Opinions of the Council on Ethical and Judicial Affairs*, 1989.)

However, the researcher may not reap profits that are not justified by the value of his or her actual efforts. Thus, for example, the researcher could not ethically sell or purchase stock in a company whose drug is being tested on the basis of preliminary results from the research. The investigator would not be profiting from his or her substantive contributions, but rather would be exploiting access to information not readily available to the public, a form of "inside" trading.

The principle that the researcher may benefit from his or her efforts is limited by the principle that potential sources of bias in research should be minimized to the extent possible, particularly where there is a direct relationship between a researcher's personal interests and the potential outcome of the research.

Applying these two principles leads to several conclusions. Once the investigator becomes involved in a research project for a company or knows that he or she might become involved in the research, he or she, as an individual, cannot ethically buy or sell the company's stock until the involvement ends and the results of the research are published or otherwise disseminated to the public. As long as the investigator is involved in research on the company's product, he or she has the potential to derive profits that stem from inside information, rather than from individual effort.

Clinical investigators may have other economic ties to the companies whose products they are testing. For example, they may serve as consultants or may be retained to lecture on behalf of the company. In these cases, the guiding principle should be that the researcher's remuneration is commensurate with his or her actual efforts on behalf of the company.

Other conflicts of interest, in addition to economic concerns, are inherent in the research process and may bias the outcome of clinical investigations. For example, the desire for public recognition or a tenured faculty position may exert an undue influence on the results of clinical research. Indeed, fraud in the publication of research results has more often been motivated by academic interests than financial interests. A subsequent report will recommend guidelines to limit the potential of abuse from other conflicts of interest in the research process.

Even when ethically permissible economic arrangements exist, safeguards are needed to protect against the appearance of impropriety. Perhaps the best mechanism available to assuage public (and professional) doubts about the propriety of a research arrangement is full disclosure. Clinical researchers should therefore disclose any ancillary ties to companies whose products they are investigating. For example, they should disclose their participation in educational activities supported by the companies; their participation in other research projects funded by the companies; and consulting arrangements. The disclosures should be made to the medical center where the research is conducted, to organizations that are funding the research, and to journals that publish the results of the research.

The Institutional Review Board (IRB) and the Institutional Animal Care and Use Committee (IACUC) are examples of mechanisms in which disclosure of economic conflicts and other appropriate information has enhanced the research process. These committees function essentially in the capacity of ombudsmen to critique and analyze investigator-initiated research projects. The IRB is an important mechanism by which human subjects are protected during the conduct of a clinical research project and the IACUC functions similarly in ascertaining that any research protocol using animals follows rigid, federally mandated rules and regulations. Institutions could easily use an already constituted Ethics Committee to examine all applications for outside funding that involves collaborative arrangements with commercial interests. Alternatively, a separate person (or committee) could be assigned to review all applications for collaborative arrangements in order to help maintain objectivity and appearance thereof through periodic review of all proposals. Any proposal deemed inappropriate could be reworked to comply with the medical center's policies on conflict of interest. Medical centers should be urged to develop these policies

and also to provide clinical researchers with guidance on the implementation of complex research relationships.

The Council on Ethical and Judicial Affairs and the Council on Scientific Affairs recommend that:

1. Professional societies inform their memberships of the real or perceived risks and benefits associated with joint ventures between medical centers and industry.
2. All medical centers be urged to develop specific guidelines for their clinical staff on conflict of interest.

These guidelines should include the following rules:

- a. Once a clinical investigator becomes involved in a research project for a company or knows that he or she might become involved, he or she, as an individual, cannot ethically buy or sell the company's stock until the involvement ends and the results of the research are published or otherwise disseminated to the public.
 - b. Any remuneration received by the researcher from the company whose product is being studied must be commensurate with the efforts of the researcher on behalf of the company.
 - c. Clinical investigators should disclose any material ties to companies whose products they are investigating. They should disclose their financial ties; participation in educational activities supported by the companies; participation in other research projects funded by the companies; consulting arrangements; and any other ties. The disclosures should be made to the medical center where the research is conducted, organizations that are funding the research, and journals that publish the results of the research.
3. The formation of review committees be encouraged at all medical centers to examine disclosures by clinical staff about financial associations with commercial corporations.

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