

### ***7.1.1 Physician Involvement in Research***

Biomedical and health research is intended to contribute to the advancement of knowledge and the welfare of society and future patients, rather than to the specific benefit of the individuals who participate as research subjects.

However, research involving human participants should be conducted in a manner that minimizes risks and avoids unnecessary suffering. Because research depends on the willingness of participants to accept risk, they must be able to make informed decisions about whether to participate or continue in a given protocol.

Physician researchers share their responsibility for the ethical conduct of research with the institution that carries out research. Institutions have an obligation to oversee the design, conduct, and dissemination of research to ensure that scientific, ethical, and legal standards are upheld. Institutional review boards (IRBs) as well as individual investigators should ensure that each participant has been appropriately informed and has given voluntary consent.

Physicians who are involved in any role in research with human participants have an ethical obligation to ensure that participants' interests are protected and to safeguard participants' welfare, safety, and comfort.

To fulfill these obligations, individually, physicians who are involved in research should:

- (a) Participate only in those studies for which they have relevant expertise.
- (b) Ensure that voluntary consent has been obtained from each participant or from the participant's legally authorized representative if the participant lacks the capacity to consent, in keeping with ethics guidance. This requires that:
  - (i) prospective participants receive the information they need to make well-considered decisions, including informing them about the nature of the research and potential harms involved;
  - (ii) physicians make all reasonable efforts to ensure that participants understand the research is not intended to benefit them individually;
  - (iii) physicians also make clear that the individual may refuse to participate or may withdraw from the protocol at any time.
- (c) Assure themselves that the research protocol is scientifically sound and meets ethical guidelines for research with human participants. Informed consent can never be invoked to justify an unethical study design.
- (d) Demonstrate the same care and concern for the well-being of research participants that they would for patients to whom they provide clinical care in a therapeutic relationship. Physician researchers should advocate for access to experimental interventions that have proven effectiveness for patients.
- (e) Be mindful of conflicts of interest and assure themselves that appropriate safeguards are in place to protect the integrity of the research and the welfare of human participants.
- (f) Adhere to rigorous scientific and ethical standards in conducting, supervising, and disseminating results of the research.

*Opinion 7.1.1, Physician involvement in research, re-organizes content from several previous opinions and associated background reports:*

CEJA Report 3-A-16 Modernized *Code of Medical Ethics*

CEJA Report 3-I-00 Managing conflicts of interest in clinical trials

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

CEJA Report 2-A-96 Ethical use of placebo controls in clinical trials

Report of the Judicial Council A-A-66 Declaration of Helsinki

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  - (ii) *physicians make all reasonable efforts to ensure that participants understand the research is not intended to benefit them individually; [New content addresses gap in current guidance.]*
  - (iii) physicians also make clear that the individual may refuse to participate or may withdraw from the protocol at any time.
- (c) Assure themselves that the research protocol is scientifically sound and meets ethical guidelines for research with human participants. Informed consent can never be invoked to justify an unethical study design.
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*AMA Principles of Medical Ethics: I,II,III,V*

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.

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\* 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 Trials<sup>1</sup>

Presented by: Herbert Rakatansky, MD, Chair

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

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## Introduction

In December 1989, the AMA House of Delegates adopted a joint report of the Council on Ethical and Judicial Affairs and the Council on Scientific Affairs entitled “Conflicts of Interest in Biomedical Research.”<sup>2</sup> It outlined how conflicts of interests could be alleviated in the context of research stemming from collaborations between academic health centers (AHC) and industry.

The report relied on a broad definition of conflicts of interest, including in its scope any “conflict between the private interests and official responsibilities of a person in a position of trust.” In the context of biomedical research, this was understood to arise primarily in cases where a researcher enters into a financial arrangement with a profit-making corporation. The report noted that in such circumstances, the researcher’s dedication to the advancement of medical knowledge could conflict with his or her desire to increase income.

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

In conclusion, the report emphasized the need to minimize potential sources of bias, particularly where there is a direct relationship between a researcher’s personal financial interests and the potential outcome of the research. These recommendations are now included in Opinion 8.031, “Conflicts of Interest: Biomedical Research,” which advises AHCs to adopt guidelines that would prevent investigators from engaging in insider trading and ensure that remuneration received would be commensurate with the efforts of the researcher. Guidelines also should require the 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.<sup>3</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5,6</sup> 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.<sup>7</sup> Investigators based in academic medical centers now represent only 46% of those  
25 conducting research, a drop from 80% ten years ago.<sup>7</sup> 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.<sup>8</sup>

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.<sup>8</sup> 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,<sup>9</sup> 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.<sup>10</sup> 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.<sup>11</sup> 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.<sup>11</sup>

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.<sup>12, 13</sup> Patients were described as  
 10 “commodities, bought and traded by testing companies and doctors.”<sup>12</sup> 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.<sup>14</sup>

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.<sup>8,15</sup> 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.<sup>16,17,18,19,20,21</sup>

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,<sup>22</sup> 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.<sup>23</sup> 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.<sup>24</sup>

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.<sup>25</sup> 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.<sup>26</sup> 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.<sup>27</sup>

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.<sup>28</sup>

13  
 14 In each of these cases, a “professional judgment concerning a primary interest (...) tends to be  
 15 unduly influenced by a secondary interest (...).”<sup>28</sup> 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.<sup>29</sup>  
 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,<sup>30</sup> 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.<sup>31</sup> In one  
 40 article,<sup>32</sup> 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 criteria<sup>33</sup> or random assignments,<sup>34</sup> 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,<sup>35</sup> 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.<sup>36,37,38,39</sup> 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.<sup>40,41</sup>

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.<sup>42</sup> 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.”<sup>43</sup>  
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,<sup>44</sup> the Health Care Financing  
13 Administration (HCFA) has been ordered to cover “routine patient care” for seniors who are  
14 enrolled in trials.<sup>45</sup> 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.<sup>46</sup> 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.<sup>46</sup> 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.<sup>47</sup>  
30

### 31 *Disclosure as a safeguard against financial conflicts*

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.<sup>48</sup> 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.<sup>49</sup> 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.<sup>50</sup> 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*,<sup>51</sup> 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.<sup>52</sup> 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.<sup>53</sup>

#### 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.<sup>54</sup>

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.<sup>55</sup>

### 13 *Non-financial incentives*

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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.<sup>48</sup> 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.<sup>8</sup> 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 Countering conflicts of interests

36  
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.<sup>28</sup> 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 Conclusion

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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 Recommendations

30  
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.<sup>1</sup>

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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> For example, one biostatistician received \$10,000 to write a letter to the Journal of the American Medical Association.<sup>5</sup> 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.<sup>6, 7</sup> 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.<sup>1</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup> 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.<sup>5</sup> 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.<sup>6</sup> 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.<sup>6</sup> 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.<sup>6</sup> 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.<sup>7</sup> 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.<sup>7,8</sup> Clearly, the CRADA program does have considerable impact upon the way researchers view themselves in relation to the profit sector.<sup>8</sup> 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.<sup>9</sup> Investigations revealed that the ophthalmologist made unauthorized modifications in the study design and minimized negative findings before selling his stock for a significant profit.<sup>10</sup>

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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REPORT OF THE COUNCIL ON ETHICAL AND JUDICIAL AFFAIRS

CEJA Report 2-A-96

Subject: Ethical Use of Placebo Controls in Clinical Trials

Presented by: Charles W. Plows, MD, Chair

Referred to: Reference Committee on Amendments to Constitution and Bylaws  
(Betty P. Stephenson, MD, Chair)

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1 Introduction\*

2

3 The House of Delegates adopted Resolution 1, Ethical Use of Placebo Controls, at the Annual  
4 Meeting in 1995. That resolution, sponsored by the Young Physician's Section, called upon the  
5 American Medical Association to "study the ethical use of placebo controls in studies evaluating  
6 drug therapies in those conditions for which effective treatment exists." In response to this charge,  
7 the Council on Ethical and Judicial Affairs presents the following examination of the use of placebo  
8 controls in circumstances where an accepted therapy is available.

9

10 Clinical Research

11

12 The advancement of scientific knowledge within the medical community is one of the fundamental  
13 duties of all physicians.<sup>1</sup> Scientific research has provided physicians with the means to satisfy their  
14 enduring commitment both to individual patient health and the collective health of society.  
15 However, clinical investigation relies upon participants who are willing to accept a certain level of  
16 risk to facilitate the improvement of medical practice. While the risks involved are generally  
17 limited, there are cases where negative outcomes have been severe,<sup>2</sup> thus forcing the scientific  
18 community to address concerns that the needs of future patients could take priority over the needs of  
19 the patient participants in clinical research.

20

21 The Council has examined this issue in previous work and has provided ethical guidelines that  
22 protect patients participating in research protocols from undue risk and exploitation in the name of  
23 some greater benefit to society.<sup>3</sup> Competent study design, careful implementation, and  
24 conscientious supervision help to ensure that clinical research satisfies its dual obligation to provide  
25 verifiable scientific data and to safeguard the rights of participants.

26

27 Placebo-controlled Trials

28

29 One fundamental requirement of clinical investigation is that it must provide scientifically valid  
30 data. In the development of new drugs, trials must therefore be designed with a control capable of

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\* In accordance with the Joint Report of the Council on Ethical and Judicial Affairs and the Council on Constitution and Bylaws (I-91), this report may be adopted, not adopted, or referred. It may be amended, with the concurrence of the Council, to clarify its meaning.

1 allowing investigators to discern the effects of the drug under investigation. One of the best means  
2 to fulfill this requirement is to compare an experimental therapy with placebo.<sup>4,5</sup>

3  
4 Despite the general support of placebo controls within the scientific community, opponents of this  
5 research model have voiced objections. A particularly heated debate erupted when, in 1977, the  
6 National Institute of Allergy and Infectious Diseases organized a 22-institution study to determine  
7 the efficacy of adenine arabinoside (ara-A) in the treatment of herpes simplex encephalitis, a disease  
8 then characterized by a mortality rate of 70 percent. Despite the nature of the disease and some very  
9 preliminary research which indicated a potential for benefit, a placebo control was used in 10 of the  
10 28 patients who met all the criteria for inclusion. As predicted by the history of the disease, 7 of the  
11 10 control patients died. Mortality in the experimental group, however, was a vastly improved 28  
12 percent.<sup>6</sup>

13  
14 Objections to this trial centered in part on the insistence of experimenters to adhere to the rigors of  
15 statistics and to subsequently include a placebo group despite the historical data which could verify  
16 a mortality rate similar to that demonstrated by the control. In essence, some critics felt that the  
17 interests of the control group had been given insufficient weight in considerations of trial design  
18 because the investigators refused to undertake a more complicated analysis based upon an historical  
19 control group.<sup>7</sup>

20  
21 This critique of the Ara-A study is not fair to the investigators involved. Many factors may  
22 contribute to the inability of past cases to provide an effective control and as a result, historically  
23 controlled trials can be difficult to interpret and often yield optimistic but inaccurate results. For  
24 instance, in 32 uncontrolled trials of portocaval shunt operations for portal hypertension, 24 reported  
25 positive results for survival. However, in six randomized studies of the same treatment, the  
26 operation was never shown to be effective.<sup>4</sup> There are a number of possible explanations for this  
27 and similar discrepancies. Patients formerly receiving treatment may have been evaluated using  
28 different criteria or they may have experienced a different medical environment affecting their  
29 response to treatment. Additionally, it may be difficult to find an equivalent patient sample as past  
30 studies may have relied upon markedly different inclusion criteria. While it may not be possible to  
31 identify all the factors contributing to the poor performance of many historically controlled studies,  
32 the results are well documented. Researchers who compared 56 historically controlled clinical  
33 studies with 50 randomized controlled studies for the same condition discovered that the  
34 experimental therapy was shown to be effective in 44 of the historically controlled trials. Those  
35 trials employing more rigorous controls achieved a far more modest success rate finding positive  
36 results in only 10 of 50 trials.<sup>4</sup>

37  
38 Despite the indicated difficulties associated with the alternative controls proposed by critics, the ara-  
39 A study was useful in providing a forum for discourse on the ethical use of placebo controls.  
40 However, the existence of federal guidelines that accommodate different study designs in the case  
41 of fatal or serious disease render many of the aforementioned objections to the majority of placebo  
42 controls difficult to sustain. In most cases the clinical research community recognizes the value of  
43 well-designed placebo controlled trials in determining the efficacy of an experimental therapy.<sup>5</sup>

1 Ethical Questions Raised by the Availability of Accepted Therapies

2  
3 Many observers can justify the risks borne by patients in a placebo group by arguing that the  
4 absence of effective treatment for a given condition warrants if not demands the rigorous study of  
5 experimental drugs. Additionally, because no adequate therapy exists, the control group may not be  
6 any worse off than non-participants. However, when a therapy does exist, support for placebo  
7 controls often dissipates in the face of what some perceive to be ideals which emphasize the  
8 potential benefits gleaned by future patients without giving sufficient weight to the interests of  
9 research participants. Under these conditions, the possibility is raised that the risks associated with  
10 receiving a placebo will include the fact that participation in the control group will often deprive  
11 patients of standard medication. An argument can be made that this substantially elevates the level  
12 of commitment demanded of enrollees by potentially requiring the tolerance of discomforts that  
13 could otherwise be avoided.

14  
15 The trials of ondansetron as a medication to control post-chemotherapy emesis are cited as an  
16 example of the certain discomfort suffered by the control group despite the availability of other  
17 effective drugs.<sup>8,9</sup> Critics find it difficult if not impossible to justify this type of suffering as it  
18 requires the physician-investigator to intentionally deprive patients of care that could provide relief.

19 They contend that such behavior violates the physician's ultimate obligation to individual patient  
20 advocacy by willfully placing the interests of the control patients behind those of future patients or  
21 society at large. This reasoning can lead to an inappropriate image of investigators as physicians  
22 who rely upon an "ends justify the means" approach to research and consequently demands careful  
23 scrutiny and educated discourse.

24  
25 Effective and Accepted Therapies

26  
27 Before the objections to placebo-controlled studies that deny participants access to accepted  
28 therapies can be addressed, it is important to appreciate the complexity of the issue by establishing  
29 the limitations of the terms "accepted" and "effective." Accepted therapies that constitute standard  
30 practice or that provide physicians with a treatment option do not always demonstrate statistically  
31 significant benefit when tested against controls. Similarly, those drugs that have been labeled  
32 "effective" through research cannot offer an unconditional guarantee of full benefit when applied  
33 clinically. Many drugs are only partially effective at alleviating the conditions they are designed to  
34 treat and even drugs that may be considered more fully effective rarely confer total benefit across all  
35 patients. Additionally, the use of many drugs is accompanied by adverse effects which may prevent  
36 their application to certain patients. These issues of uncertainty inherent in drug therapy  
37 significantly complicate any discussion of ethical positions and proposed alternatives that hinge  
38 upon the presence of established treatments.

39  
40 The ability of placebos to confer benefit in some circumstances adds a further element of  
41 complexity. Although the mechanism is unclear, there is evidence to suggest that treatment with a  
42 placebo can have a measurable effect.<sup>10</sup> Additionally, patients often improve spontaneously or as a  
43 result of the increased attention characteristic of many clinical trials. When the possible benefits of  
44 participation in a placebo group are coupled with the uncertain nature of drug therapy and the often  
45 inconsistent behavior of a particular disease under study, it becomes clear that deciding whether or  
46 not to include a placebo control is not as simple as choosing between providing and denying  
47 effective treatment.

1 Alternative Trial Designs

2  
3 The importance of conducting well designed and well controlled clinical trials is underscored by the  
4 fact that ineffective medications are financially burdensome to society and potentially dangerous to  
5 patients. Consequently, well controlled clinical trials are a necessary extension of the physician's  
6 obligation to safeguard the health interests of all patients. It is therefore imperative that any  
7 discussion concerning the potential drawbacks of placebo-controlled trials be accompanied by an  
8 evaluation of viable alternative trial designs that may be able to ensure the safety and efficacy of  
9 experimental or unproved medications.

10  
11 In circumstances where an accepted therapy exists, one of the most frequently used alternative study  
12 designs employs an active control. This type of protocol allows the investigator to compare directly  
13 the effects of the experimental drug with the effects of a standard therapy without denying any  
14 patients in the control group access to accepted medications. Aside from its apparent advantages in  
15 patient protection, it has been argued that the true goal of medical research when one therapy has  
16 already been established is to compare the experimental drug with existing drugs.<sup>8</sup> In other words,  
17 some observers maintain that what is important to researchers and practicing physicians is how well  
18 the new drug measures up to standard treatments and not how well it performs against placebo.

19  
20 It is important to recognize the shortcomings of the assumption that clinical trials are conducted  
21 only to establish the comparative efficacy of a new drug. Relative efficacy is not the sole  
22 characteristic upon which the value of a drug is measured and in fact a physician may very well  
23 prize an effective drug even if it cannot match the performance in research trials of an accepted  
24 therapy.<sup>11,12</sup> Not all patients or diseases behave according to the statistical mean of clinical  
25 research trials and consequently many patients may not respond to standard therapy. Others may  
26 have adverse reactions which preclude its use or may have cost concerns that can be alleviated by  
27 the introduction of an alternative. If drugs are compared exclusively to existing treatments, those  
28 that are less effective might be discarded despite the potential advantages they could confer to  
29 patients with varied needs. In short, a process that requires an experimental drug to demonstrate  
30 efficacy comparable to that of existing medications could reduce the variety of clinical options  
31 available to physicians. It seems clear that there are ultimately many aims of clinical research  
32 besides a need to establish the efficacy of an experimental drug as compared to that of an existing  
33 therapy.

34  
35 Even if one doesn't recognize the variety of motivations for clinical research and assumes that  
36 establishing comparative value between drugs is the primary aim of clinical research for conditions  
37 treated with an existing therapy, several other potential problems still exist and must be addressed.  
38 For instance, the abandonment of placebo controls could often result in statistical complications. In  
39 trials that attempt to evaluate the effectiveness of an experimental drug in relation to an active drug,  
40 establishing equivalence between the unknown and the control will often be the goal. However,  
41 unlike trials designed to prove a difference, there is no agreed upon standard to establish a  
42 statistically significant similarity.<sup>4,13</sup> As a result, conclusively demonstrating that two drugs have an  
43 equal effect is extremely difficult.

44  
45 Even if equivalence could be demonstrated conclusively, many accepted therapies have not  
46 consistently shown a level of response that provides a useful comparison. For instance, in the 14  
47 efficacy studies conducted on Prozac before it was granted FDA approval, it was demonstrated to be

1 significantly more effective than placebo only 5 times.<sup>14</sup> If an experimental drug is compared only  
2 to an accepted therapy with similarly inconsistent research results, demonstrating an equivalent  
3 effect between the drugs is not an inherently useful result. Under these circumstances, there would  
4 be no means to determine if both drugs were effective, if neither was effective, or if the study was  
5 simply incapable of distinguishing an effective agent from one that is ineffective. This problem is  
6 clearly illustrated by the trials of one antidepressant considered by FDA in the early eighties.<sup>15</sup> The  
7 new drug was compared both to the standard antidepressant, imipramine, and to placebo in six  
8 separate trials. When the experimental drug was compared with imipramine alone, both drugs  
9 appeared to confer substantial and equal benefit in all trials. However, when the data from the  
10 placebo group was examined, the active drugs were shown to be more effective than placebo in only  
11 one of the six trials. In fact, based on the data it would be difficult to assert that the five remaining  
12 trials even suggested the superiority of the active drugs much less a significant or demonstrable  
13 positive effect.<sup>15</sup>

14  
15 One final concern about trials designed to establish equivalence is the inherent incentive structure.  
16 Studies designed to establish a difference between a control and an experimental drug provide an  
17 incentive to conduct careful research since poor technique tends to obscure differences rather than  
18 create them.<sup>4,13,16</sup> When studies are geared toward demonstrating equivalence between two  
19 therapies however, there is less pressure on investigators to ensure that the high standards of clinical  
20 research are met. Flaws in equipment, errors in measurement and even insufficiently controlled  
21 external factors may support the conclusion rather than defeat the trial.<sup>13,16</sup> This raises the  
22 possibility that in some cases apparently favorable results may not in fact be meaningful.

23  
24 The concerns surrounding the use of active controls do not necessarily preclude their use in  
25 comparative research. The benefits of providing control group patients with standard treatments  
26 cannot be denied. Consequently, the past performance of the standard drug should be considered by  
27 study designers to determine if it could provide a sufficient point of comparison for the conditions  
28 and populations involved in a research protocol. If the standard treatment is consistently effective,  
29 as in the case of certain antibiotics, it may be more difficult to justify the use of placebo. However,  
30 the uncertainty of benefit that characterizes most medications may make them unsuitable as  
31 controls. In these cases, the use of placebo will be more easily justified.

32  
33 One possible solution to many of the difficulties associated with actively-controlled clinical trials is  
34 to combine the use of active and placebo controls.<sup>13,15</sup> The active control may allow comparisons to  
35 be made that will prove helpful in clinical practice. The placebo, meanwhile, will standardize the  
36 entire trial. If the active control is characterized by inconsistent results, the placebo will provide the  
37 necessary baseline to test the experimental drug. If the active control is well established and  
38 consistently effective, the placebo control will verify the usefulness of the study itself.<sup>17</sup> In this  
39 case, if the active control proves to be no more useful than placebo, there may be problems with the  
40 selected patient population, study design, or research technique. It is important to note that the  
41 placebo group can be relatively small and still satisfy the demands of clinical research. While this  
42 design confers substantial statistical advantages, it still requires a placebo group and may not meet  
43 the demands of critics who contend that the use of placebo is unacceptable in cases where an active  
44 control is available.

1 Additional Alternatives  
2

3 The problems associated with active control trials require the further analysis of other alternatives  
4 that may be effective at minimizing the risk to patients while still providing adequate data.  
5 Modifications to placebo-controlled trials can often satisfy these requirements. For instance, fail-  
6 safe protocols prevent seriously ill patients from being kept on placebo by implementing frequent  
7 clinical examinations and incorporating fixed criteria for determining when patients should no  
8 longer participate.<sup>4,18</sup> Patients who show any decline at the time of their first examination are  
9 removed from the trial. Likewise, those who show no improvement by the second or third  
10 evaluation are also removed. Alternatively, it is possible to monitor patients and shift those non-  
11 responders in the placebo arm of a clinical study to the active medication.<sup>13,18</sup> This simultaneously  
12 prevents patient attrition from the study and ensures that patients who require active medication are  
13 treated accordingly. Other escape clauses and rescue treatments can also be included in a trial  
14 design to prevent participants from being exposed to undue risk.<sup>4</sup>  
15

16 Some conditions may allow for the use of alternative study designs that do not require placebo. For  
17 instance, some experimental treatments can be tested with dose-response and concentration-  
18 response designs.<sup>18</sup> Whenever possible, these and other models should be considered by researchers  
19 as an alternative to placebo-controlled protocols.  
20

21 Declaration of Helsinki  
22

23 Regardless of safeguards designed to protect patients, opponents of placebo-controlled trials that  
24 would deny participants access to accepted therapies suggest that requiring such a control clearly  
25 violates the ethical considerations outlined in the Declaration of Helsinki.<sup>8,19</sup> Originally written in  
26 1964, the Declaration was augmented in 1975 to read in part, "In every medical study, every patient  
27 -- including those of a control group, if any -- should be assured of the best proven diagnostic and  
28 therapeutic method."<sup>20</sup> While this statement does appear to proscribe the use of placebo controls in  
29 circumstances where a proven therapy exists, it seems equally to preclude all clinical research as  
30 subjects in the experimental arm of any trial are guaranteed to receive an unproved therapy. A more  
31 complete reading demonstrates that the intent of the Declaration of Helsinki is not to provide unduly  
32 restrictive mandates but to protect the interests of patients who are willing to accept some risk for  
33 potential but undetermined benefit or for the benefit of others. This obligation to protect the  
34 altruistic participants was also elaborated in the Belmont Report authored in 1979 by the National  
35 Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.<sup>21</sup> These  
36 documents share the sentiment that, while eradicating all risks inherent in human research is not  
37 realistic, researchers must attempt to minimize the potential dangers involved in their respective  
38 studies.  
39

40 Informed Consent  
41

42 Ensuring rigorous adherence to the principle of informed consent is perhaps the best possible  
43 solution to the ethical difficulties associated with using a placebo control rather than an accepted  
44 therapy control. The right of patients to control their course of medical care is one of the  
45 fundamental tenets underlying standards of informed consent. A result of this freedom is that  
46 patients cannot be expected to conform to one response when presented with information that  
47 requires analysis of the risks and benefits involved.<sup>22</sup> As with other areas of medicine, patients who

1 are considering involvement in clinical research should be allowed to weigh the risks of being  
2 denied access to the standard treatment against the benefits of facilitating a more efficacious study.  
3 To assume that patients would not volunteer to suffer minor symptoms for the benefit of future  
4 generations could be construed as paternalistic. Furthermore, such an assumption may undermine  
5 the patient's legitimate, altruistic motivations and deny him or her the opportunity to contribute to  
6 medical progress.

7  
8 Informed consent, however, cannot be relied upon to justify all research proposals.<sup>23</sup> There may be  
9 research designs that would subject participants to unnecessary or extreme levels of risk and  
10 patients must be protected from these trials. Institutional Review Boards (IRB) and Ethics  
11 Committees should continue to screen research designs to evaluate the threat of possible harm to  
12 patients in an effort to minimize the risks of clinical research and to preserve the integrity of  
13 medical investigation.

14  
15 Institutional review of research proposals must be accompanied by rigorous adherence to the  
16 requirements of informed consent during the trial. This need is reinforced by studies which have  
17 shown that participants in clinical research have difficulty understanding the process and  
18 implications of controlled trials.<sup>24</sup> One such study indicated that 40 percent of patients in  
19 psychopharmacologic trials failed to recognize that some participants would be given a placebo  
20 rather than an effective treatment.<sup>25</sup> This failure to comprehend the risks involved or even the  
21 procedure itself has been attributed in part to patients' adherence to the assumption that their  
22 physician would only act in their best individual interests.<sup>25</sup> Whatever the cause of this  
23 misunderstanding, it must be addressed through the provision of comprehensive information by  
24 physicians and careful adherence to the guidelines governing informed consent. Consent forms  
25 should be reviewed by IRBs prior to a protocol's initiation to ensure that they contain all the  
26 necessary material including but not limited to study design, use of placebo controls and the  
27 subsequent implications, possible side-effects, and mechanisms for the protection of patient welfare.  
28 If the risks of a particular trial warrant additional caution, an objective third party can be included  
29 in the consent procedure to verify understanding and assent.<sup>4</sup> Finally, the standards of informed  
30 consent should never be lowered for any reason including a belief that full disclosure would deter  
31 patients from enrolling in a study thus adversely impacting the viability of that initiative.

### 32 Considerations for the Ethical Use of Placebo Controls

34  
35 The advantages of using placebo controls in clinical research are clear and the use of these controls  
36 is generally accepted in the scientific community, although exceptions have been made on ethical  
37 grounds for conditions involving predictable and irreversible consequences.<sup>26</sup> However, as  
38 previously discussed, circumstances in which the experimental drug is applied to a condition with a  
39 standard treatment raise some legitimate ethical concerns that need to be addressed in the research  
40 process. Clinical investigators studying a drug under these circumstances cannot simply assume  
41 that the use of a placebo control is justified because of its capacity to provide superior data. While  
42 statistical results that can be verified in experimentation are important to ensuring the safety and  
43 efficacy of prescription drugs, the individual needs of the research subjects must be given priority in  
44 the protocol design. When an accepted therapy exists, several factors must be considered to ensure  
45 that study proposals meet equally the demands of science and ethics.

1 Perhaps the most significant factor to consider is the condition for which treatment is being tested.  
2 Diseases that would cause irreversible damage over the course of study preclude the use of placebo  
3 controls if including them would deny patients access to medications capable of preventing or  
4 slowing illness progression.<sup>13,15,18,27,28</sup> Additionally, conditions that are characterized by severe or  
5 painful symptoms require researchers to carefully consider alternative designs and may render  
6 inappropriate the use of placebo controls. For conditions that typically cause mild symptoms, the  
7 use of placebo controls is justified if patients give their consent to participate after being adequately  
8 informed about the nature of the trial and alternatives to enrollment.

9 Another significant factor to consider is the drug against which an experimental therapy may be  
10 tested. As noted earlier, most medications are not effective across all populations. The conditions  
11 for those who are not helped by otherwise effective medications demand the continued development  
12 of competing or alternative drugs. Furthermore, those groups that are not responsive to existing  
13 medications could serve in a placebo-controlled trial with no subsequent denial of benefit.<sup>18</sup>  
14

15 The side-effects of known therapies also warrant consideration in the process of formulating a study  
16 design.<sup>27,28</sup> Some commonly used therapies can cause severe adverse effects and secondary  
17 consequences that may allow researchers ethically to conduct placebo-controlled trials even though  
18 existing therapies are effective. Following the necessary assumptions that underlie the ethical  
19 requirement of informed consent, researchers must recognize that patients cannot be expected to  
20 behave uniformly, even in identical situations. Some patients may be willing to forgo standard  
21 treatment and accept the possibility of receiving a placebo if they can avoid suffering the adverse  
22 effects of the accepted course of therapy. Within the confines of ethical practice, it is not the  
23 position of the researcher or physician to deny patients the opportunity to make that decision. If the  
24 adverse effects of a standard drug are so mild and the benefits so great as to call into question the  
25 competence of a patient who would choose to forgo that treatment, offering patients the option of  
26 entering a placebo-controlled trial would be unethical.  
27

28 The cost of existing medication might also encourage some patients to seek enrollment in a placebo-  
29 controlled trial. However, this characteristic of standard therapy must not be relied upon to attract  
30 patients in low socioeconomic groups. While cost may motivate the development of new therapies,  
31 the inability of a patient to pay for standard medication cannot be used to justify enrolling that  
32 patient in a clinical trial. Furthermore, it is unacceptable to argue that those patients who do not  
33 normally have access to standard therapies would not be deprived of treatment by entering a placebo  
34 arm and can therefore provide a control group. Such enrollment capitalizes on their misfortune and  
35 relies upon the coercive force of monetary constraints to satisfy the statistical demands that require  
36 a sufficiently large control population. It would also be unacceptable, however, to exclude them  
37 from such research solely on the basis of their monetary resources.  
38

39 Another consideration is the length of the study. It is easier to justify denying a patient standard  
40 therapies for a brief period of time than it is to support the long-term exclusion from accepted  
41 treatment. If a researcher adequately justifies a placebo-controlled study and the IRB approves the  
42 design, the obligation remains to minimize the time patients are denied access to standard treatment.  
43 Interim data review by objective observers currently allows investigators to terminate studies if  
44 they prove ineffective or dangerous. Likewise, if a drug demonstrates its efficacy and safety prior to  
45 scheduled trial termination, participants receiving a placebo are switched to the active treatment.  
46 These practices, as well as the implementation of alternative study designs that minimize the

1 exposure to placebo, should continue in order to prevent patients from being denied accepted  
2 treatment unnecessarily. Additionally, the ability of patients to end their participation in the trial  
3 must be made explicit to prevent any subjects from feeling trapped by their initial consent.

4  
5 Conclusion  
6

7 The controversy that surrounds the use of placebo controls in research is particularly intense when  
8 the experimental drug is designed to treat conditions for which known effective therapies already  
9 exist. Critics contend that their use conflicts irreconcilably with the physician's primary duty to  
10 treat the individual patient. There is little doubt that presenting a patient with a placebo in place of a  
11 more effective medicine does introduce a level of conflict with the physician-investigator's  
12 obligation to exercise every available option for each individual patient. It should be noted,  
13 however, that this conflict is similar to that involved in most clinical research that requires the  
14 physician to present the patient with a certain level of risk in return for uncertain benefit.  
15 Furthermore, the expense of abandoning placebo controls altogether would be paid by future  
16 generations of patients who might be exposed to drugs of unknown efficacy or denied a sufficient  
17 number of options to meet individual needs. This ultimately introduces a conflict with medicine's  
18 enduring commitment to providing safe and effective treatments.

19  
20 Recognizing the need to balance two distinct obligations on the part of the physician, the Council  
21 proposes the following guidelines to safeguard the interests of the individual patient in light of the  
22 need to provide adequate data for the advancement of medicine.

23  
24 1. Placebo controls are an important part of medicine's commitment to ensuring that the safety  
25 and efficacy of new drugs are sufficiently established. Used appropriately, placebo controls can  
26 safely provide valuable data and should continue to be considered in the design of clinical trials.  
27 The existence of an accepted therapy does not necessarily preclude the use of such controls.

28  
29 2. Investigators must be extremely thorough in obtaining informed consent from patients. To  
30 the extent that research is dependent upon the willingness of patients to accept a level of risk, their  
31 understanding of the potential harms involved must be a top priority of any clinical investigation.  
32 The possibility presented in some studies that patients often do not fully understand the research  
33 protocol and therefore truly can not give informed consent demonstrates a need to heighten the  
34 efforts of researchers to impress upon their subjects the nature of clinical research and the risks  
35 involved. Patients are capable of making decisions when presented with sufficient information and  
36 it is the responsibility of the IRB and the individual investigators involved to ensure that each  
37 subject has been adequately informed and has given voluntary consent. Each patient must also be  
38 made aware that they can terminate their participation in a study at any time.

39  
40 3. Informed consent cannot be invoked to justify an inappropriate trial design. IRBs as well as  
41 investigators have an obligation to evaluate each study protocol to determine whether a placebo  
42 control is necessary and whether an alternative study design with another type of control would be  
43 sufficient for the purposes of research. Protocols that involve conditions causing death or  
44 irreversible damage cannot ethically employ a placebo control if alternative treatment would  
45 prevent or slow the illness progression. When studying illnesses characterized by severe or painful  
46 symptoms, investigators should thoroughly explore alternatives to the use of placebo controls. In  
47 general, the more severe the consequences and symptoms of the illness under study, the more

1 difficult it will be to justify the use of a placebo control when alternative therapy exists.  
2 Consequently, there will almost certainly be conditions for which placebo controls cannot be  
3 justified. Similarly, the use of a placebo control will more easily be justified as the severity and  
4 number of negative side-effects of standard therapy increase.

5  
6 4. Researchers and IRBs should continue to minimize the amount of time patients are given  
7 placebo. The rationale provided by investigators for the length of study will give IRBs the  
8 opportunity to ensure that patients are given placebo therapy for as short a time as possible to  
9 provide verifiable results. Additionally, the interim data analysis and monitoring currently in  
10 practice will allow researchers to terminate the study because of either positive or negative results,  
11 thus protecting patients from remaining on placebo unnecessarily.

12  
13 5. Science should continue to pursue alternative study designs that will allow investigators to  
14 test new drugs effectively without exposing patients to a withdrawal from standard treatments.

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## REPORTS OF STANDING COMMITTEES OF THE HOUSE OF DELEGATES

### JUDICIAL COUNCIL

The following reports (A, C, D) were presented by Dr. E. G. Shelley, *Vice Chairman*. Report B, "Eulogy for James H. Berge, MD," appears on page 12. Report E, "Nominations for Affiliate Membership in the American Medical Association" appears on page 163.

#### A. Declaration of Helsinki

During the past several years, the American Medical Association has given much attention to the subject of ethical guidelines for clinical medical investigation. A number of meetings have been held at which representatives of the Association and other organizations such as the American Federation for Clinical Research, the American Society for Clinical Investigation, the Central Society for Clinical Research, and the American College of Physicians, have discussed the desirability of adopting guidelines or standards or rules for clinical medical investigation. It is the consensus of knowledgeable individuals in this field that guidelines for medical clinical investigation should be developed and promulgated. It is the further thinking of these individuals, and the Judicial Council concurs in this thinking, that the Declaration of Helsinki adopted by the World Medical Association in 1954 is the expression of basic principles to which all honorable physicians and investigators can subscribe and may be accepted as guides to ethical conduct in medical investigation.

The Judicial Council has reviewed the Declaration of Helsinki and is of the opinion that it is in accord with the *Principles of Medical Ethics* of the American Medical Association. The Judicial Council, therefore, submits this Declaration to the House of Delegates with the recommendation that the House of Delegates endorse the Declaration of Helsinki as a guide to those who are engaged in clinical medical investigation.

#### DECLARATION OF HELSINKI RECOMMENDATIONS GUIDING DOCTORS IN CLINICAL RESEARCH

It is the mission of the doctor to safeguard the health of the people. His knowledge and conscience are dedicated to the fulfillment of this mission. The Declaration of Geneva of the World Medical Association binds the doctor with the words: "The health of my patient will be my first consideration" and the International Code of Medical Ethics declares that "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest." Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to suffering humanity, the World Medical Association has prepared the following recommendations as a guide to each doctor in clinical research. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

In the field of clinical research a fundamental distinction must be recognized between clinical research in which the aim is essentially therapeutic for a patient, and the clinical research, the essential object of which is purely scientific and without therapeutic value to the person subjected to the research.

##### I. Basic Principles

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.
2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.
3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others.
5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

##### II. Clinical Research Combined with Professional Care

1. In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgment it offers hope of saving life, re-establishing health, or alleviating suffering. If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity, the permission of the legal guardian replaces that of the patient.
2. The doctor can combine clinical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that clinical research is justified by its therapeutic value for the patient.

### III. Non-Therapeutic Clinical Research

1. In the purely scientific application of clinical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom clinical research is being carried out.
2. The nature, the purpose and the risk of clinical research must be explained to the subject by the doctor.
- 3a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured.
- 3b. The subject of clinical research should be in such a mental, physical and legal state as to be able to exercise fully his power of choice.
- 3c. Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the research worker; it never falls on the subject even after consent is obtained.
- 4a. The investigator must respect the right of each individual to safeguard his personal integrity, especially if the subject is in a dependent relationship to the investigator.
- 4b. At any time during the course of clinical research the subject or his guardian should be free to withdraw permission for research to be continued. The investigator or the investigating team should discontinue the research if, in his or their judgment, it may, if continued, be harmful to the individual.

REPORT OF REFERENCE COMMITTEE ON AMENDMENTS TO CONSTITUTION AND BYLAWS: On recommendation of the Reference Committee, the House voted to adopt Report A of the Judicial Council and Report M (p. 51) of the Board of Trustees and urged publication of the Declaration of Helsinki in state and local journals for the information of all physicians.

The following report was presented by Dr. Philip H. Jones, *Chairman*:

Report A of the Judicial Council and Report M (p. 51) of the Board of Trustees urge that the Declaration of Helsinki, already adopted by the World Medical Association, be endorsed by the House of Delegates as a guide to those who are engaged in clinical medical investigation. The Judicial Council report further indicates that the Declaration of Helsinki is in accord with the *Principles of Medical Ethics* of the American Medical Association.

#### C. Special Report Concerning Unethical Hospital Assessments

At the Clinical Convention of the AMA House of Delegates in November 1965, the Pennsylvania delegation introduced resolution no. 13. The resolution reads as follows:

WHEREAS, A 'bed tax' has been imposed on doctors serving on the medical staffs of hospitals under the guise of voluntary contributions to intern and resident educational programs; and  
 WHEREAS, Physicians have lost their hospital privileges as a result of refusing to pay such 'contributions';  
 and  
 WHEREAS, Such taxes have been declared in violation of the *Principles of Medical Ethics* of the American Medical Association; Section 7, paragraph 9, which reads as follows;

"Compulsory Assessments, that is, assessments which, if not paid, would automatically cause doctors to lose staff membership, are not in the best traditions of ethical practice. It is not proper to condition medical staff membership on compulsory assessments for any purpose." (Judicial Council, 1962);

therefore be it

*Resolved*, That it is hereby declared to be a violation of the *Principles of Medical Ethics* of the American Medical Association for a physician, group or organization of physicians to take any action that imposes payment by physicians to a hospital for any purpose when such payment or nonpayment will, in any way, affect the granting or retention of hospital privileges to any physician.

The Reference Committee on Insurance and Medical Service, believing that the *Resolved* clause of resolution no. 13 broadens the area of previous Judicial Council opinions, recommended that resolution no. 13 be referred to the Judicial Council for consideration and such action as it deems necessary.

In 1952 the Judicial Council called attention to proposals whereby some hospitals suggested that physicians who utilize the hospital facilities pay to the hospital a percentage of the fees which they receive from their patients while being cared for in the hospital. The Council expressed its opinion that this was a form of fee splitting or sharing of professional fees with a lay organization which should not render professional services in the first place, but which in addition, has already levied its regular bill for the services which it legitimately rendered.

At the June 1958 Annual Convention of the Association, resolution no. 55 asked that the House of Delegates reiterate its position with regard to condemning compulsory assessments of members of medical staffs for building funds and the practice of required audits of staff members' financial records as a requisite for continued staff appointment. The Reference Committee on Medical Education and Hospitals recommended