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AMERICAN
MEDICAL COLLEGES

Protecting Subjects, Preserving Trust, Promoting Progress–

Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research

Task Force on Financial Conflicts of Interest
in Clinical Research

December 2001

AAMC Task Force on Financial Conflicts of Interest In Clinical Research

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* Due to unanticipated professional obligations arising from the September 11th, 2001, attacks, Hedrick Smith was unable to participate in the drafting of this report.

** Susan Hellman, M.D., declines to endorse the report, primarily due to her concern that its recommendations present an impediment to research innovation.

The work of the Task Force was supported in part by a grant from the Howard Hughes Medical Institute.

Preface

In October of 2000, in a speech entitled *Trust Us to Make A Difference*, Dr. Jordan Cohen, President of the Association of American Medical Colleges (AAMC), announced the formation of a new Task Force on Conflicts of Interest in Clinical Research chaired by Dr. William Danforth, Chancellor Emeritus of Washington University of St. Louis.[1] Dr. Cohen charged this Task Force to respond to deepening public concern over researchers' perceived conflicts of interest by forging consensus principles and guidelines for the oversight of financial interests in research involving human subjects.

To achieve a broad consensus in support of new policy recommendations, the AAMC selected Task Force members not only from the leadership of academic medicine, but also from the ranks of prominent clinical investigators, patient representatives, former legislators, drug and device company executives, and journalists. The Task Force met in May and September of 2001 and engaged in consultation and extensive deliberations.[2] The first product of these efforts is this document, entitled *Guidelines for Developing and Implementing A Policy Concerning Individual Financial Interests in Research*. The 2001 *Guidelines* are intended to augment and impart greater specificity to the AAMC's 1990 *Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research*.

In creating new guidance, Task Force members drew upon their varied experience as discoverers, developers, producers, and consumers of medical products, but remained focused on a shared objective: to preserve public trust in clinical research while sustaining medical progress. As a result, the 2001 *Guidelines* recommend policies that will strengthen the protection of human subjects, while enabling the robust, productive collaborations between industry and academic medicine that have developed in the past three decades and have contributed greatly to improvements in patient care and to the success of American medicine.

The 2001 *Guidelines* provide a model for baseline standards and practices in the oversight of financial interests in research. This guidance addresses the financial interests of

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[1] Cohen, J.J. Trust us to make a difference: Ensuring public confidence in the integrity of clinical research. Acad. Med. 2001; 76:209-214.

[2] The Task Force acknowledges the prior efforts of a group of leaders from academic medicine who met in November of 2000 for a consensus conference moderated by Dr. Joseph B. Martin, Dean of the Faculty of Medicine at Harvard Medical School. The Consensus Statement produced by this group contains a number of the recommendations endorsed in the AAMC's 2001 *Guidelines*.

individual faculty, staff, employees, students, fellows and trainees of our member institutions. Currently, the Task Force is considering principles for oversight of the financial interests that institutions and their officers may hold in human subjects research. Informed by these deliberations, the AAMC intends to issue a second guidance document on institutional financial interests in human subjects research within the coming year.

I. Introduction

Institutions in which faculty, staff, or students conduct research involving human subjects must ensure that the safety and welfare of those subjects and the integrity of the research are never subordinated to, or compromised by, financial interests or the pursuit of personal gain. The AAMC Task Force on Financial Conflicts of Interest in Clinical Research acknowledges significant ongoing public concern about the existence of financial interests in human subjects research, and strongly encourages academic institutions to respond in ways that instill confidence in their capacity to identify these interests and to manage them safely and effectively.

Competing interests, particularly those engendered by a desire to advance scientific knowledge or to achieve professional recognition, are an inescapable fact of academic life. Most are managed through institutional policies and practices, and through the constraints imposed by the scientific method.[3] Yet financial interests in human subjects research are distinct from other interests inherent in academic life that might impart bias or induce improper behavior, because financial interests are discretionary, and because the perception is widespread that they may entail special risks. Specifically, opportunities to profit from research may affect - or appear to affect - a researcher's judgements about which subjects to enroll, the clinical care provided to subjects, even the proper use of subjects' confidential health information. Financial interests also threaten scientific integrity when they foster real or apparent biases in study design, data collection and analysis, adverse event reporting, or the presentation and publication of research findings.

At the same time, a principled partnership between industry and academia is essential if we are to preserve medical progress and to continue to improve the health of our citizenry. The generous public support of scientific research in America's universities since World War II has been predicated on the expectation that scientific advancements will yield tangible public benefits - a robust economy, strong national security, and a healthy citizenry. Yet, public research support is, for the most part, purposefully limited in scope to basic research, and essentially ceases at the point at which scientific invention enters the pathway of product development. In biomedicine, with rare exceptions, it is the private sector, not academia, that develops diagnostic, therapeutic, and preventative products and brings them to market. At the crucial interface between innovation and development, researchers from academic medicine often play a critical role by conducting the

[3] D. Korn, Conflicts of interest in biomedical research. JAMA 2000; 284: 2234-2237.

early translational research that gives rise to new products, and by testing these novel products for safety and efficacy.

As the AAMC first noted in its 1990 *Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research*, the opportunity for researchers to receive financial rewards from these endeavors is not intrinsically unacceptable, as long as this opportunity does not adversely influence scientific or clinical decision-making. Importantly, however, though a researcher may strive to insulate his or her decision-making from bias, the mere appearance of a conflict between financial interests and professional responsibilities may weaken public confidence in the researcher's objectivity. The real and apparent risks posed by financial interests likewise have the potential to threaten public support for the research mission of academic institutions. The credibility of academic medicine - and the public trust we prize so highly - could be undermined by revelations that an institution has failed to exercise rigorous oversight of financial interests in human subjects research and may thereby have exposed research subjects to avoidable harms.

Because the safety and welfare of human beings are at stake, financial interests in human subjects research are rightly the focus of intense scrutiny. Renewed attention to what are often termed "financial conflicts of interest" is occurring at a time when academic medical institutions are turning increasingly to private funds as a source of support for clinical research. Moreover, current federal policies encourage institutions to seek private investment as a vehicle for translating academic biomedical research into medically useful products. Under the regulations implementing the Bayh-Dole Act of 1980,[4] institutions and researchers are to share in the return on successful inventions arising from federally-funded research.

Bayh-Dole is widely viewed as having created incentives for socially useful collaboration between academia and industry. The resulting commercialization of research harnesses the collective intellectual and creative talents of university faculty, speeds the development of new and improved therapies, stimulates regional economic growth, and contributes to the economic viability of research institutions.[5] Notwithstanding these benefits, the increasing involvement of academics in commercially-sponsored research places new

[4] "Rights to Inventions Made by Nonprofit Organizations and Small Business Firms," codified at 37 CFR Part 401.

[5] University-Industry Research Collaboration Initiative of the Business-Higher Education Forum, *Working Together, Creating Knowledge: The University-Industry Research Collaboration Initiative* (June 2001).

demands on institutions to be scrupulous in crafting and enforcing their conflict of interest policies, and on investigators to be diligent in adhering to them.

Current federal regulations concerning financial interests in research were intended to promote objectivity in federally-funded research and to ensure the reliability of data submitted to the Food and Drug Administration (FDA) - not to protect human subjects *per se*.[6] Under these regulations, institutions applying for Public Health Service (PHS) funding[7] must solicit annual financial disclosure statements from each investigator who plans to participate in PHS-funded research, review these statements for evidence of a "significant financial interest" that "would reasonably appear to be affected by the research," and then "manage, reduce, or eliminate" the interest within 60 days.[8] Institutions must report to the funding agency the existence, though not the nature or details, of any "conflicting" financial interest that the institution determines could directly and significantly affect the research, and assure the funding agency that the interest has been appropriately managed, reduced, or eliminated.[9]

In 1999 the FDA adopted financial disclosure regulations that require parties who submit applications for approval of a new drug, device, or biological product to provide certain information about financial relationships between sponsors and investigators. Typically academic institutions are not required to collect this information; instead, the responsibility rests with the sponsoring company.[10] FDA's regulations for marketing applicants differ from the rules that apply to recipients of PHS research funds in important

[6]The PHS regulations are found at 42 C.F.R. Subpart F, the FDA regulations at 21 C.F.R. Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860. The National Science Foundation has adopted a financial disclosure policy that is similar to that of the PHS. 60 Fed. Reg. 132, 35809 (July 11, 1995).

[7]This includes all institutions seeking research grants from the National Institutes of Health, a PHS agency.

[8]The PHS regulations define a "significant financial interest" as "anything of monetary value" except for the following: salary, royalties, or other remuneration from the institution; ownership interests in institutional applicants for SBIR grants; income from public or non-profit sources for lecturing, teaching, or serving on advisory boards or review panels; equity interests that do not exceed $10,000 or 5% ownership of a single entity; or other payments that in the aggregate are not expected to exceed $10,000 during the next 12 months. 42 C.F.R. §50.603.

[9]The regulations state that a conflict of interest exists "when the designated official(s) reasonably determines that a Significant Financial Interest could directly and significantly affect the design, conduct, or reporting of the PHS-funded research." 42 C.F.R. § 50.605.

[10]The exception would occur when an academic institution holds the investigational new drug (IND) application or investigational device exemption (IDE) for the product studied in the research. FDA has stated that in this circumstance, the IND or IDE holder must collect financial disclosure information for the benefit of the party who will eventually file the marketing application. Food and Drug Administration, Guidance: Financial Disclosure by Clinical Investigators (March 20, 2001) <available at http://www.fda.gov/oc/guidance/financialdis.html>.

respects: the FDA requirements are retrospective, meaning that financial interests must only be reported to the agency once the research is complete and the data are submitted in a marketing application; FDA exempts a greater dollar amount from the disclosure obligation; and FDA's disclosure obligation is narrower, applying only to certain "covered clinical studies" and requiring the applicant to submit only information about the investigator's financial interests in the research sponsor.

What the existing federal financial disclosure regulations *do not* require is a comprehensive system of disclosure and oversight, pursuant to which institutions would collect and carefully review information on all significant financial interests in human subjects research, whether such research is federally-funded or privately sponsored. Equally important, federal financial disclosure regulations do not mandate special scrutiny of financial interests in human subjects research, nor do they acknowledge the unique obligations that attend research involving human beings.

Mindful of these obligations, the Task Force asserts that academic medicine must look beyond the scope of current federal financial disclosure requirements and delineate more fully the bounds of acceptable conduct for those who conduct research with human subjects. Some institutions have made exemplary efforts in this regard. For others, revising policies and practices in the manner that we recommend might require a significant investment of time and resources, and perhaps a discomfiting change in institutional culture. We are convinced nonetheless that all institutions can rise to this challenge. These 2001 *Guidelines for Developing and Implementing a Policy Concerning Individual Financial Interests in Human Subjects Research* are evidence of our collective willingness to seek, to merit, and to sustain public trust in the research mission of academic medicine.

Core Principles to Guide Policy Development

This document offers guidance to institutions in their efforts to provide responsible and effective oversight of financial interests in human subjects research. Academic institutions share common concerns, yet each retains its own unique culture and mode of self-governance. Institutional procedures for the oversight of financial interests in research will vary accordingly. These guidelines create a model for baseline standards and practices, without limiting the prerogative of institutions to implement conflict of interest policies in a manner best suited to local needs. The Task Force recognizes that some institutions may determine that additional restrictions are appropriate. Likewise, we do not discourage institutional variations in process or in the allocation of the oversight responsibilities described in this guidance, provided that the review and management functions that we advocate are performed fully.

As a starting point, we emphasize that the Task Force does not assume that financial interests in human subjects research are categorically improper, or that those who hold such interests cannot conduct research with the requisite scientific objectivity and integrity or protect the welfare of human research subjects. Recognizing, however, that research with human subjects is a privilege that imposes unique obligations, the Task Force believes that the following principles should animate institutional policies concerning financial interests in such research:

A. With the welfare of research subjects always of foremost concern, an institution should regard all significant financial interests in human subjects research as potentially problematic and, therefore, as requiring close scrutiny. Institutional policies should establish the rebuttable presumption that an individual who holds a significant financial interest in research involving human subjects may not conduct such research. The intent is not to suggest that every financial interest jeopardizes the welfare of human subjects or the integrity of research, but rather to ensure that institutions systematically review any financial interest that might give rise to the perception of a conflict of interest, and further, that they limit the conduct of human subjects research by financially interested individuals to those situations in which the circumstances are compelling. The presumption against significant financial interests in human subjects research should apply whether the research is funded by a public agency, a non-profit entity, or a commercial sponsor, and wherever the research may be carried out.

B. In the event of compelling circumstances, an individual holding significant financial interests in human subjects research may be permitted to conduct the research. Whether the circumstances are deemed compelling will depend in each case upon the nature of the science, the nature of the interest, how closely the interest is related to the research, and the degree to which the interest may be affected by the research. When the financial interest is directly related to the research and may be substantially affected by it, (e.g., an equity interest in a start-up company that manufactures the investigational product) the risk is greatest and the bar must be high; however, even direct and potentially lucrative financial interests may be justified in some circumstances. For example, when the individual holding such interests is uniquely qualified by virtue of expertise and experience and the research could not otherwise be conducted as safely or effectively without that individual, he or she should be permitted the opportunity to rebut the presumption against financial interests by demonstrating these facts to the satisfaction of an institution's conflict of interest

(COI) committee.[11] The COI committee might approve the involvement of such an individual in the research, subject to conditions that ensure effective management of the conflict and credible oversight of the research.[12]

C. Institutional policies should require full *prior reporting* of each covered individual's significant financial interests that would reasonably appear to be affected by the individual's research, *updated reporting* of any relevant change in financial circumstances, and *review* of any significant financial interests in a research project by the institution's COI committee *prior to final IRB approval of the research*. COI committee findings and determinations should inform the IRB's review of any research protocol or proposal, although the IRB may require additional safeguards or demand reduction or elimination of the financial interest. The Task Force recommends that, as between the COI committee and the IRB, the more stringent determination should be dispositive. Institutional policies should *specify which responsible institutional officials are empowered to make final and binding decisions* about who may conduct IRB-approved research.

D. Institutional policies governing financial interests in human subjects research should be comprehensive, unambiguous, well-publicized, consistently applied, and enforced through effective sanctions. Moreover, in today's research environment, which is both increasingly entrepreneurial and subject to intense public scrutiny, *transparency* must be the watchword for the oversight of financial interests. Transparency is achieved through full and ongoing internal reporting and external disclosure of significant financial interests that would reasonably appear to affect the welfare of subjects or the conduct or communication of research.

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[11] The Task Force recognizes that institutional practices may differ in their allocation of responsibilities for COI reviews between designated committees and officials, and that in some institutions an IRB may perform a substantive review of financial conflicts of interest. The Task Force strongly recommends that the COI process be separate from the IRB, although with clear channels of communication between them. In all cases the same rebuttable presumption against the financial interest should apply, and the financially interested individual should be given the opportunity to demonstrate "compelling circumstances" to the cognizant authority.

[12] To illustrate, the inventor of an implantable medical device, who under the Bayh-Dole Act might receive royalty income, and who might also be compensated by the device manufacturer for training other physicians to use the device, may also be the individual who is best qualified to implant the device in human subjects safely under experimental conditions. The COI committee might, at its discretion, agree to permit this financially-interested inventor to participate in a clinical study of the device at the institution, subject to management conditions crafted to minimize the potential conflict of interest. These conditions could include, in addition to full disclosure of the interest (to research subjects and others as described in this guidance), requirements that informed consent be obtained by a clinician with no financial ties to the research, and that the research be overseen by a monitoring board.

E. Transparency, though necessary to sustain public confidence in academic research, is not sufficient to protect human subjects. When an institution finds that financial interests in human subjects research are justified by compelling circumstances, those interests and the research in question must be managed through *rigorous, effective, and disinterested monitoring* undertaken by individuals with no financial or professional ties to the research or direct reporting relationships to the researchers. Approaches to monitoring might include the following: regular audits of the informed consent and enrollment process, the involvement of a patient representative or ombudsman when subjects are recruited and informed consent is obtained, a requirement to escrow the financial interest until the investigational product has been approved and on the market for a specified time period, and the use of data safety monitoring boards. In some circumstances monitoring boards might be composed wholly of institutional representatives; however, when the institution itself holds a financial interest in the research, disinterested monitoring might require the participation of individuals from outside the institution.

F. Institutions and individual faculty, staff, employees, students, fellows, and trainees *bear a shared responsibility* for the oversight of financial interests in human subjects research, *yet each remains accountable* for the effectiveness of the oversight system. Individuals who conduct human subjects research must familiarize themselves with their institutions' COI policies and act diligently to fulfil the requirements imposed by these policies.

II. Policy Guidelines

An institutional policy on individual financial interests in human subjects research should be consistent with PHS regulations, and should contain the following elements:

- *Definitions* of key terms.
- A description of the *scope and substantive requirements* of the policy.
- A description of *the process by which covered individuals will report significant financial interests in human subjects research* to institutional officials.
- A description of the *process by which financial reports will be reviewed* by institutional officials (e.g., the institution's COI committee).
- A description of the *criteria the COI committee will apply* to determine *whether a "financially interested individual" has demonstrated compelling circumstances that justify allowing that individual to conduct human subjects research.*
- A description of the *process by which summary information concerning the nature and amount of any significant financial interest* in human subjects research, *COI committee determinations* concerning that interest, and *any conditions or management plan* will be *reported* to IRBs and to appropriate institutional officials.
- A description of the *process by which significant financial interests* in human subjects research *will be disclosed* to research subjects, editors of publications, the public, and as otherwise required by the policy.
- A description of the *process by which* the institution will *implement* and *monitor compliance* with the policy.
- A description of the *sanctions* to be imposed for violations of the policy and the *procedures for adjudication and appeal.*

A. Definitions

Compelling Circumstances are those facts that convince the institution's COI committee that a financially interested individual should be permitted to conduct human subjects research. When considering a request by a financially-interested individual to conduct human subjects research, the circumstances that the COI committee should evaluate include the nature of the research, the magnitude of the interest and the degree to which it is related to the research, the extent to which the