



ASSOCIATION OF
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

Task Force Chair

William Danforth, M.D.
Chancellor Emeritus and Vice-Chairman, Board of Trustees,
Washington University at St. Louis

John Thomas Bigger, M.D.
Professor of Medicine and
Pharmacology
Columbia University

Frank Davidoff, M.D.
Editor
Annals of Internal Medicine

Martin J. Delaney
Founding Director
Project Inform

Susan Dentzer
NewsHour with Jim Lehrer

Susan H. Ehringhaus, Esq.
Vice Chancellor and General Counsel
University of North Carolina at Chapel
Hill

Ginger Graham
Group Chairman
Guidant Corporation

*Susan Hellmann, M.D., M.P.H.***
Chief Medical Officer
Genentech

Jeffrey Kahn, Ph.D., M.P.H.
Director
Center for Bioethics
University of Minnesota

Marvin Kalb
Executive Director, Washington Office
Joan Shorenstein Center for the Press,
Politics and Public Policy
John F. Kennedy School of Government

Russel E. Kaufman, M.D.
Vice Dean
Education and Academic Affairs
Duke University School of Medicine

Robert P. Kelch, M.D.
Dean
University of Iowa College of Medicine

Mark R. Laret
Chief Executive Officer
University of California, San Francisco
Medical Center

Joan S. Leonard, Esq.
Vice President and General Counsel
Howard Hughes Medical Institute

Ronald Levy, M.D.
Robert K. and Helen K. Summy
Professor in the School of Medicine
Stanford University

Constance E. Lieber
President
NARSAD

Joseph B. Martin, M.D., Ph.D.
Dean, Faculty of Medicine
Harvard Medical School

Edward D. Miller, M.D.
Dean, Johns Hopkins School of
Medicine
CEO, Johns Hopkins Medicine

Thomas H. Murray, Ph.D.
President and Chief Executive Officer
The Hastings Center

Charles P. O'Brien, M.D., Ph.D.
Chief of Psychiatry
Philadelphia Veterans Affairs Medical
Center
Kenneth Appel Professor and Vice-
Chair of Psychiatry
University of Pennsylvania

Hon. John E. Porter, Esq.
Partner
Hogan and Hartson, L.L.P.

Roger Porter, M.D.
Vice President Clinical Research and
Development
Wyeth-Ayerst Research

Paul G. Ramsey, M.D.
Vice President for Medical Affairs and
Dean of the School of Medicine
University of Washington

Dorothy K. Robinson, Esq.
Vice President and General Counsel
Yale University

*Hedrick Smith**
President
Hedrick Smith Productions, Inc.

Frances M. Visco, Esq.
President
The National Breast Cancer Coalition

Savio Woo, Ph.D.
Director and Professor
Institute for Gene Therapy
Mount Sinai School of Medicine

Alastair J. J. Wood, M.D.
Assistant Vice Chancellor for Research
Professor of Medicine
Professor of Pharmacology
Vanderbilt University School of Medicine

AAU Liason

Richard J. Turman
Director of Federal Relations
The Association of American
Universities
1200 New York Avenue, NW, Suite 550

AAMC Staff

David Korn, M.D.
Senior Vice President
Association of American Medical
Colleges
Division of Biomedical and Health
Sciences Research

Jennifer Kulynych, J.D., Ph.D.
Director
Association of American Medical
Colleges
Division of Biomedical and Health
Sciences Research

* 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

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 those 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) funding⁷ 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

⁶The 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).

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

⁸The 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.

⁹The 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.

¹⁰The 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.

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

interest could be directly and substantially affected by the research, and the degree of risk to the human subjects involved that is inherent in the research protocol. The committee should also consider the extent to which the interest is amenable to effective oversight and management.

Conducting Research means, with respect to a research protocol, designing research, directing research or serving as the principal investigator, enrolling research subjects (including obtaining subjects' informed consent) or making decisions related to eligibility to participate in research, analyzing or reporting research data, or submitting manuscripts concerning the research for publication.

Covered Individual includes any faculty (fully-, partially-, or non-salaried) or faculty agent, staff, student, fellow, trainee, or administrator who, under the aegis of the institution or pursuant to the review and approval of the institution's IRB, conducts research involving human subjects.

Disclosure means a release of relevant information about significant financial interests in human subjects research to parties outside the institution's COI review and management processes (e.g., to research subjects or journal editors).

Financially Interested Company means a commercial entity with financial interests that would reasonably appear to be affected by the conduct or outcome of the research.¹³ This term includes companies that compete with the sponsor of the research or the manufacturer of the investigational product, if the covered individual actually knows that the financial interests of such a company would reasonably appear to be affected by the research. This term also includes any entity acting as the agent of a financially interested company (e.g., a contract research organization).

Financially Interested Individual means a covered individual who holds a significant financial interest that would reasonably appear to be affected by the individual's human subjects research.

¹³ Under the standard articulated in the PHS regulations, institutions must solicit and review information about investigators' significant financial interests in any entity "whose financial interests would reasonably appear to be affected by the [PHS-funded] research." 42 C.F.R. §50.604(c)(1)(ii).



Human Subjects Research includes *all* research meeting the definition of “research” performed with “human subjects” as these terms are defined in the federal Common Rule (45 C.F.R. Part 46 and 21 C.F.R. Part 56), regardless of the source of research funding or whether the research is otherwise subject to federal regulation. In the event that the Common Rule definitions of “human subjects” or “research” are modified through rulemaking, any such revisions shall apply for the purposes of this guidance.

Rebuttable Presumption Against Financial Interests in Human Subjects Research means the institution will presume, in order to assure that all potentially problematic circumstances are reviewed, that a financially interested individual may not conduct the human subjects research in question. This rule is not intended to be absolute: a financially interested individual may rebut the presumption by demonstrating facts that, in the opinion of the COI committee, constitute compelling circumstances. The individual would then be allowed to conduct the research under conditions specified by the COI committee and approved by the responsible IRB.

Reporting means the provision of information about significant financial interests in human subjects research by a covered individual to responsible institutional officials and to the institutional COI committee, or the transmission of such information within institutional channels (e.g., from the COI committee to the IRB).

Responsible Institutional Official means a Dean, Provost, CEO, or other institutional official who is responsible for the oversight of research programs within the institution.

Responsible IRB is the institutional review board (or boards) with jurisdiction over the research as specified in the multiple projects assurance (MPA) (or the federal-wide assurance (FWA)) that the institution has provided to the U.S. Department of Health and Human Services, or as otherwise established under DHHS or FDA regulation or policy.

Significant Financial Interests in Research include the following interests of the covered individual (and his or her spouse and dependent children), or of any foundation or entity controlled or directed by the individual or his or her spouse:

- Consulting fees, honoraria (including honoraria from a third party, if the original source is a financially interested company), gifts or other emoluments, or “in kind” compensation from a financially interested company (or entitlement to the same), whether for consulting, lecturing, travel, service on an advisory board, or for any other purpose not directly related to the reasonable costs of conducting the research (as specified in the research agreement), that in the aggregate have in the prior calendar year exceeded the de minimis amount established in PHS regulation (presently \$10,000), or are expected to exceed that amount in the next twelve months.
- Equity interests, including stock options, of any amount in a non-publicly-traded financially interested company (or entitlement to the same).
- Equity interests (or entitlement to the same) in a publicly-traded financially interested company that exceed the defined de minimis amount (see exceptions below).
- Royalty income or the right to receive future royalties under a patent license or copyright, where the research is directly related to the licensed technology or work.¹⁴
- Any non-royalty payments or entitlements to payments in connection with the research that are not directly related to the reasonable costs of the research (as specified in the research agreement between the sponsor and the institution). This includes any bonus or milestone payments to the investigators in excess of reasonable costs incurred, whether such payments are received from a financially interested company or from the institution (note *prohibition* in B(11) on milestone payments tied to the achievement of particular research results).
- Service as an officer, director, or in any other fiduciary role for a financially interested company, whether or not remuneration is received for such service.

Exceptions. Significant financial interests in research *do not include* the following:

- Interests of any amount in publicly traded, diversified mutual funds.
- Stock in a publicly-traded company that (when valued in reference to current public prices) meets the de minimis criteria established in PHS financial dis-

¹⁴When evaluating future royalty interests, in addition to the factors listed in the definition of compelling circumstances, the COI committee might consider the anticipated time interval between the research and marketing approval of the investigational product.

closure regulations (presently, an interest that does not exceed \$10,000 in value and does not represent more than a 5% ownership interest in any single entity).

- Stock options in a publicly-traded company that (when valued using accepted valuation methods) meet the de minimis criteria established in PHS financial disclosure regulations (presently, an interest that does not exceed \$10,000 in value and does not represent more than a 5% ownership interest in any single entity).
- Payments to the institution, or via the institution to the individual, that are directly related to reasonable costs incurred in the conduct of research as specified in the research agreement(s) between the sponsor and the institution.
- Salary and other payments for services from the institution.

B. Scope and Substance of Policy

1. Conflict of Interest (COI) Official and Committee. Federal regulations require PHS-funded institutions to appoint a COI official to review financial interests in PHS-sponsored research.¹⁵ The Task Force recommends that institutions also establish a standing COI committee.¹⁶ COI committee membership should include individuals who conduct human subjects research at the institution, as well as the institution's COI official and other officials experienced in the oversight of conflicts of interest and familiar with applicable laws and regulations. A liaison to the IRB is recommended. Institutions might also consider means of involving community or patient representatives in the COI oversight process.

Institutions should ensure that the COI committee responsibilities include the following:

- a. Review of any request by a financially interested individual to rebut the presumption that he or she may not conduct human subjects research.*
- b. Documentation of the committee's findings and the bases for any recommendation to permit or to recommend against permitting a financially interested*

¹⁵ 42 C.F.R. § 50.604(b).

¹⁶ References in this guidance to the "institution's COI committee" apply to the institution's COI official in the event that an institution chooses not to establish a standing COI committee.

individual to conduct human subjects research. In either case the COI committee should prepare a summary report describing the nature and amount of the financial interest and the committee's recommendations. This summary report should be made available to the IRB. When the COI committee has recommended that a financially interested individual be permitted to conduct human subjects research and the IRB has approved the research and the individual's participation, the summary report should be provided to research subjects or the public, upon request.

- c. *Management and oversight* when a financially interested individual is permitted to conduct human subjects research. As a first principle, the COI committee should encourage the financially interested individual to minimize the potential for conflict of interest by reducing or eliminating the interest or the individual's direct involvement in the research. The COI committee should specify the monitoring procedures or other conditions to be imposed when a financially interested individual will be permitted to conduct human subjects research.
- d. *Communication* to the IRB, and to responsible institutional officials, of summary information about the nature and amount of any significant financial interest in human subjects research, along with the committee's findings and recommendations concerning requests by financially interested individuals to conduct such research.

2. Process. Every institution should adopt mechanisms that ensure the following:

- a. The financial reports of covered individuals are collected and maintained in a format that is readily accessible to the COI committee and responsible institutional officials;
- b. The responsible IRB and responsible institutional officials are alerted whenever a financially interested individual proposes to conduct human subjects research;
- c. Prior to the IRB's final approval (whether initial or continuing approval) of human subjects research, the COI committee has informed the IRB and responsible institutional officials of any significant financial interests held by

financially interested individuals who will conduct the research, as well as the COI committee's findings and recommendations concerning the same;

- d. Financially interested individuals are provided an avenue for appealing decisions of the COI committee; and
- e. When financially interested individuals will be permitted to conduct human subjects research, the financial interests in question are disclosed in accordance with the institution's COI policies.

3. Written Policy. Every institution engaged in human subjects research should have a written policy on financial interests in such research. This policy should define all key terms clearly and should detail substantive prohibitions and restrictions, as well as the procedures for reporting financial interests, reviewing financial reports, disclosing reported information, implementing the policy, appealing decisions concerning the policy, and sanctioning non-compliance with the policy. The written policy should explain the criteria that the COI committee will apply when reviewing a request by a financially interested individual to rebut the presumption that he or she may not conduct human subjects research. The policy and related information should be readily accessible to covered individuals and to the public; in addition to conventional means of communication, the policy should be placed on the institution's website, if one exists.

4. Rebuttable Presumption that Financially Interested Individuals May Not Conduct Human Subjects Research. The policy should establish the presumption that, in the absence of compelling circumstances, a financially interested individual may not conduct human subjects research. This presumption should be rebuttable when compelling circumstances exist.

- a. The policy should allow the COI committee, after it reviews the relevant facts and circumstances and documents the compelling circumstances, to recommend that a financially interested individual be permitted to conduct the research, and to make recommendations for appropriate monitoring and oversight.
- b. A summary report indicating the nature and amount of the financial interest and COI committee recommendations should be transmitted to the responsible IRB and to responsible institutional officials.

5. **Monitoring.** The policy should specify procedures for internal, and, when deemed necessary, external monitoring when a financially interested individual is permitted to conduct human subjects research.
6. **Reporting by Covered Individuals.** The policy should require covered individuals to report to the institution all significant financial interests that would reasonably appear to be affected by the individual's current or anticipated human subjects research. In making such reports, each covered individual should be required to declare explicitly whether he or she does *or does not* have such financial interests; the failure to report is unacceptable.
 - a. Reports should be required at least annually, with prompt updating whenever there is an interim, material change in significant financial interests.
 - b. Some institutions currently require a researcher to indicate on the institutional face sheet accompanying the research proposal whether the researcher holds any significant financial interest in the research. All institutions should consider adopting this practice for research involving human subjects.
7. **Reporting to Supervisor.** When the COI committee determines that a financially-interested individual should be permitted to conduct human subjects research, a copy of the committee's summary report describing the financial interest and any conditions to be imposed upon the research should be provided to the head of the unit (e.g., department chair) in which the covered individual resides administratively, and to the responsible dean, provost, CEO, or other official who has institutional responsibility for monitoring the activities of the covered individual.
8. **Investigator Certification to IRB.** When a research proposal is submitted to the IRB for review, including continuing review (where applicable), each covered individual who will conduct the research should attest in writing to the IRB that financial report information on file for that individual is current and will be updated promptly to reflect relevant changes in financial circumstances. The IRB should forward any information that it receives concerning a significant financial interest in human subjects research to the COI committee.
9. **COI Committee Review of Significant Financial Interest Created by Licensing Agreements.** Prior to executing a technology licensing agreement, the Office of

Technology Licensing must determine whether the agreement would create a significant individual financial interest in ongoing or proposed human subjects research, and if so, inform the institution's COI committee of the proposed terms of the agreement. The COI committee should either approve the conduct of the research by the individual who will hold the financial interest, subject to an appropriate monitoring plan, or determine that the individual may not conduct the research if he or she wishes to retain the financial interest.

10. Disclosure of Significant Financial Interests.

- a. The policy should require disclosure of the existence of significant financial interests in human subjects research as follows: to state and federal officials, as required by statute or regulation; to research funders or sponsors; to the editors of any publication to which a covered individual submits a manuscript concerning the research;¹⁷ and in any substantive public communication of the research results, whether oral or written.
- b. If an institution participating in a multi-center trial has judged a financially-interested individual eligible to conduct human subjects research at its site, that fact should be made known to the Principal Investigator or Sponsor, and to the IRBs of other institutions participating in the trial.
- c. Research consent forms should, as a matter of institution's COI policy, disclose the existence of any significant financial interest held by a covered individual who is conducting the human subjects research. The precise wording of disclosure in the consent form should be determined by the IRB, but should include an explanation of the fact that the financial interest in question has been reviewed by the COI committee, approved subject to committee oversight, and determined by both the committee and the IRB not to pose any additional significant risk to the welfare of research subjects or the integrity of the research.

¹⁷ Disclosure to journal editors should take the form of an affirmative statement on behalf of each covered individual who conducted the research that he or she either does or does not hold significant financial interests in the research. This requirement is consistent with the recent uniform disclosure requirements published by a group of editors of major medical journals. F. Davidoff, C. D. DeAngelis, J.M. Drazen, et al. Sponsorship, authorship, and accountability. *JAMA*; 286;10:1232-1234.

¹⁸ The National Human Research Protections Advisory Commission has recommended this approach to the disclosure of researchers' financial interests to research subjects. Letter from Mary Faith Marshall, Ph.D., Chair, NHRPAC, to Assistant Surgeon General/Acting Principal Deputy Assistant Secretary for Health Arthur J. Lawrence, Ph.D., dated August 23, 2001.

- d. If the institution's COI committee has authorized a financially interested individual to conduct human subjects research, the disclosure statement in the research consent form should indicate that additional information (to include the COI summary report describing the nature and amount of the financial interest) will be provided to research subjects upon request.¹⁸

11. Prohibition on Payments for Results. The policy should prohibit payments from the institution or the sponsor to a covered individual, if such payments are conditioned upon a particular research result or are tied to successful research outcomes. Payments for subject enrollment or for referral of patients to research studies should be permitted only to the extent that such payments:

- a. Are reasonably related to costs incurred, as specified in the research agreement between the sponsor and the institution;
- b. Reflect the fair market value of services performed; and
- c. Are commensurate with the efforts of the individual(s) performing the research.

12. Affirmation of Institutional Policies on Intellectual Property and Publication Rights. The COI policy should affirm an investigator's accountability for the integrity of any publication that bears his or her name. The policy should also affirm the right of a principal investigator to receive, analyze, and interpret all data generated in the research, and to publish the results, independent of the outcome of the research. Institutions should not enter, nor permit a covered individual to enter, research agreements that permit a sponsor or other financially interested company to require more than a reasonable period of pre-publication review,¹⁹ or that interfere with an investigator's access to the data or ability to analyze the data independently.²⁰

¹⁹ For sponsored research, a reasonable period of review would be no more than 90 days, unless both parties agree that extenuating circumstances require an extension of time. The Task Force notes that for research involving NIH-funded research tools, the NIH has stated that it would consider a 30-60 day review period to be reasonable. National Institutes of Health, Principles and Guidelines for Recipients of NIH Research Grants and Contract on Obtaining and Disseminating Biomedical Research Resources, 64 Fed. Reg. 246, 72090 (Dec. 23, 1999).

²⁰ When research involves more than one institution and numerous investigators (e.g., a multi-center trial), the investigators may delegate primary authorship to a subset who will take responsibility for the publication.

13. Protection of Students and Trainees. Commercially sponsored research may give rise to financial incentives that conflict with a supervising researcher's responsibility to foster the academic development of students and trainees. Agreements with sponsors or financially interested companies that place restrictions on the activities of students or trainees or that bind students or trainees to non-disclosure provisions should ordinarily be prohibited. When deemed unavoidable, such agreements should be subjected to close scrutiny by the responsible university official and the institution's COI committee, and should be fully disclosed to all students and trainees prior to their involvement in the research. Under no circumstance should a student or trainee be permitted to participate in research if the terms and conditions of participation would prevent him or her from meeting applicable institutional degree requirements (e.g., completion and public defense of a thesis or dissertation). The institution's policy on financial interests in research should reaffirm, or explicitly cross-reference, the relevant institutional documents that address these matters.

14. Legal Obligations. The policy documents should alert covered individuals to all state and federal requirements applicable to financial interests in research, including state financial disclosure laws (if applicable), state licensure and professional conduct standards relevant to conflict of interest, federal laws relative to "finders fees" for research subjects, and SEC prohibitions against insider trading. The policy should also direct investigators who conduct FDA-regulated research to familiarize themselves with FDA policies concerning promotional activities.

15. Sanctions. The policy should define the range of possible sanctions for non-compliance, up to and including dismissal. The policy should reference the procedures to be followed for sanctioning violations and for appealing adverse determinations.

C. Policy Implementation

1. Information Flow. Institutions should implement policies, procedures, and systems that will facilitate prompt reporting of significant financial interests to the institution and enable the timely flow of accurate and complete information to and from the COI committee, the responsible IRB(s), the institutional Office of Technology Licensing, and responsible institutional officials.

2. **Electronic Reporting Form.** To enhance the efficiency of the reporting process, institutions should consider adopting an electronic disclosure form and permitting covered individuals to make and update financial reports on-line and in real time.
3. **Resources.** Implementation of a comprehensive, effective COI policy may require institutions to devote new resources to their compliance effort. Institutions should ensure that adequate resources and personnel are allocated to support effective, credible oversight of financial interests in human subjects research.
4. **Written Acknowledgement Required.** Institutions should require that all individuals who conduct human subjects research read and acknowledge in writing that they understand and agree to comply with the institution's COI policies.
5. **Education and Training.** Institutions should adopt mechanisms for disseminating COI policies to all faculty, staff, students, and trainees, and for providing appropriate education and training in these policies.
6. **Compliance Monitoring.** Institutions should regularly assess compliance with COI policies through the use of internal audit mechanisms and other appropriate self-evaluation strategies.
7. **Accreditation.** The effectiveness of COI policies and a formal assessment of institution-wide compliance with these policies should be examined as an element of any accreditation process for the institution's human subjects protection program.

Epilogue

During the past two decades, remarkable advancements in biomedical research and the stimulus of the Bayh-Dole Act have vastly increased the breadth and depth of engagement of academic medicine with industry. The growth of the biotechnology industry is a celebrated accomplishment of the U.S. economy during the second half of the 20th century, and together with the information technology industry has spurred public perception of research universities as engines of economic development and social betterment. But at the same time, the public insists that universities remain unblemished by financial self-interest and continue to serve society as trusted and impartial arbiters of knowledge. This “conflict of public expectations” is nowhere more intense than in academic medicine and in research involving human subjects, where the steadily deepening engagement of clinical research with the world of commerce is seen by many influential observers as threatening both research integrity and the welfare of research participants.

The Task Force acknowledges the enormous benefits that have inured to the public from the commercial development of medical inventions made in academic medical centers and anticipates that the relationships of these centers with industry will only continue to deepen in an era in which terms like genomics, proteomics, and physiomics are becoming commonplace. But the Task Force also recognizes that the public's extraordinary support of academic biomedical research will remain critically dependent upon public confidence and trust that are especially vulnerable in research involving human subjects. This is the reality, and it must be appreciated by industry as much as by academe if their future interactions are to thrive.

This first report from the AAMC Task Force on Financial Conflicts of Interest in Clinical Research deals with individual financial interests. It intends to raise the standards of institutional oversight and management of financial conflicts of interest, and make them more uniform across academic medicine. The report respects institutional autonomy: the recommended policy and guidance provide a floor that permits institutions to adopt even more stringent provisions if they wish. The report eschews a “one size fits all approach:” it recognizes that each case of potential financial conflict of interest in research must be closely examined on its merits, and must respect the particular institutional, individual, and scientific circumstances that may attend it.



The Task Force does not believe, and does not intend, that adoption of the recommended policy and guidelines by the academic medical community should interfere with healthy academic- industry relationships or with the continued robust flow of academic biomedical invention into beneficial products. The Task Force does believe that these policies and guidance can help to ensure that the relationships remain principled, protective of research subjects and scientific integrity, and capable of withstanding intense public scrutiny.