Managing Conflicts of Interest and Attorney Ethics in Research Relationships Between Industry and Healthcare Entities

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TITLE 42--PUBLIC HEALTH

CHAPTER I--PUBLIC HEALTH SERVICE,
DEPARTMENT OF HEALTH AND
HUMAN SERVICES

PART 50--POLICIES OF GENERAL APPLICABILITY--Table of Contents

Subpart F--Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is Sought

Authority: 42 U.S.C. 216, 289b-1, 299c-3.

Source: 60 FR 35815, July 11, 1995; 60 FR 39076, July 31, 1995, unless otherwise noted.

Sec. 50.601 Purpose.

This subpart promotes objectivity in research by establishing standards to ensure there is no reasonable expectation that the design, conduct, or reporting of research funded under PHS grants or cooperative agreements will be biased by any conflicting financial interest of an Investigator.

Sec. 50.602 Applicability.

This subpart is applicable to each Institution that applies for PHS grants or cooperative agreements for research and, through the implementation of

this subpart by each Institution, to each Investigator participating in such research (see Sec. 50.604(a)); provided, that this subpart does not apply to SBIR Program Phase I applications. In those few cases where an individual, rather than an institution, is an applicant for PHS grants or cooperative agreements for research, PHS Awarding Components will make case-by-case determinations on the steps to be taken to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest of the individual.

Sec. 50.603 Definitions.

As used in this subpart:

HHS means the United States Department of Health and Human Services, and any components of the Department to which the authority involved may be delegated.

Institution means any domestic or foreign, public or private, entity or organization (excluding a Federal agency).

Investigator means the principal investigator and any other person who is responsible for the design, conduct, or reporting of research funded by PHS, or proposed for such funding. For purposes of the requirements of this subpart relating to financial interests, ``Investigator'' includes the Investigator's spouse and dependent children.

PHS means the Public Health Service, an operating division of the U.S. Department of Health and Human Services, and any components of the PHS to which the authority involved may be delegated.

PHS Awarding Component means the organizational unit of the PHS that funds the research that is subject to this subpart.

Public Health Service Act or PHS Act means the statute codified at 42 U.S.C. 201 et seq.

Research means a systematic investigation designed to develop or contribute to generalizable knowledge relating broadly to public health, including behavioral and social-sciences research. The term encompasses basic and applied research and product development. As used in this subpart, the term includes any such activity for which research funding is available from a PHS Awarding Component through a grant or cooperative agreement, whether authorized under the PHS Act or other statutory authority.

Significant Financial Interest means anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interests (e.g., stocks, stock options or other ownership interests); and intellectual property rights (e.g., patents, copyrights and royalties from such rights). The term does not include:

(1) Salary, royalties, or other remuneration from the applicant institution;

(2) Any ownership interests in the institution, if the institution is an applicant under the SBIR Program;

(3) Income from seminars, lectures, or teaching engagements sponsored by public or nonprofit entities;

(4) Income from service on advisory committees or review panels for public or nonprofit entities;

(5) An equity interest that when aggregated for the Investigator and the Investigator's spouse and dependent children, meets both of the following tests: Does not exceed $10,000 in value as determined through reference to public prices or other reasonable measures of fair market value, and does not represent more than a five percent ownership interest in any single entity; or

(6) Salary, royalties or other payments that when aggregated for the Investigator and the Investigator's spouse and dependent children over the next twelve months, are not expected to exceed $10,000.

Small Business Innovation Research (SBIR) Program means the extramural research program for small business that is established by the Awarding Components of the Public Health Service and certain other Federal agencies under Pub. L. 97-219, the Small Business Innovation Development Act, as amended. For purposes of this subpart, the term SBIR Program includes the Small Business Technology Transfer (STTR) Program, which was established by Pub. L. 102-564.

Sec. 50.604 Institutional responsibility regarding conflicting interests of investigators.

Each Institution must:

(a) Maintain an appropriate written, enforced policy on conflict of interest that complies with this subpart and inform each Investigator of that policy, the Investigator's reporting responsibilities, and of these regulations. If the Institution carries out the PHS-funded research through subgrantees, contractors, or collaborators, the Institution must take reasonable steps to ensure that Investigators working for such entities comply with this subpart, either by requiring those Investigators to comply with the Institution's policy or by requiring the entities to provide assurances to the Institution that will enable the Institution to comply with this subpart.

(b) Designate an institutional official(s) to solicit and review financial disclosure statements from each Investigator who is planning to participate in PHS-funded research.

(c)(1) Require that by the time an application is submitted to PHS each Investigator who is planning to participate in the PHS-funded research has submitted to the designated official(s) a listing of his/her known Significant Financial Interests (and those of his/her spouse and dependent children):

(i) That would reasonably appear to be affected by the research for which PHS funding is sought; and

(ii) In entities whose financial interests would reasonably appear to be affected by the research.

(2) All financial disclosures must be updated during the period of the award, either on an annual basis or as new reportable Significant Financial Interests are obtained.

(d) Provide guidelines consistent with this subpart for the designated official(s) to identify conflicting interests and take such actions as necessary to ensure that such conflicting interests will be managed, reduced, or eliminated.

(e) Maintain records of all financial disclosures and all actions taken by the Institution with respect to each conflicting interest for at least three years from the date of submission of the final expenditures report or, where applicable, from other dates specified in 45 CFR 74.53(b) for different situations.

(f) Establish adequate enforcement mechanisms and provide for sanctions where appropriate.

(g) Certify, in each application for the funding to which this subpart applies, that:

(1) There is an effect at that Institution a written and enforced administrative process to identify and manage, reduce or eliminate conflicting interests with respect to all research projects for which funding is sought from the PHS,

(2) Prior to the Institution's expenditure of any funds under the award, the Institution will report to the PHS Awarding Component the existence of a conflicting interest (but not the nature of the interest or other details) found by the institution and assure that the interest has been managed, reduced or eliminated in accordance with this subpart; and, for any interest that the Institution identifies as conflicting subsequent to the Institution's initial report under the award, the report will be made and the conflicting interest managed, reduced, or eliminated, at least on an interim basis, within sixty days of that identification;

(3) The Institution agrees to make information available, upon request, to the HHS regarding all conflicting interests identified by the Institution and how those interests have been managed, reduced, or eliminated to protect the research from bias; and

(4) The Institution will otherwise comply with this subpart.

Sec. 50.605 Management of conflicting interests.

(a) The designated official(s) must: Review all financial disclosures; and determine whether a conflict of interest exists and, if so, determine what actions should be taken by the institution to manage, reduce or eliminate such conflict of interest. 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. Examples of conditions or restrictions that might be imposed to manage conflicts of interest include, but are not limited to:

(1) Public disclosure of significant financial interests;

(2) Monitoring of research by independent reviewers;

(3) Modification of the research plan;

(4) Disqualification from participation in all or a portion of the research funded by the PHS;

(5) Divestiture of significant financial interests; or

(6) Severance of relationships that create actual or potential conflicts.

(b) In addition to the types of conflicting financial interests described in this paragraph that must be managed, reduced, or eliminated, an Institution may require the management of other conflicting financial interests, as the Institution deems appropriate.

Sec. 50.606 Remedies.

(a) If the failure of an Investigator to comply with the conflict of interest policy of the Institution has biased the design, conduct, or reporting of the PHS-funded research, the Institution must promptly notify the PHS Awarding Component of the corrective action taken or to be taken. The PHS Awarding Component will consider the situation and, as necessary, take appropriate action, or refer the matter to the Institution for further action, which may include directions to the Institution on how to maintain appropriate objectivity in the funded project.

(b) The HHS may at any time inquire into the Institutional procedures and actions regarding conflicting financial interests in PHS-funded research, including a requirement for submission of, or review on site, all records pertinent to compliance with this subpart. To the extent permitted by law, HHS will maintain the confidentiality of all records of financial interests. On the basis of its review of records and/or other information that may be available, the PHS Awarding Component may decide that a particular conflict of interest will bias the objectivity of the PHS-funded research to such an extent that further corrective action is needed or that the Institution has not managed, reduced, or eliminated the conflict of interest in accordance with this subpart. The PHS Awarding Component may determine that suspension of funding under 45 CFR 74.62 is necessary until the matter is resolved.

(c) In any case in which the HHS determines that a PHS-funded project of clinical research whose purpose is to evaluate the safety or effectiveness of a drug, medical device, or treatment has been designed,

conducted, or reported by an Investigator with a conflicting interest that was not disclosed or managed as required by this subpart, the Institution must require the Investigator(s) involved to disclose the conflicting interest in each public presentation of the results of the research.

Sec. 50.607 Other HHS regulations that apply.

Several other regulations and policies apply to this subpart. They include, but are not necessarily limited to:

42 CFR part 50, subpart D--Public Health Service grant appeals procedure
45 CFR part 16--Procedures of the Departmental Grant Appeals Board
45 CFR part 74--Uniform Administrative Requirements for Awards and Subawards to Institutions of Higher Education, Hospitals, Other Non-Profit Organizations, and Commercial Organizations; and Certain Grants and Agreements with States, Local Governments and Indian Tribal Governments
45 CFR part 76--Government-wide debarment and suspension (non-procurement)
45 CFR part 79--Program Fraud Civil Remedies
45 CFR part 92--Uniform Administrative Requirements for Grants and Cooperative Agreements to State and Local Governments

Financial Conflict of Interest: HHS Guidance (2004)

Department of Health and Human Services

Final Guidance Document

Financial Relationships and Interests in Research Involving Human Subjects: Guidan for Human Subject Protection

This document replaces the “HHS Draft Interim Guidance: Financial Relationships in Clinic Research: Issues for Institutions, Clinical Investigators, and IRBs to Consider when Dealing Issues of Financial Interests and Human Subject Protection” dated January 10, 2001. This document is intended to provide guidance. It does not create or confer rights for or on any person and does not operate to bind the Department of Health and Human Services (HHS, or Department), including the Food and Drug Administration (FDA), or the public. An alternat approach may be used if such approach satisfies the requirements of the applicable statutes a regulations.

I. Introduction

A. Purpose

In this guidance document, HHS raises points to consider in determining whether specific financial interests in research affect the rights and welfare of human subjects1 and if so, what actions could be considered to protect those subjects. This guidance applies to human subjects research conducted or supported by HHS or regulated by the FDA. The consideration of financial relationships, as discussed in this document relates to human subject protection in research conducted under the HHS or FDA regulations (45 CFR part 46, 21 CFR parts 50, 56)2

This document is nonbinding and does not change any existing regulations or requirements, and does not impose any new requirements. Institutions and individuals involved in human subjects research may establish financial relationships related to or separate from particular research projects. Those financial relationships may create financial interests of monetary value, such as payments for services, equity interests, or intellectual property rights. A financial interest related to a research study may be a conflicting financial interest. The Department recognizes that some conflicting financial interests in research may affect the rights and welfare of human subjects. This document provides some possible approaches to consider in assuring that human subjects are adequately protected. Institutional review boards (IRBs), institutions, and investigators engaged in human subjects research each have appropriate roles in ensuring that financial interests do not compromise the protection of research subjects.3

B. Target Audiences

The principal target audiences include investigators, IRB members and staffs, institutions engaged in human subjects research and their officials, and other interested members of the research community.

C. Underlying Principles

The regulations protecting human research subjects are based on the ethical principles described in the Belmont report:4 respect for persons, beneficence, and justice. The Belmont principles should not be compromised by financial relationships. Openness and honesty are indicators of respect for persons, characteristics that promote ethical research and can only strengthen the research process.

D. Basis for This Document

The HHS human subject protection regulations (45 CFR part 46) require that institutions performing HHS conducted or supported non-exempt research involving human subjects have the research reviewed and approved by an IRB whose goal is to help ensure that the rights and welfare of human subjects are protected. The comparable FDA regulations (21 CFR parts 50 and 56) require that FDA regulated research involving human subjects is reviewed and approved by such an IRB. Under these regulations, IRBs are responsible for, among other things, determining that:

- Risks to subjects are minimized (45 CFR 46.111(a)(1), 21 CFR 56.111(a)(1));
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects (45 CFR 46.111(a)(2), 21 CFR 56.111(a)(2));
- Selection of subjects is equitable (45 CFR 46.111(a)(3), 21 CFR 56.111(a)(3));
- Informed consent will be sought from each prospective subject (45 CFR 46.111(a)(4), 21 CFR 56.111(a)(4)); and,
- The possibility of coercion or undue influence is minimized (45 CFR 46.116, 21 CFR 50.20).

In addition the IRB may

- Require that additional information be given to subjects “when in the IRB's judgment the information would meaningfully add to protection of the rights and welfare of subjects” (45 CFR 46.109(b), 21 CFR 56.109(b)).

For HHS conducted or supported research, the funding agency may impose additional conditions as necessary for the protection of human subjects (45 CFR 46.124).

IRBs are also responsible for ensuring that members who review research have no conflicting interest. 45 CFR 46.107(e) directly addresses conflicts of interest by requiring that “no IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.” FDA regulations include identical language at 21 CFR 56.107(e).

Concerns have grown that financial conflicts of interest in research, derived from financial relationships and the financial interests they create, may affect the rights and welfare of human subjects in research. Financial interests are not prohibited, and not all financial interests cause conflicts of interest or affect the rights and welfare of human subjects. HHS recognizes the complexity of the relationships between government, academia, industry and others, and recognizes that these relationships often legitimately include financial relationships. However, to the extent financial interests may affect the rights and welfare of human subjects in research, IRBs, institutions, and investigators need to consider what actions regarding financial interests may be necessary to protect those subjects.

In May 2000, HHS announced five initiatives to strengthen human subject protection in clinical research. One of these was to develop guidance on financial conflict of interest that would serve to further protect research participants. As part of this initiative, HHS held a conference on the topic of human subject protection and financial conflict of interest on August 15-16, 2000. A draft interim guidance document, “Financial Relationships in Clinical Research: Issues for Institutions, Clinical Investigators, and IRBs to Consider when Dealing with Issues of Financial Interests and Human Subject Protection,” based on information obtained at and subsequent to that conference was made available to the public for comment on January 10, 2001.5 This document replaces that draft interim guidance. The Department notes that other organizations have also addressed financial interests in human research via reports, guidance and recommendations.6 Many of these contain strong and sound ideas for actions to deal with potential financial conflicts of interest on the part of institutions, investigators and IRBs.

II. Guidance for Institutions, IRBs and Investigators

A. General Approaches to Address Financial Relationships and Interests in Research Involving Human Subjects

The Department recommends that in particular, IRBs, institutions, and investigators consider whether specific financial relationships create financial interests in research studies that may adversely affect the rights and welfare of subjects. These entities may find it useful to include the following questions in their deliberations:

- What financial relationships and resulting financial interests could cause potential or actual conflicts of interest?

- At what levels should those potential or actual financial conflicts of interest be managed or eliminated?
- What procedures would be helpful, including those to
  - collect and evaluate information regarding financial relationships related to research,
  - determine whether those relationships potentially cause a conflict of interest, and
  - determine what actions are necessary to protect human subjects and ensure that those actions are taken?
- Who should be educated regarding financial conflict of interest issues and policies?
- What entity or entities would examine individual and/or institutional financial relationships and interests?

B. Points for Consideration

Financial interests determined to create a conflict of interest may be managed by eliminating them or mitigating their impact. A variety of methods or combinations of methods may be effective. Some methods may be implemented by institutions engaged in the conduct of research, and some methods may be implemented by IRBs or investigators. Some of those may apply before research begins, and some may apply during the conduct of the research.

In establishing and implementing methods to protect the rights and welfare of human subjects from conflicts of interest created by financial relationships of parties involved in research, the Department recommends that IRBs, institutions engaged in research, and investigators consider the questions below. Additional questions may be appropriate. The Department's intent is not to be exhaustive, but to suggest ways to examine the issues so that appropriate actions can be taken to protect the rights and welfare of human research subjects. The Department recognizes that a number of institutions currently address such issues in their consideration of financial interests of parties involved in human subject research.

- Does the research involve financial relationships that could create potential or actual conflicts of interest?
  - How is the research supported or financed?
  - Where and by whom was the study designed?
  - Where and by whom will the resulting data be analyzed?
- What interests are created by the financial relationships involved in the situation?
  - Do individuals or institutions receive any compensation that may be affected by the study outcome?
  - Do individuals or institutions involved in the research:

- have any proprietary interests in the product, including patents, trademarks, copyrights, or licensing agreements?

- have an equity interest in the research sponsor and, if so, is the sponsor a publicly held company or non-publicly held company?

- receive significant payments of other sorts? (e.g., grants, compensation in the form of equipment, retainers for ongoing consultation, or honoraria)

- receive payment per participant or incentive payments, and are those payments reasonable?

- Given the financial relationships involved, is the institution an appropriate site for the research?
- How should financial relationships that potentially create a conflict of interest be managed?
- Would the rights and welfare of human subjects be better protected by any or a combination of the following:

  - reduction of the financial interest?

  - disclosure of the financial interest to prospective subjects?

  - separation of responsibilities for financial decisions and research decisions?

  - additional oversight or monitoring of the research?

  - an independent data and safety monitoring committee or similar monitoring body?

  - modification of role(s) of particular research staff or changes in location for certain research activities, e.g., a change of the person who seeks consent, or a change of investigator?

  - elimination of the financial interest?

C. Specific Points for Consideration

1. Institutions

The Department recommends that institutions engaged in HHS conducted or supported human subjects research consider whether the following actions or other actions would help ensure that financial interests do not compromise the rights and welfare of human research subjects.

Actions to consider:

- Establishing the independence of institutional responsibility for research activities from the management of the institution's financial interests.
- Establishing conflict of interest committees (COICs)7 or identifying other bodies or persons and procedures to

  - deal with individuals' or institutional financial interests in research or verify the absence of such interests and

  - address institutional financial interests in research.

- Establishing criteria to determine what constitutes an institutional conflict of interest, including identifying leadership positions for which the individual's financial interests are such that they may need to be treated as institutional financial interests.
- Establishing clear channels of communication between COICs and IRBs.
- Establishing policies on providing information, recommendations, or findings from COIC deliberations to IRBs.
- Establishing measures to foster the independence of IRBs and COICs.
- Determining whether particular individuals should report financial interests to the COIC. These individuals could include IRB members and staff and appropriate officials of the institution, along with investigators, among those who report financial interests to COICs.
- Establishing procedures for disclosure of institutional financial relationships to COICs.
- Providing training to appropriate individuals regarding financial interest requirements.
- Using independent organizations to hold or administer the institution's financial interest.
- Including individuals from outside the institution in the review and oversight of financial interests in research.
- Establishing policies regarding the types of financial relationships that may be held by parties involved in the research and circumstances under which those financial relationships and interests may or may not be held.

2. IRB Operations

The Department recommends that institutions engaged in human subjects research and IRBs that review HHS conducted or supported human subjects research or FDA regulated human subjects research consider whether establishing policies and procedures addressing IRB member potential and actual conflicts of interest as part of overall IRB policies and procedures would help ensure that financial

interests do not compromise the rights and welfare of human research subjects. As noted, 45 CFR 46.107 (e) and 21 CFR 56.107(e) prohibit an IRB member with a conflicting interest in a project from participating in the IRB's initial or continuing review, except to provide information as requested by the IRB.

Policies and procedures to consider:

- Reminding members of conflict of interest policies at each meeting and documenting any actions taken regarding IRB member conflicts of interest related to particular protocols.
- Developing educational materials for IRB members to ensure their awareness of federal regulations and institutional policies regarding financial relationships and interests in human subjects research.

3. IRB Review

The Department recommends that IRBs reviewing HHS conducted or supported human subjects research or FDA regulated human subjects research consider whether the following actions, or other actions related to conduct or oversight of research, would help ensure that financial interests do not compromise the rights and welfare of human research subjects.

Actions to consider:

- Determining whether methods used for management of financial interests of parties involved in the research adequately protect the rights and welfare of human subjects.
- Determining whether other actions are necessary to minimize risks to subjects.
- Determining the kind, amount, and level of detail of information to be provided to research subjects regarding the source of funding, funding arrangements, financial interests of parties involved in the research, and any financial interest management techniques applied.

4. Investigators

The Department recommends that investigators conducting human subjects research consider the potential effects that a financial relationship of any kind might have on the research or on interactions with research subjects, and what actions to take.

Actions to consider:

- Including information in the informed consent document, such as
  - the source of funding and funding arrangements for the conduct and review of research, or
  - information about a financial arrangement of an institution or an investigator and how it is being managed.

- Using special measures to modify the informed consent process when a potential or actual financial conflict exists, such as

  - having a another individual who does not have a potential or actual conflict of interest involved in the consent process, especially when a potential or actual conflict of interest could influence the tone, presentation, or type of information presented during the consent process.

  - Using independent monitoring of the research.

Dated: /May 5, 2004/

/Signed/

Tommy G. Thompson

Secretary

Department of Health and Human Services.

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1 Under the Public Health Service Act and other applicable law, HHS has authority to regulate institutions engaged in HHS conducted or supported research involving human subjects. For a description of what is meant by institutions engaged in research see the Office for Human Research Protections (OHRP) engagement policy. Under the Federal Food, Drug, and Cosmetic Act, FDA has the authority to regulate Institutional Review Boards (IRBs) and investigators involved in the review or conduct of FDA-regulated research.

2 This document does not address HHS Public Health Service regulatory requirements that cover institutional management of the financial interests of individual investigators who conduct Public Health Service (PHS) supported research (42 CFR part 50, subpart F, and 45 CFR part 94). This document also does not address FDA regulatory requirements that place responsibilities on sponsors to disclose certain financial interests of investigators to FDA in marketing applications (21 CFR part 54). Guidelines interpreting the application of the PHS regulations to research conducted or supported by the National Institutes of Health (NIH) that involve human subjects are available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm. Guidance interpreting the provisions of the FDA regulations appears at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm.

The PHS regulations require grantee institutions and contractors to designate one or more persons to review investigators' financial disclosure statement describing their significant financial interests and ensure that conflicting financial interests are managed, reduced, or eliminated before expenditure of funds (42 CFR 50.604(b), 45 CFR 94.4(b)). The PHS threshold for significant financial interest is $10,000 per year income or equity interests over $10,000 and 5 percent ownership in a company (42 CFR 50.603, 45 CFR 94.3). The regulations give several examples of methods for managing investigators' financial conflicts of interest (42 CFR 50.605(a), 54 CFR 94.5(a)).

Sponsors are required to disclose certain financial interests of clinical investigators to FDA in marketing approval applications under the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 CFR part 54). FDA regulations at 21 CFR part 54 address requirements for the disclosure of certain financial interests held by clinical investigators. The purpose of these regulations is to provide additional information to allow FDA to assess the reliability of the clinical data (21 CFR 54.1). The FDA regulations require sponsors seeking marketing approval for products to certify that investigators do not have certain financial interests, or to disclose those interests to FDA (21 CFR 54.4). These regulations require sponsors to report (1) financial arrangements between the sponsor and the investigator whereby the value of the investigator's compensation could be influenced by the outcome of the trial, (2) any proprietary interest in the product studied held by the investigator; (3) significant payments of other sorts over $25,000 beyond costs of the study; or (4) any significant equity interest in the sponsor of a covered study (21 CFR 54.4).

Note that when the PHS regulations were promulgated, the National Science Foundation (NSF) Investigator Financial Disclosure Policy was revised to match closely the PHS regulations. The NSF conflict of interest policy appears at http://www.gpo.gov/fdsys/pkg/FR-1995-07-11/html/95-16800.htm.

3 The Department recognizes that some non-financial conflicting interests related to research also may affect the rights and welfare of human subjects. However, non-financial interests are beyond the scope of this guidance document.

4. Belmont Report

5 Financial Relationships in Clinical Research

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6 Recent Federal and Private Sector Activities: In addition to the HHS initiative, several Federal organizations have examined the issues related to financial relationships in human subjects research:

* The National Bioethics Advisory Commission (NBAC), in a comprehensive examination of the “Ethical and Policy Issues in Research Involving Human Participants,” in Chapter 3 recommended development of federal, institutional, and sponsor policies and guidance to ensure that research subjects' rights and welfare are protected from the effects of conflicts of interest (http://www.georgetown.edu/research/nrcbl/nbac/human/overvol1.pdf).

* The HHS Office of the Inspector General (OIG) has issued a series of reports examining regulation and activities of IRBs. A June 2000 OIG report addressed recruitment practices and found that about onequarter of the surveyed IRBs consider financial arrangements with sponsors of research as part of their protocol review (http://oig.hhs.gov/oei/reports/oei-01-97-00195.pdf).

* The National Human Research Protections Advisory Committee (NHRPAC) offered advice to HHS regarding the content and finalization of the HHS Draft Interim Guidance in August, 2001 (http://ohrp.osophs.dhhs.gov/nhrpac/documents/aug01a.pdf).

* In December 2001, the General Accounting Office released report 02-89 “Biomedical Research: HHS Direction Needed to Address Financial Conflicts of Interest.” The report recommended that the Secretary of Health and Human Services develop specific guidance or regulations concerning institutional financial conflicts of interest (http://www.gao.gov/).

* A number of nongovernmental organizations recently have addressed financial interests in reports and issued new or updated policies or guidelines of varying scope and specificity, including the Association of American Universities, October 2001 (http://www.aau.edu/research/COI.01.pdf), the Association of American Medical Colleges, December 2001 and October 2002 (http://www.aamc.org/members/coitf/firstreport.pdf and http://www.aamc.org/members/coitf/2002coireport.pdf), the International Committee of Medical Journal Editors October 2001 (http://www.icmje.org/sponsor.htm), the American Medical Association, January 2002 (http://jama.ama-assn.org/cgi/content/short/287/1/78), and opinions E-8.0315 Managing Conflicts of Interest in the Conduct of Clinical Trials (http://www.ama-assn.org/ama/pub/category/8471.html) and E-8031 Conflicts of Interest: Biomedical Research (http://www.ama-assn.org/ama/pub/category/8470.html), the American Society of Gene Therapy, April 2000 (http://www.asgt.org/policy/index.html), the American Society of Clinical Oncology, June 2003 (http://www.jco.org/cgi/content/full/21/12/2394), and the Institute of Medicine, October 2002,report “Responsible Research: A Systems Approach to Protecting Research Participants” (http://www.nap.edu/books/0309084881/html/).

* Two accrediting bodies for human subject protection programs have included elements addressing individual and institutional conflicts of interest in their accreditation evaluations, the Association for the Accreditation of Human Research Protection Programs (http://www.aahrpp.org/images/Evaluation_Instrument_1.pdf) and the National Committee for Quality Assurance, (http://www.ncqa.org/Programs/QSG/VAHRPAP/vahrpapfindstds.pdf).

Internationally, the World Medical Association's revision in 2000 of the Declaration of Helsinki, (http://www.wma.net/e/policv/17-c_e.html) principle 22, includes “sources of funding” among the items of information to be provided to subjects. A number of individual institutions also have developed policies for their own situations, as noted in the NIH Guide Notice issued in June 2000 (http://grants.nih.grants/guide/notice-files/NOT-OD-00-040.html). Some of these policies involve conflicts of interest management methods and address institutional financial interests as well as individual interests.

7 The acronym COIC will be used to represent the body or person(s) designated to review financial interests.

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Guidance for Clinical Investigators, Industry, and FDA Staff

Financial Disclosure by Clinical Investigators

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health

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Contains Nonbinding Recommendations

Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators

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Center for Devices and Radiological Health

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Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Guidance for Clinical Investigators, Industry, and FDA Staff[1] Financial Disclosure by Clinical Investigators

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist clinical investigators, industry, and FDA staff in interpreting and complying with the regulations governing financial disclosure by clinical investigators, 21 CFR part 54. This document is a revision of the *Guidance for Industry: Financial Disclosure by Clinical Investigators* dated March 20, 2001. In order to address issues raised by the Office of the Inspector General (OIG), Department of Health and Human Services, in its report, OEI-05-07-00730, *The Food and Drug Administration's Oversight of Clinical Investigators' Financial Information*[2] as well as questions FDA has received from industry and the public, FDA issued a revised guidance in draft in May 2011 for public comment. Comments were received from 13 individuals and entities, which were considered in preparing this final guidance. FDA encourages applicants and sponsors to contact the agency for advice concerning specific circumstances regarding financial disclosures that may raise concerns as early in the product development process as possible.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The Financial Disclosure by Clinical Investigators regulation (21 CFR part 54) requires applicants who submit a marketing application for a drug, biological product or device to submit certain information concerning the compensation to, and financial interests and arrangements of, any clinical investigator conducting clinical studies covered by the regulation (see generally the

[1] This revised guidance was prepared by the Office of the Commissioner, with input from the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) and Center for Devices and Radiological Health (CDRH).

[2] The OIG's report is available at http://oig.hhs.gov/oei/reports/oei-05-07-00730.pdf.

purpose of the regulation at 21 CFR § 54.1). The regulation, which became effective on February 2, 1999, applies to clinical studies submitted in a marketing application, including a supplement or amendment to an original application, that the applicant or FDA relies on to establish that the product is effective, and any study in which a single investigator makes a significant contribution to the demonstration of safety (21 CFR §§ 54.2(e) and 54.3). The regulation requires applicants to certify the absence of certain financial interests and arrangements of clinical investigators that could affect the reliability of data submitted to FDA, or to disclose those financial interests and arrangements to the agency and identify steps taken to minimize the potential for bias (21 CFR § 54.4(a)). If the applicant does not include certification and/or disclosure, or does not certify that it was unable to obtain the information despite exercising due diligence, the agency may refuse to file the application (21 CFR § 54.4(c)).

III. FINANCIAL DISCLOSURE REQUIREMENTS

Under the applicable regulations,[3] an applicant is required to submit to FDA a list of all clinical investigators who conducted covered clinical studies and to identify those who are full-time or part-time employees of the sponsor of each covered study (21 CFR § 54.4). For each clinical investigator who was not a full-time or part-time employee of a sponsor of the clinical study, the applicant must provide either a certification, using FORM FDA 3454, that none of the financial interests or arrangements described in 21 CFR § 54.4(a)(3) (see Section III.B. below) exists, or completely and accurately disclose, using FORM FDA 3455, the nature of those interests and arrangements to the agency and describe any steps taken to minimize the potential for bias resulting from those interests and arrangements (21 CFR § 54.4(a)). If the applicant acts with due diligence to obtain the required information but is unable to do so, the applicant may certify that it acted with due diligence but was unable to obtain the information and include the reason the information could not be obtained (21 CFR § 54.4).

FDA generally expects that applicants will be able to provide this information. Under 21 CFR §§ 312.53(c), 812.20(b)(5) and 812.43(c), a sponsor is required to obtain clinical investigator financial information before allowing the clinical investigator to participate in a covered clinical study. Under 21 CFR § 54.4(b), each clinical investigator who is not a full-time or part-time employee of the sponsor of the covered clinical study is required to provide the sponsor with sufficient accurate financial information to allow for complete disclosure or certification and to update this information if any relevant changes occur during the study and for one year following its completion.

A. Definitions

Clinical Investigator – For purposes of part 54, "clinical investigator" means a "listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects," including the spouse and each dependent child of the investigator or subinvestigator. (See 21 CFR § 54.2(d).) See Section IV.D, Clinical Investigator, for additional information. Clinical investigators are included in the definition even if they did not participate for the entire length of the study. If a clinical investigator did not participate in the entire study,

[3] 21 CFR parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860

information collected should be for the period of time he or she participated in the study and for one year following the end of his or her participation.

Covered clinical study – The part 54 regulations define "covered clinical study" to mean "any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase 1 tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols and parallel track protocols." (See 21 CFR § 54.2(e).) This definition includes clinical studies submitted in support of new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), abbreviated new drug applications (ANDAs) under section 505(j) of the FD&C Act, premarket notification submissions under section 510(k) of the FD&C Act, reclassification petitions under section 513 of the FD&C Act, premarket approval applications (PMAs) under section 515 of the FD&C Act, and biologics licensing applications (BLAs) submitted under section 351 of the Public Health Services Act (PHS Act), as well as studies submitted in support of amendments or supplements to any such applications. (See 21 CFR §§ 54.3 and 54.4(a).) Covered clinical studies would generally not include expanded access under section 561 of the FD&C Act. If an applicant is unsure of whether a particular study is included in this definition, it may consult with FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with financial disclosure requirements. (21 CFR § 54.2(e).) See Section IV.G, Covered Clinical Study, for additional information.

Applicant – "Applicant" means the party who submits a marketing application to FDA for approval of a drug, device or biologic product or who submits a reclassification petition. The applicant is responsible for submitting the required certification and disclosure statements. (See 21 CFR § 54.2(g).) Note that for purposes of financial disclosure the term "applicant" includes "submitter" and the term "application" includes "510(k) submission." See Section IV.F, Applicant, for additional information.

Sponsor of the covered clinical study – For purposes of part 54, "sponsor of the covered clinical study" means "a party supporting a particular study at the time it was carried out." (See 21 CFR § 54.2(h).) A covered clinical study may have more than one sponsor for whom financial information will need to be collected. For example, if one party designed and conducted the covered clinical study, a second party provided funding, and a third party provided the test product, there would be three sponsors of the covered clinical study. However, if the third party in this example was reimbursed for the test product, it would not be considered a sponsor of the covered clinical study and the study would be considered to have two sponsors. Note also that the definition of "sponsor" for purposes of part 54 is different than the definition of "sponsor" for purposes of investigational new drug applications (INDs) and investigational device exemptions applications (IDEs) (see 21 CFR §§ 312.3(b) and 812.3(n)). See Section IV.E, Sponsor, for additional information.

B. Disclosable Financial Interests and Arrangements

The financial interests, arrangements, and payments that must be disclosed (see 21 CFR § 54.4(a)(3), referred to herein as "disclosable financial interests and arrangements") are described below.[4] Note that the dollar amounts that trigger reporting are the combined financial interests of the investigator, spouse, and dependent children.

1. Any compensation made to the investigator by any sponsor of the covered clinical study in which the value of compensation could be affected by study outcome.

2. A proprietary interest in the tested product including, but not limited to, a patent, trademark, copyright or licensing agreement.

3. Any equity interest in any sponsor of the covered clinical study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study.

4. Any equity interest in any sponsor of the covered study if the sponsor is a publicly held company and the interest exceeds $50,000 in value. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study.

5. Significant payments of other sorts (SPOOS) are payments that have a cumulative monetary value of $25,000 or more and are made by any sponsor of a covered study to the investigator or the investigator's institution during the time the clinical investigator is carrying out the study and for one year following completion of the study. This would include payments that support activities of the investigator (e.g., a grant to the investigator or to the institution to fund the investigator's ongoing research or compensation in the form of equipment), exclusive of the costs of conducting the clinical study or other clinical studies, or to provide other reimbursements such as retainers for ongoing consultation or honoraria. See Section IV, Questions C.4, C.5, and C.6 for additional information on SPOOS.

C. Agency Actions

The agency may refuse to file a marketing application that does not contain the financial information required by 21 CFR part 54 or a certification by the applicant that the applicant has

[4] These are the requirements for studies begun on or after the effective date of the part 54 regulations, February 2, 1999. For older studies, the disclosure requirements vary based on the study's status as of the effective date of the regulation. For studies that were completed prior to February 2, 1999, disclosure of financial interests and arrangements described in paragraphs 1 through 3 is required. For studies ongoing as of February 2, 1999, disclosure of financial interests and arrangements described in paragraphs 1 through 4 is required as well as payments as described in paragraph 5 that were made on or after February 2, 1999. (See *Federal Register*, volume 63, December 31, 1998, page 72172-3.)

acted with due diligence to obtain the information but was unable to do so stating a sufficient reason. (21 CFR § 54.4(c).)

If FDA determines that the financial interests or arrangements of any clinical investigator raise a serious question about the integrity of the data, FDA will take any action it deems necessary to ensure the reliability of the data (21 CFR § 54.5(c)) including:

1. Initiating agency audits of the data derived from the clinical investigator in question;

2. Requesting that the applicant submit further analyses of data, e.g., to evaluate the effect of the clinical investigator's data on the overall study outcome;

3. Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study; and

4. Refusing to treat the covered clinical study as providing data that can be the basis for an agency action.

IV. QUESTIONS AND ANSWERS

A. GENERAL

A.1. Q: Why did FDA develop the financial disclosure regulations?

A: In June 1991, the Inspector General of the Department of Health and Human Services submitted a management advisory report[5] to FDA stating that FDA's failure to have a mechanism for collecting information on "financial conflicts of interest" of clinical investigators who study products that undergo FDA review could constitute a material weakness under the Federal Managers' Financial Integrity Act. As stated in the preamble to the final rule, although FDA determined that a material weakness did not exist, the agency did conclude that there was a need to address this issue through regulation.[6] During the rulemaking process, FDA also learned about potentially problematic financial interests and arrangements through published newspaper articles, Congressional inquiries, and public testimony and comments. Based on the information gathered, FDA determined that it was appropriate to require the submission of certain financial information with marketing applications that, in part, rely on clinical data.

[5] Office of the Inspector General (OIG), Department of Health and Human Services (DHHS), *Management Advisory Report – Financial Involvement of Clinical Investigators with Sponsors of Research Leading to Food and Drug Administration Marketing Approval*, June 1991, OI-HQ-91-003.

[6] The final rule was published in the *Federal Register*, Vol. 63, February 2, 1998, pages 5233-5254. The referenced statement appears on page 5235.

A.2. Q: What is the purpose of FDA's review of clinical investigator financial disclosure information and how can sponsors minimize bias?

A: FDA's review of clinical investigator financial disclosure information alerts FDA staff to financial interests and arrangements that could lead to bias in covered clinical studies. The financial disclosure process also provides FDA with information regarding whether and to what extent the sponsors have taken steps to minimize the risk of bias. An important means of minimizing the potential for bias resulting from such financial interests and arrangements is through proper study design (see 21 CFR § 54.5(b)). For example, using randomization and blinding helps to minimize the potential for bias in assigning subjects to receive the test article or placebo and in assessing study outcomes and analyzing results. Similarly, having someone with no financial interests or arrangements evaluate study endpoints, especially in an unblinded study, can help minimize potential bias in assessing therapy outcomes.

FDA staff consider the financial disclosure information and the methods the sponsor used to minimize bias during the review of marketing applications to assess the reliability of the clinical data (see 21 CFR § 54.1). Additionally, because sponsors of studies conducted under INDs and IDEs are required to collect financial information from clinical investigators prior to study initiation,[7] sponsors can work with FDA to minimize any potential bias. FDA strongly encourages sponsors of studies not conducted under an IND/IDE to collect financial information prior to study initiation for the same reasons.

B. FORMS AND INFORMATION TO BE SUBMITTED

B.1. Q: What financial disclosure information is to be included in a marketing application?

A: The application must contain a list of all clinical investigators who conducted each covered clinical study (21 CFR § 54.4). For purposes of this list, investigators and subinvestigators who meet the definition of "clinical investigator" in 21 CFR § 54.2(d) must be included. Note that the term clinical investigator includes the spouse and each dependent child of a clinical investigator (21 CFR § 54.2(d)). This list must also identify those clinical investigators who are full or part-time employees of the sponsor of the covered study (21 CFR § 54.4). If a spouse or dependent child is an employee of a sponsor, that clinical investigator should be identified as an employee for purposes of financial disclosure. For each clinical investigator who is not identified as an employee of the sponsor, one of the following must be submitted (21 CFR § 54.4(a)):

[7] 21 CFR §§ 312.53(c)(4), 812.20(b)(5), and 812.43(c)

1. FORM FDA 3455, Disclosure Statement,[8] for each clinical investigator who, or whose spouse or dependent child, had disclosable financial interests in and/or arrangements with any sponsor of the covered clinical study. The form should include an attachment with detailed information about those financial interests and arrangements (for example, the nature of the contingent payment or the equity holdings of the investigator, or the investigator's spouse or dependent child, that exceeded the threshold) and a description of the steps taken to minimize the potential for bias resulting from the disclosed financial interests and arrangements (21 CFR § 54.4(a)(3)). See Section IV.C for additional information;

2. FORM FDA 3454, Certification, for any clinical investigator who has no disclosable financial interests in or arrangements with any sponsor of the covered clinical study (21 CFR § 54.4(a)(1)); the applicant may append a list of investigator names to a single FORM FDA 3454 for those investigators with no disclosable financial interests or arrangements; or

3. If the applicant was unable to obtain some or all of the financial information needed to disclose or certify for a clinical investigator, the applicant must identify any disclosable financial interests or arrangements of which it is aware, certify that it acted with due diligence to obtain the information (listed as option 3 on FORM FDA 3454), and include an attachment identifying the reason why any missing information could not be obtained (21 CFR § 54.4). FDA expects that in the vast majority of cases, applicants will be able to provide a complete financial Certification or Disclosure Statement and that the need to certify that they acted with due diligence will be rare. See Question B.7 and Question F.2 for additional information on due diligence.

FDA encourages applicants to submit financial disclosure information in a format that will ensure all required information is included. For example, applicants should provide the total number of investigators in the study and a table indicating, for each clinical investigator listed who is not identified as an employee, whether they are providing a Certification (FORM FDA 3454), a Disclosure Statement (FORM FDA 3455) or certification that they acted with due diligence but were unable to obtain the information (option 3 on FORM FDA 3454). Applicants should also ensure that all required attachments, as identified above, are included. Applicants with questions about acceptable formats for submitting the financial disclosure information should contact the Center representatives identified in Question K.1.

[8] As an alternative to a separate FORM FDA 3455 for each clinical investigator with information to disclose, applicants may submit a single FORM FDA 3455, with attachments clearly identifying all clinical investigators with information to disclose and, for each investigator, identifying the study, the specific details of their financial interests and arrangements and the steps taken to minimize the potential for bias. Applicants with questions about alternative formats should contact the Center representatives identified in Question K.1.

B.2. Q: May an applicant rely upon the policies and procedures of the clinical investigator's institution for disclosure, review and management of financial conflicts of interest of their employees (including spouse and dependent children)?

A: Each applicant is responsible for disclosing or certifying as required by 21 CFR part 54. Compliance with institutional policies or procedures by an investigator is not a substitute for compliance with part 54.

Although a clinical investigator's institution may take steps to manage a clinical investigator's financial interests and arrangements, in order to minimize study bias, FDA must make its own evaluation of the clinical investigator's financial interests and arrangements (21 CFR § 54.5). When a clinical investigator has disclosable financial interests and arrangements, the disclosure statement submitted to FDA is required to include a description of any steps taken to minimize the potential for bias resulting from any of the disclosed financial interests and arrangements (21 CFR 54.4(a)(3)(v)). A description of the steps taken by the institution to minimize bias should be included with the disclosure statement, if pertinent. See Section IV, Question D.7 for additional information.

B.3. Q: Where in a marketing application for a drug or a biological product should an applicant include the certification or disclosure forms and attachments?

A: Applicants using the format described in FORM FDA 356h (Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use) should include the clinical investigator list and financial certification and/or disclosure forms and attachments as part of item 19 (Financial Information) of the application.[9] Applicants using the Common Technical Document (CTD) format should include this information in Module 1.3.4.[10]

B.4. Q: Where should the information be included in a device marketing application?

A: Applicants should submit the clinical investigator list and financial certification/disclosure forms and attachments according to the format outlined in the appropriate submission guidance.[11]

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[9] Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use, available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM082348.pdf.

[10] The eCTD Backbone Files Specification for Module 1, available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163552.pdf.

[11] For premarket notification submissions, see "Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s," available at www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm.
For premarket approval applications, see "Guidance for Industry and FDA Staff: Premarket Approval Application Filing Review," available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089430.htm.

B.5. Q: How should the financial information be submitted?

A: The financial information is required to be submitted using FORMS FDA 3454 and/or 3455 (21 CFR § 54.4(a)), which are available on the Web at the following Internet address: http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm (Forms are listed in numerical order).

B.6. Q: Who, specifically, is responsible for signing the financial certification/disclosure forms?

A: The forms are to be signed and dated by the chief financial officer or other responsible corporate official or representative of the applicant. FDA recommends that the "other responsible corporate official or representative" be a senior official who has the authority to ensure the information is collected and reported accurately. Depending on company structure, such an individual could be the person in charge of regulatory or clinical affairs.

B.7. Q: What does FDA mean by the term "due diligence"?

A: "Due diligence" is a measure of activity expected from a reasonable and prudent person under a particular circumstance, in this case, collecting information about financial interests or arrangements. FDA expects that applicants will typically be able to obtain the required information because investigators are required to provide financial disclosure information to sponsors before participating in a clinical study. (21 CFR §§ 54.4, 312.53(c), 812.43(c) and 812.20(b)(5).) In the rare circumstance where applicants are unable to obtain required financial information, applicants must certify that they acted with due diligence and explain why the information was not obtainable (21 CFR § 54.4).

If all of the information required to make a complete certification or disclosure is not available from a sponsor, applicants should make appropriate efforts to obtain the information by other means. That may mean contacting an individual investigator or subinvestigator directly. If an investigator's whereabouts are unknown, for example because the investigator left a study prior to its completion or prior to one year following completion of the study, FDA recommends that sponsors and/or applicants try to locate the clinical investigator. Sponsors and applicants should exercise reasonable judgment regarding the appropriate amount of effort to expend when attempting to contact investigators, which may include consideration of the role of the investigator in the study and the importance of the investigator's data contribution.

In most cases, FDA suggests that more than one attempt at contacting an investigator would be appropriate and that more than one method of contact be attempted. FDA also recommends that each attempt to contact the investigator be documented, for example, by maintaining copies of e-mails and letters and documenting telephone calls and conversation by written memoranda. FDA also suggests that sponsors and applicants consider using a method of contacting investigators that allows verification of receipt, such as certified mail or reliable courier service that provides notice of recipient's receipt

of a letter. When such methods are used, copies of the delivery notice or undeliverable notice should be maintained.

If an investigator is no longer at the institution where the study was conducted, FDA recommends that the sponsor or applicant make a reasonable attempt to locate the investigator, for example, by requesting contact information from the institution where the study was conducted or the institution with which the investigator was affiliated, contacting professional associations the investigator may have been affiliated with, and/or conducting Internet searches.

If a clinical investigator cannot be located or information for some other reason cannot be obtained from the investigator, the sponsor should have access to certain disclosable financial information and arrangements, for example, payments made specifically to the investigator or information related to product sales that may generate royalties due to the investigator. On request from an applicant, sponsors should check their records for such information and, subject to any privacy laws (noting that other countries' laws may differ from United States law), the sponsor should then provide disclosable information to the applicant. In addition, and as necessary, efforts should be made to obtain disclosable financial information from other reasonably available, reliable, public sources of information. For example, information on proprietary interests in the test product, such as patents and trademarks, should be available from publicly available sources.[12] Another possible source of information is the clinical investigator's institution, which may have collected financial information and, if consistent with their policies, may release this information to the applicant upon request. Appropriate certifications, disclosures, and/or explanations should be provided to FDA on the basis of information obtained. See Question F.2 for additional information.

An applicant must exercise due diligence whether a covered study is conducted at foreign or domestic sites. The agency expects that a reasonable and prudent applicant will take affirmative steps at the first opportunity to see that the financial information required for a complete certification or disclosure under part 54 is collected and maintained. This is not only to ensure that the applicant will be able to make a complete submission but also to ensure that the study sponsor will take steps to protect the study against possible bias. See Questions E.3, E.5, and F.3 for additional information.

B.8. Q: Is clinical investigator financial disclosure information required in IND or IDE applications?

A: No, IND/IDE sponsors are not required to submit information regarding clinical investigator financial interests or arrangements in IND or IDE applications. They are, however, required to collect this information before a clinical investigator participates in a clinical study (see 21 CFR §§ 312.53(c)(4), 812.20(b)(5), and 812.43(c)(5)), and

[12] Such sources include the Patent and Trademark Office website and, once available, the federal reporting website proposed by the Centers for Medicare & Medicaid Services as required by Section 6002 of the Patient Protection and Affordable Care Act. See the final rule, "Transparency Reports and Reporting of Physician Ownership or Investment Interests," *Federal Register*, Vol. 78, February 8, 2013, page 9458.

clinical investigators are required to disclose financial information to sponsors (see 21 CFR §§ 312.64(d) and 812.110(d)). The information need not be submitted to FDA until a marketing application is submitted containing the results of the covered clinical study (21 CFR § 54.4).

Study sponsors are encouraged to consult with FDA prior to and during clinical studies about the management of specific situations involving potential bias on the part of a clinical investigator. During these consultations, FDA staff should focus on the protection of research subjects and the minimization of bias from all potential sources.

C. FINANCIAL INTERESTS AND ARRANGEMENTS SUBJECT TO DISCLOSURE

C.1. Q: What information about a financial interest or arrangement should be disclosed to the agency? For example, if an investigator owns more than $50,000 of stock in a publicly held company, can the applicant just disclose that there is an interest that exceeds the $50,000 threshold or is it necessary to disclose in written detail the interest or arrangement in question?

A: The applicant must make a complete and accurate disclosure (21 CFR § 54.4(a)(3)). The specific details of the financial interest or arrangement, including its size and nature, should be disclosed as should any steps taken to minimize the potential for study bias resulting from the interest or arrangement. In describing financial interests, for example, the applicant might list: stock valued at $77,000, speaking fees of $7,500, consulting fees of $22,000, and a grant of $125,000 and include a discussion of the specific steps taken to minimize potential bias. Sponsors should request that clinical investigators provide sufficient detail about their financial disclosure information to allow the appropriate disclosures to be made.

C.2. Q: Should a clinical investigator report all fluctuations above and below the $50,000 level during the course of the investigation and one year after completion of the study?

A: In light of the potential volatility of stock prices, FDA recognizes that the dollar value of an investigator's equity holding in a sponsoring company is likely to fluctuate during the course of a study. Clinical investigators should report an equity interest when the investigator becomes aware that the holding has exceeded the threshold and the investigator should use judgment in updating and reporting on fluctuations in equity interests exceeding $50,000. FDA does not expect the investigator to report when an equity interest fluctuates below that threshold. See Question E.4 for additional information.

C.3. Q: Are equity interests in mutual funds and 401(k)s reportable?

A: FDA expects that equity interests held in publicly traded mutual funds will not be reportable in the vast majority of cases. If, however, an investigator would have control

over buying or selling stocks in a mutual fund, equity interests held in such publicly traded mutual funds would be reportable.

If an investigator holds an equity interest in a sponsor over $50,000 in a 401(k) or equivalent account, and has control over whether to buy or sell the interest, the equity interest is reportable.

C.4. Q: How do significant payments of other sorts (SPOOS) relate to the variety of payments the sponsor might make to an individual or institution for various activities?

A: The term "significant payments of other sorts" was intended to capture substantial payments or other support that has a value of more than $25,000 provided to an investigator or institution that could create a sense of obligation to the sponsor.

These payments do not include payments for the cost of conducting the clinical study of the product under consideration or clinical studies of other products, under a contractual arrangement, but do include other payments made directly to the investigator or to an institution for direct support of the investigator.

“Significant payments of other sorts” would include, for example, payments, retainers and honoraria from a sponsor to a clinical investigator for activities such as participating on committees, providing consultation, or serving as a preceptor (21 CFR § 54.2(f)). Grants to fund ongoing research, including laboratory activities and equipment, and compensation in the form of actual equipment for the laboratory/clinic would also be considered significant payments of other sorts. This means that if an investigator were given equipment or money to purchase equipment for use in the laboratory/clinic but not in relation to the conduct of the clinical study, payment would be considered a significant payment of other sorts (21 CFR § 54.4(a)(3)(ii)). If, however, the investigator were provided with computer software or money to buy software needed for use in the clinical study, that payment would not need to be reported.

Payments made to the institution that are not made on behalf of the investigator and are not specifically targeted towards the investigator generally would not need to be reported. Under certain circumstances, however, a grant made to an institution would be considered targeted towards the investigator (and therefore considered reportable); for example, if the grant is worded in such a way that only the investigator could fulfill it.

Finally, payments that meet the criteria for significant payments of other sorts that are made to other researchers at the institution, who are not part of the covered study, do not need to be reported.

C.5. Q: Are payments made to investigators to cover travel expenses (such as transportation, lodgings and meal expenses) reportable as significant payments of other sorts (SPOOS)?

A: Generally, reasonable payments made to investigators to cover reimbursable expenses such as transportation, lodgings and meals do not fall within the definition of SPOOS and, therefore, would not need to be reported. Payment for other expenses that are generally considered outside of normal reimbursable expenditures and not expenses necessary to conduct the study would be considered SPOOS. Such payments would include, for example, entertainment costs, travel costs associated with transporting and/or providing lodgings and meals for family members, and other payments that exceed reasonable expectations (for example, if an investigator was flown to a resort location for an extra week of vacation). These types of expenses are reportable and should be tracked as SPOOS. FDA understands that such payments may be limited or prohibited by industry ethical codes.[13] To the extent such payments are made, they would be SPOOS.

C.6. Q: Is the dollar amount that triggers reporting of significant payments of other sorts (SPOOS) cumulative over the course of the study or is it based on the amount received on an annual basis?

A: The $25,000 threshold amount for reporting SPOOS is based on the cumulative amount of SPOOS received by the clinical investigator (including payments made to the spouse and dependent children) over the course of the study and for one year following completion of the study.

C.7. Q: Does FDA have expectations about how the financial information should be collected? Will FDA consider it acceptable practice for a company to use a questionnaire to collect financial information from investigators rather than constructing an internal system to collect and report this information?

A: FDA regulations do not prescribe a particular method for collecting financial information from investigators. Sponsors/applicants have the flexibility to collect the information in the most efficient and least burdensome manner that will allow for complete and accurate certifications and disclosures. They may use questionnaires completed by the clinical investigators and/or information already available to the sponsor, as appropriate. FDA does not require sponsors to establish elaborate systems to collect and track financial information.

If sponsors intend to use a questionnaire to collect financial information from investigators, FDA recommends that they develop forms suited to that purpose. FORM FDA 3455 was designed for applicants to use to report financial information they collected from clinical investigators to FDA. It does not include the background

[13] Examples of industry ethical codes would be the "Principles on Conduct of Clinical Trials and Communication of Clinical Trials Results" from the Pharmaceutical Research and Manufacturers of America (PhRMA) and the "Code of Ethics on Interactions with Health Care Professionals" from the Advanced Medical Technology Association (AdvaMed).

information needed for clinical investigators to be aware of the financial information to be provided. For example, there is no statement that the reporting requirements apply to the spouse and dependent children as well as to the investigator; no information as to the dollar amounts triggering reporting of equity interests or SPOOS; and no statement that the investigator must report the details of the financial interests and arrangements, not just a statement, for example, of equity interest greater than $50,000. In addition, when there is more than one sponsor for financial disclosure purposes, the investigator should be apprised that the dollar amounts triggering reporting apply separately to each sponsor. This type of explanatory information should be provided to the clinical investigators to ensure that the financial disclosure information collected is as accurate and complete as possible. Please see the Appendix for considerations for collecting financial disclosure information from clinical investigators.

C.8. Q: The regulation requires that investigators provide information on financial interests and arrangements during the course of the study and for one year after completion of the study (see 21 CFR § 54.4(b)). What does "during the course of the study" mean? What does "completion of the study" mean?

A: "During the course of the study" refers to the time from the date the clinical investigator entered into an agreement with the sponsor to conduct the study until the completion of the study. For the purposes of financial disclosure under part 54, completion of the study means that all study subjects have been enrolled and follow-up of primary endpoint data on all subjects has been completed in accordance with the clinical protocol. Many studies have more than one phase (e.g., a study could have a short-term endpoint and a longer term follow-up phase). "Completion of the study" here refers to the part of the study that is being submitted in the application. If there were a subsequent application based on longer term data, completion of the study would be defined using completion of follow-up for the longer term data. An applicant is not required to submit updated financial information to FDA after submission of the application, but applicants must retain complete records (21 CFR § 54.6). Where there is more than one study site, the sponsor may consider completion of the study to occur when the last study site is complete, or may consider each study site individually as it is completed.

C.9. Q: What if the sponsor changes during the course of the study or within one year of completion of the study, for example, through purchase or merger?

A: Agency regulations require that an IND/IDE sponsor collect financial information from all clinical investigators and that clinical investigators promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study (21 CFR §§ 54.4, 312.53(c)(4), 312.64(d), 812.43(c)(5) and 812.110(d)). Therefore, if the study sponsor changes during the course of the study, the clinical investigators will need to update their financial disclosure information relevant to the new sponsor. The new sponsor is responsible for collecting this information, and to ensure that the new sponsor has complete financial disclosure information, the new sponsor should seek this information from the original sponsor, and the agency encourages the original sponsor to share their records with the new sponsor.

With respect to covered clinical studies conducted outside the United States not pursuant to an IND or IDE (such as studies submitted pursuant to § 312.120 or § 814.15), the agency expects applicants to take affirmative action, at the earliest opportunity, to see that this information is collected and available to make a complete disclosure and/or certification under part 54.

D. CLINICAL INVESTIGATOR

D.1. Q: Who is included in the definition of "clinical investigator"?

A: Under part 54, "clinical investigator means only a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects" (21 CFR § 54.2(d)). This definition is intended to identify the individuals for whom reporting under this regulation is required. Generally, these individuals are considered to be the investigators and subinvestigators taking responsibility for the study at a given study site. The definition also includes the spouse and each dependent child of such an investigator or subinvestigator.

It should be noted that hospital staff, including nurses, residents, fellows, and office staff who provide ancillary or intermittent care but who do not make direct and significant contribution to the data are not meant to be included under the definition of clinical investigator. Additionally, individuals who only collect specimens or perform routine tests (such as blood pressure, EKG, x-ray) are not meant to be included under the definition of clinical investigator for purposes of financial disclosure.

D.2. Q: How does the definition of "clinical investigator" in the financial disclosure regulation (21 CFR part 54) relate to the definition in the IND regulations (21 CFR part 312)?

A: For drugs and biological products, an investigator under 21 CFR part 312 is defined as "an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. 'Subinvestigator' includes any other individual member of that team." (21 CFR § 312.3(b).)

For purposes of the financial disclosure regulation, a clinical investigator is an investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects (21 CFR § 54.2(d)). Therefore, the term clinical investigator in this context would generally include anyone who fits any of the following criteria: signs the FORM FDA 1572 (Statement of Investigator), is identified as an investigator in initial submissions or protocol amendments under an IND, or is identified as an investigator in the marketing application. This could include individuals identified as subinvestigators

on a FORM FDA 1572.[14] For studies not conducted under an IND, the sponsor will need to identify the investigators and subinvestigators they consider covered by the regulation and provide FORMS FDA 3454 and/or 3455 as appropriate. FDA expects that there will be at least one such person at each clinical site. If other individuals are responsible for a study at a site, those persons should also be included as clinical investigators.

D.3. Q: How does the definition of "clinical investigator" in the financial disclosure regulation (21 CFR part 54) relate to the definition in the medical device regulations (21 CFR part 812)?

A: For medical devices, investigator is defined under 21 CFR part 812 as an individual under whose immediate direction the subject is treated and the investigational device is administered, including follow-up evaluations and treatments. Where an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. (21 CFR § 812.3(i).)

In general, investigators and subinvestigators sign "investigator agreements" in accordance with 21 CFR § 812.43(c), and it is these individuals whose financial interests and arrangements should be reported as they would fall under the definition at 21 CFR § 54.2(d). For studies not conducted under an FDA-approved IDE (that is, a non-significant risk IDE or an exempt study), the sponsor would need to identify the investigators and subinvestigators they consider covered by the regulation and provide FORMS FDA 3454 and/or 3455, as appropriate. We expect that there will be at least one such person at each clinical site.

D.4. Q: Is it necessary to collect financial information on spouses and dependent children of clinical investigators?

A: Yes. The definition of clinical investigator in 21 CFR part 54 includes the spouse and dependent children of the investigators and subinvestigators who are required to report. Therefore, the financial interests and arrangements of the spouse and each dependent child of each investigator and subinvestigator are to be included in the disclosure (21 CFR § 54.2(d)). The dollar amount that triggers reporting is the total of the financial interests of the investigator, spouse, and dependent children (21 CFR § 54.2(d)). If a spouse or dependent child is an employee of the sponsor, the clinical investigator should be identified as an employee of the sponsor and no further disclosure is required. (See 21 CFR § 54.4.)

D.5. Q: Who is considered a "dependent child"?

A: For purposes of clinical investigator financial disclosure under part 54, a dependent child is the investigator's child (whether by blood or adoption), stepchild or foster child who is unmarried, and for whom the investigator provides more than one-half of the

[14] For guidance on who should be listed as an investigator or subinvestigator on Form FDA 1572, please see FDA's Information Sheet Guidance, "Frequently Asked Questions – Statement of Investigator (Form FDA 1572)" available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf.

child's support. This would include a child who, at any time during the course of the study and for one year following completion of the study, is under the age of 19, under the age of 24 if a full-time student, or who is permanently and totally disabled. Such a child would generally have the same principal residence as the investigator.

D.6. Q: What obligations does the clinical investigator have under the financial disclosure regulations?

A: Clinical investigators are to provide sponsors sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements (see 21 CFR §§ 54.4, 312.53(c)(4), 312.64(d), 812.43(c)(5) and 812.110(d)). Clinical investigators must provide this information to sponsors and also promptly update the information if any relevant changes occur during the course of the investigation and for one year following the completion of the study (see 21 CFR §§ 54.4(b), 312.53(c)(4), 312.64(d), 812.43(c)(5) and 812.110(d)). See also Question C.2.

D.7. Q: May a clinical investigator rely on the information he/she provided to comply with his/her institution's policies and procedures pertaining to financial conflicts of interest to comply with the investigator obligations for financial disclosure under FDA's regulations?

A: The financial information a clinical investigator provides to his/her institution is based on the institution's requirements, which may not be sufficient to meet FDA's regulations. FDA's regulations require the clinical investigator to provide sufficient and accurate financial information to the sponsor to allow the sponsor to submit complete and accurate certification or disclosure statements under FDA's clinical investigator financial disclosure regulations (21 CFR § 54.4(b)). However, if an investigator determines that the financial information he/she provided to his/her institution adequately fulfills the disclosure requirements in FDA's regulations, a clinical investigator could provide the same information to the sponsor. The clinical investigator would still need to commit to promptly updating the financial information if any relevant changes occur during the course of the study and for one year following completion of the study (21 CFR § 54.4(b)).

E. SPONSOR

E.1. Q: How does the definition of "sponsor" in the financial disclosure regulation (21 CFR part 54) relate to the definition in the IND/IDE regulations (21 CFR parts 312 and 812)?

A: In 21 CFR part 54, the term "sponsor of the covered clinical study" means "the party supporting a particular study at the time it was carried out" (21 CFR § 54.2(h)). FDA interprets "support" to include those who provide material support, for example, monetary support or the test product under study. (See Question E.9 for further explanation of "material support.") This differs from the meaning of "sponsor" in other FDA regulations (such as 21 CFR parts 312 and 812), where the sponsor may be the

person who initiates or takes responsibility for a clinical investigation (21 CFR §§ 312.3(b) and 812.3(n)). While the definition of sponsor under part 54 usually would include the sponsor of an IND/IDE (as defined in 21 CFR parts 312 and 812), it also includes any other individuals who provide material support for the study. Therefore, a covered clinical study may have more than one sponsor for financial disclosure purposes. When there is more than one sponsor, FDA interprets the regulation to mean that the dollar amounts triggering reporting apply separately to each sponsor.

E.2. Q: What obligations do IND and IDE sponsors have regarding information collection prior to study start?

A: The IND and IDE regulations provide that, before permitting an investigator to begin participation in an investigation, the IND/IDE sponsor (that is, the sponsor as defined in 21 CFR parts 312 and 812) must obtain sufficient and accurate financial information that will allow an applicant to submit complete and accurate certification or disclosure statements as required under 21 CFR part 54 (21 CFR §§ 312.53 and 812.43). In order to fulfill these requirements and ensure complete disclosure, the IND/IDE sponsor should identify all "sponsors of the covered clinical study" (as defined in 21 CFR § 54.2(h)) for investigators because the identity of all parties providing support may not be known to investigators.

The sponsor is also required to obtain the investigator's commitment to promptly update this information if any relevant changes occur during the course of the investigation and for one year following the completion of the study (21 CFR §§ 312.53 and 812.43). By collecting the information prior to the study start, the sponsor will be aware of any potential problems, can consult with the agency early on, and can take steps to minimize any possibility for bias.

E.3. Q: Why is the IND/IDE sponsor responsible for obtaining financial information from investigators?

A: Although reporting to the FDA is the responsibility of the applicant, the IND/IDE sponsor is required to collect the financial information before permitting an investigator to participate in a clinical study (21 CFR §§ 312.53, 812.20(b)(5), and 812.43). The purpose of this requirement is twofold:

1. to alert the IND/IDE sponsor of the study of any potentially problematic financial interests or arrangements as early in the product development process as possible in order to minimize the potential for study bias, and

2. to facilitate the accurate collection of financial information that may not be submitted until several years later.

The IND/IDE sponsor, who is in contact with the investigator, is best placed to inquire as to the financial interests and arrangements of investigators, and this obligation applies to any IND/IDE sponsor (e.g., commercial, government, or contract research organization

(CRO)). The IND/IDE sponsor is required to maintain complete and accurate records showing any financial interest in, or arrangement with, a sponsor of the covered study, as described in 21 CFR § 54.4(a)(3)(i-iv) (21 CFR §§ 312.57(b) and 812.140(b)(3)). The IND/IDE sponsor is also best situated to ensure that required financial information is collected and made available to the applicant company, so that the information can be included in the marketing application. (Refer to 21 CFR §§ 54.4, 312.53, 312.57(b), 812.43, and 812.140(b)(3).)

IND/IDE sponsors conducting covered clinical studies outside the United States should note that the part 54 regulations do not distinguish between foreign and domestic sites. See Question F.3 for additional information.

E.4. Q: Is the IND/IDE sponsor responsible for obtaining 1-year follow-up financial information from clinical investigators?

A: As noted in response to Question E.2 above, the IND/IDE sponsor is required to obtain financial information from clinical investigators before permitting the investigators to begin participation in an investigation and to obtain the investigator's commitment to promptly update this information if any relevant changes occur during the course of the study and for one year following the completion of the study (21 CFR §§ 312.52 and 812.43). The regulations do not specifically require the IND/IDE sponsor to obtain information from clinical investigators one year following completion of the study. The regulations, however, do require IND/IDE sponsors to maintain complete and accurate records concerning all financial interests and arrangements of clinical investigators subject to part 54 (see 21 CFR §§ 312.57(b) and 812.140(b)(3)) and to secure investigator compliance with the regulations (see 21 CFR §§ 312.56(b) and 812.46(a)). Therefore, an IND/IDE sponsor should take steps to ensure clinical investigator compliance, such as reminding the clinical investigators of the requirement to promptly update their financial information when any relevant changes occur during the study and for one year following completion.

E.5. Q: What if the IND/IDE sponsor is not the party who will be submitting a marketing application?

A: In many cases, the IND/IDE sponsor, the part 54 sponsor, and the applicant will be the same party. However, there may be times when they are not. For example, consider the case when an academic institution serves as the IND/IDE sponsor and a drug company serves as the part 54 sponsor by providing funding or the investigational drug for the study. When a marketing application is submitted, the drug company is likely to be the applicant. If, however, the drug company was sold to another company, the applicant may be neither the IND/IDE sponsor nor a part 54 sponsor.

It should be noted, however, that even if the IND/IDE sponsor will not be submitting the marketing application, the IND/IDE sponsor is still responsible for collecting financial information from the clinical investigators. The responsibility for reporting financial information to FDA falls upon the applicant; that is, part 54 requires the applicant to

submit financial information when the marketing application is submitted to FDA (21 CFR § 54.4(a)).

As stated above and in Question E.3, an IND/IDE sponsor is responsible for collecting financial information from both foreign and domestic clinical investigators. If a sponsor did not collect this information, for example, because the sponsor conducted a foreign study that was not conducted under an IND/IDE and was not originally intended for submission to the FDA, the applicant is expected to contact the sponsor and/or clinical investigators to retrospectively obtain the financial disclosure information. See Questions F.2 and F.3 for additional information.

E.6. Q: If a contract research organization (CRO) is conducting a covered clinical study on behalf of another company, should the CRO collect the financial information from investigators? Is it necessary to collect financial information from investigators who have financial interests in or arrangements with CROs?

A: If a CRO meets the definition of an IND/IDE sponsor or has contracted to collect financial information from clinical investigators on behalf of a sponsor, the CRO must collect financial information on clinical investigators' interests in any sponsors of the covered clinical study. See 21 CFR § 312.52. To satisfy the requirements in part 54, if the CRO provides material support for a covered study, financial information on clinical investigators' financial interests in and arrangements with the CRO is to be collected. If another entity provided material support for the study, and the CRO was responsible for collecting the information, then the CRO also would collect financial information relative to that entity.

E.7. Q: Suppose a public or academic institution conducts a covered clinical study without any support from a commercial sponsor, but the study is later used by an applicant to support its marketing application. In that case, who is the "sponsor" of the study and what information should the applicant submit?

A: In this case, the part 54 sponsor of the study is the public or academic institution. Because such institutions are often not commercial entities, there may not be relevant equity interests to report. However, if the clinical investigator is not a full-time or part-time employee of the public or academic institution, the clinical investigator would need to report any relevant interests under 21 CFR § 54.4, such as any proprietary interest in the tested product, including but not limited to a patent, trademark, copyright or licensing agreement, and reportable financial arrangements with the institution, such as compensation affected by the outcome of studies or significant payments of other sorts. The clinical investigator's financial interests in and arrangements with the applicant would not need to be reported because the company was not a sponsor of the covered clinical study.

If, however, the applicant provided material support for the study (for example, by providing the study product for free), then it would be considered a sponsor for financial disclosure purposes. The academic institution conducting the study would need to collect

information regarding the clinical investigators' financial interests and arrangements with the company.

E.8. Q: If a subsidiary of a larger parent company is conducting a covered clinical study, are the financial interests and arrangements of the clinical investigators with only the subsidiary reported? Or, are the financial interests of the investigators in the parent company to be reported also?

A: If the subsidiary company meets the definition of a sponsor of the covered study as defined in 21 CFR part 54, the IND/IDE sponsor is required to collect clinical investigators' financial information related to the subsidiary company. If the parent company is a 21 CFR part 54 sponsor of the study, the IND/IDE sponsor also must collect financial information related to the parent company. If there are multiple companies providing material support for a covered study, the IND/IDE sponsor is responsible for collecting financial information from clinical investigators related to all companies providing that support (21 CFR §§ 54.4, 312.53 and 812.43). The company that will submit the marketing application is ultimately responsible for submitting to the agency the disclosable financial interests and arrangements of clinical investigators with respect to all the covered study's sponsors, as defined in 21 CFR part 54, at the time the marketing application is submitted (21 CFR § 54.4).

E.9. Q: What is considered "material support" when identifying sponsors of the covered study?

A: Parties that provide "material support" are considered sponsors of the covered clinical study. This would include providing direct funding or other monetary support such as through a grant, or providing services or materials. If a party receives reimbursement for the services and/or materials it is providing, then that party generally would not be considered a sponsor. For example, a CRO paid by a sponsor to perform services would not be considered a sponsor of the covered clinical study. Materials could include the product under study as well as other products and/or equipment that are needed for the conduct of the study, such as ancillary medication and equipment used in testing required by the protocol.

F. APPLICANT

F.1. Q: Do applicant companies need to collect information for a year after completion of the study? Who is responsible for collecting/providing this information?

A: The investigator must promptly provide updated financial information to the sponsor whenever any relevant changes occur during the course of the investigation and for a one-year period following completion of the study (21 CFR §§ 54.4(b), 312.64(d) and 812.110(d)). In addition, sponsors should record SPOOS that are paid to the investigator or the investigator's institution to support activities of the investigator that have a cumulative monetary value of more than $25,000, exclusive of the costs of conducting the covered clinical studies, both during the study and for one year following completion

of the study (21 CFR §§ 54.2(f) and 54.4(a)(3)(ii)). FDA specified the one-year time frame because anticipation of payments or expectation of employment may be as influential as payments already received. Applicants need only report these financial interests and arrangements when the marketing application is submitted, but sponsors and applicants are responsible for keeping updated financial information from the investigators in company files (21 CFR §§ 54.6, 312.57 and 812.140).

F.2. Q: Suppose an applicant has obtained the results of a clinical study conducted by another sponsor and that sponsor certifies it has no financial disclosure information in its files. Is the applicant obligated to use due diligence in attempting to contact the clinical investigators directly to obtain the information? Is the applicant obligated to provide any certification as to proprietary interests? Is the sponsor obligated to provide the applicant with a statement as to outcome payments?

A: The applicant is required to provide financial disclosure information in a marketing application or certify that it acted with due diligence to obtain necessary information but was unable to do so and state the reason (21 CFR § 54.4). (See Question B.7 for a further explanation of "due diligence.") The sponsor should collect financial disclosure information from the clinical investigators, and, regardless of whether it collected all necessary financial information, should have information on any outcome payments (that is, payment that is dependent on the outcome of the study) and/or SPOOS made to the investigators. The applicant should request this information from the sponsor. The applicant should also make reasonable efforts to contact the clinical investigators to obtain disclosable financial information. Information on proprietary interests, such as patents and trademarks, should also be available to the applicant from publicly available sources.

F.3. Q: Do applicants need to provide information on investigators who participate in foreign studies?

A: The applicant has the same financial disclosure obligations (21 CFR part 54) with respect to studies conducted at foreign and domestic sites. An applicant must include a certification or disclosure of information for each investigator participating in a foreign covered study, or, to the extent the applicant is unable to obtain sufficient information to certify or disclose, it must certify that it acted with due diligence but was unable to obtain the information and state the reason why (21 CFR § 54.4).

Sponsors of foreign covered studies should obtain financial disclosure information from clinical investigators prior to study initiation and provide this information to applicants.[15]

The agency believes that a prudent applicant would take affirmative action at its earliest opportunity to collect financial information relating to a foreign covered study or to ensure that the information is collected by the study sponsor. Where possible, the agency strongly encourages the applicant to arrange for the collection of financial information

[15] If a foreign study is conducted pursuant to an IND or IDE, the sponsor has a legal obligation to comply with applicable rules, including the requirement to collect and maintain financial disclosure information.

prior to study initiation – to ensure that the information is preserved so that a complete submission can be made and to take any steps necessary to minimize potential bias. Where this is not possible, for example, because an applicant is submitting a foreign covered study sponsored by another entity and the applicant did not oversee, support, or direct the study, the applicant should take appropriate steps to obtain financial information from the study sponsor, investigators, or other reasonably available sources. See Question F.2.

G. COVERED CLINICAL STUDY

G.1. Q: Disclosure of financial interests and arrangements is required only for covered clinical studies, specifically, those studies relied upon to provide support for the effectiveness of a product or in which a single investigator makes a significant contribution to the demonstration of safety (21 CFR §§ 54.2(e) and 54.3). An IND sponsor, acting much earlier, must inquire into investigator financial interests and arrangements before the ultimate role of a study in the application is determined (21 CFR § 312.53). How will the IND sponsor determine which studies will ultimately require certification/disclosure statements?

A: The IND sponsor will need to consider the potential role of a particular study based on study size, design, and other considerations. Almost any controlled effectiveness study could, depending on outcome, become part of a marketing application, but other studies might be critical too, such as a pharmacodynamic study in a population subset or a bioequivalence study supporting a new dosage form. So, for many studies, it would be prudent to collect the information in the event that the study will ultimately require certification and disclosure statements.

G.2. Q: Do the reporting requirements apply to studies that include large numbers of investigators and multiple sites? Will the agency consider a waiver mechanism to exempt applicants from collecting information from clinical investigators conducting these kinds of studies?

A: Large multi-center efficacy studies with many investigators are considered covered clinical studies within the meaning of the regulation (21 CFR § 54.2(e)). Data from investigators having only a small percentage of the total subject population (in a study with large numbers of investigators and multiple sites) could still affect the overall study results depending on the impact of their results on the overall study results. Or, if a sponsor submitted data from a large, multi-center, double-blind study that included several thousand subjects, a single clinical investigator at a large site could be responsible for a significant number of study subjects. In either case, if the investigator fabricated data or otherwise affected the integrity of the data, the results could have been influenced.

By contrast, large open safety studies and treatment protocols that have large numbers of investigators would generally not be considered covered clinical studies. As discussed in the preamble to the final rule,[16] in these large open safety studies and treatment protocols,

[16] See *Federal Register*, volume 63, February 2, 1998, page 5239.

the large number of investigators generally means that no single investigator has a major impact on the data. In addition, important adverse events will generally be apparent because they lead to cessation of therapy and submission of the case report form. Although it is possible that a financial interest could be important in these studies, it is relatively unlikely.

The regulations[17] allow a sponsor to seek a waiver of certain requirements, including financial disclosure requirements. FDA believes it is highly unlikely, however, that a waiver would be justified for studies begun after February 2, 1999, the effective date of the regulation, because the sponsor should already have begun collecting the information on an ongoing basis. FDA will evaluate any request for waiver on a case-by-case basis.

G.3. Q: The definition of a covered clinical study includes "any study in which a single investigator makes a significant contribution to the demonstration of safety." What does this mean?

A: Examples of commonly conducted studies in which a single investigator makes a significant contribution to the demonstration of safety would be studies that are designed to address a particular safety concern. For example, an endoscopy study to evaluate a product's effect on the stomach lining or a study in a subset of patients with a particular pre-existing condition or disease, such as significant cardiovascular risk factors or a history of poor (adverse) response to other treatments. Such studies could have a single investigator, or could involve more than one clinical investigator. If each investigator makes a significant contribution to the study and, therefore, to a demonstration of safety, such studies would be considered covered clinical studies and subject to financial disclosure.

Studies that generally would not be covered studies are large open safety studies (where a large number of clinical investigators enroll subjects) that are designed to look at adverse events in general and do not focus on specific safety concerns.

G.4. Q: Can a literature report be considered a covered clinical study?

A: Yes, a literature report could be considered a covered clinical study if it is being relied upon by the applicant or FDA to establish that the product is effective (including showing equivalence to an effective product) or where a single investigator makes a significant contribution to the demonstration of safety.[18] When an applicant relies on a literature report in this manner, clinical investigator financial disclosure is required. The author(s) and clinical investigators in the study should be contacted for this information to allow the applicant to submit the certification and/or disclosure forms or, if the applicant is unable to obtain the information, certification that the applicant acted with due diligence to obtain the information. Because the financial interests and arrangements

[17] See 21 CFR §§ 312.10, 812.10, 314.90 and 814.20.

[18] Applicants should be aware that additional information may be needed in order for the agency to be able to use published literature reports in support of a marketing application. For example, details about study methodology, the actual products studied, specifics about the patient population, patient accounting, etc. may be needed.

to be reported are those relating to the sponsor(s) of the covered clinical study and the product under study, the clinical investigators would not be required to report their financial interests in and arrangements with the applicant unless the applicant was a sponsor of the covered study.

G.5. Q: Does the regulation include abbreviated new drug applications (ANDAs)? Does the regulation include 510(k)s that include clinical data? What about biosimilars?

A: The regulation requires an applicant whose submission relies in part on clinical data to disclose certain financial interest and arrangements. A "covered clinical study" means any study of a drug (including a biological product) or device in humans submitted in a marketing application or reclassification petition that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product), or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase 1 tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, and expanded access protocols. (21 CFR §§ 54.2 and 54.3.) ANDAs are subject to 21 CFR part 54 (21 CFR § 314.94(a)(13)), as are 510(k)s (21 CFR § 807.87(i)). In addition, applications for biological products, including applications submitted under 351(k) of the Public Health Services Act, are also subject to the regulation.

G.6. Q: Does the regulation apply to studies in support of labeling changes?

A: The regulation applies to studies submitted in a supplement when those studies meet the definition of a covered clinical study. The definition includes studies to support safety labeling changes where individual investigators make a significant contribution to the safety information. Studies to support the effectiveness of a new claimed indication are also included. (21 CFR §§ 54.2 and 54.3.)

G.7. Q: Do actual use and labeling comprehension studies conducted to support a request to switch a drug product from prescription to over-the-counter (OTC) status fit the definition of covered clinical study?

A: Applicants who file supplements requesting that FDA approve a switch of a prescription drug to OTC status or who file a new drug application for OTC use often conduct actual use and labeling comprehension studies. These may be intended to demonstrate that the product is safe and effective when used without the supervision of a licensed practitioner; in other cases, they may test labeling comprehension or other aspects of treatment by consumers. Actual use studies performed to support these applications are considered covered clinical studies if they are used to demonstrate effectiveness in the OTC setting or if they represent a safety study where any investigator makes a significant contribution (21 CFR §§ 54.2 and 54.3). Labeling comprehension studies would not be considered covered studies.

G.8. Q: Are clinical investigators of in vitro diagnostics (IVDs) covered under this regulation?

A: Yes. Applicants who submit marketing applications for IVDs that include covered clinical studies must provide the appropriate financial certification or disclosure information (21 CFR § 54.3). Although IVD studies may only involve specimens, under 21 CFR § 812.3(p), "subject" is defined as a "human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control." Under 21 CFR § 812.3(h), an "investigation" is defined as a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device." Thus, if an investigation of an IVD is used to support a marketing application and it meets the definition of a covered clinical study, it would be subject to this regulation (21 CFR § 54.3).

H. FDA REVIEW

H.1. Q: Under what circumstances relating to financial disclosure would FDA refuse to file an application?

A: FDA may refuse to file any marketing application supported by covered clinical studies that does not contain, for each clinical investigator who is not an employee of the sponsor, a certification that no financial interest or arrangement specified in 54.4(a)(3) exists, a disclosure statement identifying the specified financial interests or arrangements and the steps taken to minimize bias, or a certification that the applicant has acted with due diligence to obtain the required information but was unable to do so and stating the reason (21 CFR § 54.4(c)). In general, if, during the filing review, an FDA reviewer identifies missing information, an attempt will be made to contact the applicant to obtain the missing information; however, applicants should take reasonable steps to ensure that applications are complete upon submission. Applicants are encouraged to discuss their concerns on particular matters about financial information with FDA.

H.2. Q: Who will review a disclosure of the specified financial interests and arrangements when such information is submitted in a marketing application?

A: FDA review staff, which may include project managers, consumer safety officers, medical officers, and/or others with regulatory or scientific expertise or supervisory authority, will evaluate financial disclosure information.

H.3. Q: What will FDA reviewers consider when evaluating the financial disclosure information?

A: FDA reviewers will evaluate the information disclosed about each covered clinical study in an application to determine the impact of any disclosed financial interests or arrangements on the reliability of the data. See 21 CFR § 54.5(a). FDA may consider many factors in making its evaluation (21 CFR §§ 54.5(a) and (b)).

Part 54 does not categorically prohibit financial interests or arrangements, but it does require applicants to submit a list of clinical investigators who are full-time and part-time employees of the sponsor and to disclose or certify with respect to other investigators so that FDA can assess the possibility of bias. The type of financial interest or arrangement disclosed is important because some financial interests and arrangements are of greater concern than others when assessing the reliability of the data. For example, outcome payments (that is, payment that is dependent on the outcome of the study) elicit the highest concerns, followed by proprietary interests in the test article (such as patents, royalties, etc.). With respect to equity interests and/or SPOOS, the amount and nature of the equity interests and payments may be considered.

When a clinical investigator has disclosable financial interests or arrangements, the FDA reviewer will carefully consider the steps taken by the sponsor to minimize bias[19] as described in the attachment to the FORM FDA 3455. These steps may include study design, use of multiple clinical investigators and study sites, and replication of study results. The agency also gives careful scrutiny to data from clinical investigators who are full-time or part-time employees of the sponsor, because of the possibility of significant financial interests in the outcome of studies. (Hereafter, we refer to these investigator types jointly as "disclosing investigators.") Investigators for whom the applicant is not able to disclose or certify, despite exercising due diligence, will be considered on a case by case basis.

The FDA reviewer may consider elements of the study design, including the method of randomization, the level of blinding (double-blind, single-blind), the presence or absence of a control group, whether placebo or active, the nature of the primary and secondary endpoints (objective, subjective), the method of endpoint assessment, the method of evaluation (including whether someone other than the disclosing investigator measured the endpoints), and whether many investigators, most of whom were not disclosing investigators, participated in the study. The FDA reviewer may also consider the total number of investigators and subjects in the study, the number and percentage of subjects enrolled by the disclosing investigator, information obtained from on-site inspections, and the data (including adverse events) of the disclosing investigator compared to other investigators in the study. The reviewer may look at a re-analysis of the data performed either by the applicant or FDA that excludes the disclosing investigator's results, other relevant types of reanalysis, and/or whether the results were replicated over multiple studies.

The reviewer will make a judgment as to whether the financial interests or arrangements disclosed may have affected the interpretation of study results or otherwise require further action. For example, if a disclosing investigator was a participant in a covered clinical study that (1) had randomized assignment of patients to treatment, (2) had a clearly objective endpoint (such as survival) or an endpoint assessed by a blinded observer other than the clinical investigator, (3) had multiple study sites (so that each investigator enrolled a small fraction of the total number of subjects), and (4) had results generally similar to the results of other investigators, then provided there were no other

[19] See Question A.2 for a discussion of methods to minimize bias.

material, countervailing considerations, the reviewer might determine that a financial interest, employment relationship, or lack of certification or disclosure does not raise serious questions about the integrity of the covered study that require further action. On the other hand, if the results of the disclosing investigator are clearly more favorable than results of the other investigators or centers and the disclosing investigator's results could have influenced outcome, the reviewer would generally need to consider further action. (21 CFR § 54.5(c).)

FDA reviewers should consult with their management as needed to determine appropriate actions.

H.4. Q: What actions may FDA take when a clinical investigator is the employee of a sponsor or has disclosable financial interests or arrangements?

A: If FDA determines that an investigator's financial interests raise a serious question about the integrity of the data, FDA will take any action it deems necessary to ensure the reliability of the data (21 CFR § 54.5(c)). Please see Section III.C of this guidance for actions that may be taken.

H.5. Q: How is the review to be documented?

A: Each FDA Center provides review templates or checklists for their review staff to use that include a section on financial disclosure issues.

In general, the review should document that a list of clinical investigators for each covered clinical study was provided, and that, as applicable, there was either certification or documentation of disclosable financial interests and arrangements for each investigator on the list who is not an employee of the sponsor[20] (21 CFR § 54.4).

When a disclosure of financial interests and arrangements is included (FORM FDA 3455), reviewers should ensure that the details of the disclosable financial interests and arrangements are attached to the forms along with a description of the steps the sponsor has taken to minimize the potential bias of clinical study results by any of the disclosed interests or arrangements (21 CFR § 54.4(a)(3)). The reviewer will address the question of whether these interests and arrangements raise questions about the integrity of the data and describe any actions taken to minimize bias. The reviewer will also describe any actions taken by the agency to address any questions raised by a disclosable financial interest or provide an explanation for why no action was indicated (21 CFR § 54.5). This documentation should be included in the appropriate section of the review template.

When a sponsor certifies that he/she acted with due diligence to obtain information regarding the clinical investigator's financial interests and arrangements but was unable to obtain it, reviewers should ensure that an explanation of the reason why the information could not be obtained and the efforts made to obtain the information is

[20] If the spouse or dependent child of an investigator is an employee of the sponsor, the investigator should be identified as an employee and further financial disclosure under this provision is not required.

attached to the FORM FDA 3454 (21 CFR § 54.4). See Question B.7 for a discussion of due diligence.

H.6. Q: Under what circumstances will FDA publicly discuss financial interests and arrangements disclosed to the agency?

A: As discussed in the preamble to the 1998 final rule,[21] FDA's policy is that certain types of financial information requested under the rule, notably clinical investigators' equity interests, will be protected from public disclosure unless circumstances relating to the public interest clearly outweigh the clinical investigator's identified privacy interest. FDA cited the example of a financial interest or arrangement so affecting the reliability of a study as to warrant its public disclosure during evaluation of the study by an advisory panel. FDA expects that only rarely would an investigator's privacy interest be outweighed by the public interest and thus warrant disclosure of the details of financial interest or arrangement. The agency will carefully evaluate each circumstance on a case-by-case basis.

FDA recognizes, however, that there is increased interest in the financial arrangements between clinical investigators and sponsors of the clinical trials in which the investigators participate. For this reason, FDA intends to provide information about the number of clinical investigators with disclosable financial interests or arrangements in the new product reviews FDA posts for an approval decision. This information would not identify clinical investigators by name but likely would include information such as the number of clinical investigators in the study and the number of investigators, if any, with disclosable financial interests or arrangements.[22]

I. RECORDKEEPING

I.1. Q: What are the recordkeeping requirements for financial disclosure information?

A: The recordkeeping requirements for applicants are described in 21 CFR § 54.6. Applicants must retain certain information on clinical investigators' financial interests and arrangements (21 CFR § 54.6(a)) and permit FDA employees to have access to the information and to copy the records at reasonable times (21 CFR § 54.6(b)(2)). Records are to be maintained for two years after the date of approval of the application (21 CFR § 54.6(b)(1)).

Additionally, IND and IDE sponsors are required to maintain complete and accurate records of financial disclosure information as part of the records for the investigation (21

[21] *Federal Register*, February 2, 1998, 63 *FR* 5233

[22] FDA also recognizes that subjects participating in a clinical trial may be interested in the financial interests/arrangements of the clinical investigator at the site where the subject is considering participation. The Department of Health and Human Services Guidance Document, "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection," which is applicable to FDA regulated research, recommends that consideration be given to providing potential subjects with information about the financial interests and arrangements of the parties involved in the research. This guidance is available at http://www.hhs.gov/ohrp/policy/fguid.pdf.

CFR §§ 312.57(b) and 812.140(b)(3)) and to retain the records pursuant to the required retention periods identified in the IND and IDE regulations (21 CFR §§ 312.57(c) and 812.140(d)).

I.2. Q: What kind of documentation is necessary for applicants to keep in case questions about certification and/or disclosure arise?

A: To the extent that applicants have relied on investigators as the source of information about potentially disclosable financial interests and arrangements, the underlying documentation (e.g., copies of executed questionnaires returned by investigators, correspondence on the subject of financial disclosure, mail receipts, etc.) should be retained. Likewise, to the extent that applicants who did not sponsor a covered clinical study rely on information furnished by the sponsor, the underlying documentation, including all relevant correspondence with and reports from the sponsor, should be retained. To the extent that applicants rely upon information available internally, all appropriate financial documentation regarding the financial interests or arrangements in question should be retained. For example, in the case of significant payments of other sorts, applicants should keep documentation including, but not limited to, records of electronic financial transactions, certified mail delivery receipts, etc. (21 CFR §§ 54.6(a), 312.57(b) and 812.140(b)(3).)

If storage space is a concern, sponsors and applicants may use electronic storage. For example, required records may be scanned as certified copies [23] of the original and stored electronically, as long as the records remain accessible for inspection and copying by FDA (see Question J.1). If electronic records are used, you should consult guidance on electronic storage of clinical trial records under part 11, "Computerized Systems Used in Clinical Investigations,"[24] for further information about maintaining scanned documents.

J. FDA INSPECTIONS

J.1. Q: Will financial disclosure information be reviewed during a bioresearch monitoring program (BIMO) inspection of the sponsor?

A: During a sponsor inspection, it is FDA's policy to review financial disclosure information that clinical investigators provide to the sponsor, although FDA may request access to these records at other reasonable times. FDA has the authority to access and copy documents supporting an applicant's certification or disclosure statement submitted to the agency in a marketing application (21 CFR § 54.6(b)(2)). FDA's regulations require sponsors to establish and maintain records of data obtained during investigational

[23] FDA's guidance on "Computerized Systems Used in Clinical Investigations" defines "certified copy" as a copy of original information that has been verified, as indicated by dated signature, as an exact copy having all the same attributes and information as the original.

[24] This guidance may be accessed at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf.

studies of drugs, biological products, and devices that will enable the agency to evaluate a product's safety and effectiveness.[25]

J.2. Q: Will financial disclosure be part of a BIMO inspection of a clinical site?

A: It is FDA's policy that FDA investigators should ask the clinical investigator if he/she submitted information to the sponsor prior to initiation of the study and updated that information, as needed, for up to one year after completion of the study at the site.

J.3. Q: Are there any instructions for FDA's inspectional staff with respect to reviewing records pertaining to financial disclosure?

A: FDA has provided instructions in the Compliance Program Guidance Manual (CPGM) chapters on clinical investigator inspections[26] and sponsor inspections.[27]

K. CONTACTS

K.1. Q: Who may be contacted in each FDA Center to answer questions regarding this regulation?

A: The following entities may be contacted: Division of Drug Information in the Center for Drug Evaluation and Research, phone 888-463-6332 or 301-796-3400, Division of Small Manufacturers, International and Consumer Assistance in the Center for Devices and Radiological Health, phone 800-638-2041 or 301-796-7100, and the Office of Communication, Outreach and Development in the Center for Biologics Evaluation and Research, phone 800-835-4709 or 301-827-1800.

[25] 21 CFR §§ 54.6, 312.57, 312.58, 812.140 and 812.145.
[26] http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm
[27] http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133777.htm

APPENDIX

Considerations for Collecting Financial Disclosure Information from Clinical Investigators

Suggested items to provide to clinical investigators to assist them in complying with financial disclosure reporting requirements:

1) Identify the sponsor(s) of the covered clinical study. **See Section IV.E.**

2) Identify whose financial interests and arrangements need to be reported (e.g., clinical investigators, their spouses and dependent children). **See Section IV.D.**

3) Identify the financial interests and arrangements that must be disclosed in detail. **See Section III.B and Question C.1.**

   NOTE: The threshold amounts apply separately for each sponsor (**see Question E.1**) but are cumulative for the investigator and his/her spouse and dependent children (**see Section III.B**).

   a) Employment by any sponsor. **See Section III and Questions B.1 and D.4.**

   b) Any compensation by any sponsor in which the value of compensation is affected by study outcome. **See Section III.B.1.**

   c) Any proprietary interest in the tested product. **See Section III.B.2.**

   d) Any equity interest in any sponsor of the covered clinical study whose value cannot be readily determined through reference to public prices. **See Section III.B.3.**

   e) Any equity interest in any sponsor of the covered clinical study if that sponsor is a publicly held company and the interest exceeds $50,000. **See Section III.B.4 and Questions C.2 and C.3.**

   f) Significant payments of other sorts (SPOOS) that have a cumulative monetary value of $25,000 or more made to the investigator or the investigator's institution. **See Section III.B.5 and Questions C.4, C.5 and C.6.**

4) Remind investigators of obligation to promptly update their financial disclosure information when relevant changes occur during the study and for one year following study completion. **See Questions C.2 and D.6.**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: March 31, 2019

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated
Name of clinical investigator

as a clinical investigator in the submitted study _____
Name of

_____ is submitted in accordance with 21 CFR part 54. The
clinical study

named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable check boxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
FIRM/ORGANIZATION	
SIGNATURE	Date *(mm/dd/yyyy)*

This section applies only to the requirements of the Paperwork Reduction Act of 1995.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 5 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Do NOT send your completed form to the PRA Staff email address below.

Department of Health and Human Services
Food and Drug Administration
Office of Operations
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

SAVE

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

1. Identifying information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

Definitions.

Entity: government agency, foundation, commercial sponsor, academic institution, etc.
Grant: A grant from an entity, generally [but not always] paid to your organization
Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting , lectures, speakers bureaus, expert testimony, employment, or other affiliations
Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
Issued: The patent has been issued by the agency
Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name)

2. Surname (Last Name)

3. Date

4. Are you the corresponding author? ☐ Yes ☐ No

5. Manuscript Title

6. Manuscript Identifying Number (if you know it)

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☐ No

ADD

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☐ Yes ☐ No

ADD

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☐ No

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☐ No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Generate Disclosure Statement

Evaluation and Feedback

Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.

RULE 1.13: ORGANIZATION AS CLIENT

(a) When a lawyer employed or retained by an organization is dealing with the organization's directors, officers, employees, members, shareholders or other constituents, and it appears that the organization's interests may differ from those of the constituents with whom the lawyer is dealing, the lawyer shall explain that the lawyer is the lawyer for the organization and not for any of the constituents.

(b) If a lawyer for an organization knows that an officer, employee or other person associated with the organization is engaged in action or intends to act or refuses to act in a matter related to the representation that (i) is a violation of a legal obligation to the organization or a violation of law that reasonably might be imputed to the organization, and (ii) is likely to result in substantial injury to the organization, then the lawyer shall proceed as is reasonably necessary in the best interest of the organization. In determining how to proceed, the lawyer shall give due consideration to the seriousness of the violation and its consequences, the scope and nature of the lawyer's representation, the responsibility in the organization and the apparent motivation of the person involved, the policies of the organization concerning such matters and any other relevant considerations. Any measures taken shall be designed to minimize disruption of the organization and the risk of revealing information relating to the representation to persons outside the organization. Such measures may include, among others:

(1) asking reconsideration of the matter;

(2) advising that a separate legal opinion on the matter be sought for presentation to an appropriate authority in the organization; and

(3) referring the matter to higher authority in the organization, including, if warranted by the seriousness of the matter, referral to the highest authority that can act in behalf of the organization as determined by applicable law.

(c) If, despite the lawyer's efforts in accordance with paragraph (b), the highest authority that can act on behalf of the organization insists upon action, or a refusal to act, that is clearly in violation of law and is likely to result in a substantial injury to the organization, the lawyer may reveal confidential information only if permitted by Rule 1.6, and may resign in accordance with Rule 1.16.

(d) A lawyer representing an organization may also represent any of its directors, officers, employees, members, shareholders or other constituents, subject to the provisions of Rule 1.7. If the organization's consent to the concurrent representation is required by Rule 1.7, the consent shall be given by an appropriate official of the organization other than the individual who is to be represented, or by the shareholders.

RULE 1.7: CONFLICT OF INTEREST: CURRENT CLIENTS

(a) Except as provided in paragraph (b), a lawyer shall not represent a client if a reasonable lawyer would conclude that either:

(1) the representation will involve the lawyer in representing differing interests; or

(2) there is a significant risk that the lawyer's professional judgment on behalf of a client will be adversely affected by the lawyer's own financial, business, property or other personal interests.

(b) Notwithstanding the existence of a concurrent conflict of interest under paragraph (a), a lawyer may represent a client if:

(1) the lawyer reasonably believes that the lawyer will be able to provide competent and diligent representation to each affected client;

(2) the representation is not prohibited by law;

(3) the representation does not involve the assertion of a claim by one client against another client represented by the lawyer in the same litigation or other proceeding before a tribunal; and

(4) each affected client gives informed consent, confirmed in writing.

RULE 1.6: CONFIDENTIALITY OF INFORMATION

(a) A lawyer shall not knowingly reveal confidential information, as defined in this Rule, or use such information to the disadvantage of a client or for the advantage of the lawyer or a third person, unless:

(1) the client gives informed consent, as defined in Rule 1.0(j);

(2) the disclosure is impliedly authorized to advance the best interests of the client and is either reasonable under the circumstances or customary in the professional community; or

(3) the disclosure is permitted by paragraph (b).

"Confidential information" consists of information gained during or relating to the representation of a client, whatever its source, that is (a) protected by the attorney-client privilege, (b) likely to be embarrassing or detrimental to the client if disclosed, or (c) information that the client has requested be kept confidential. "Confidential information" does not ordinarily include (i) a lawyer's legal knowledge or legal research or (ii) information that is generally known in the local community or in the trade, field or profession to which the information relates.

(b) A lawyer may reveal or use confidential information to the extent that the lawyer reasonably believes necessary:

(1) to prevent reasonably certain death or substantial bodily harm;

(2) to prevent the client from committing a crime;

(3) to withdraw a written or oral opinion or representation previously given by the lawyer and reasonably believed by the lawyer still to be relied upon by a third person, where the lawyer has discovered that the opinion or representation was based on materially inaccurate information or is being used to further a crime or fraud;

(4) to secure legal advice about compliance with these Rules or other law by the lawyer, another lawyer associated with the lawyer's firm or the law firm;

(5) (i) to defend the lawyer or the lawyer's employees and associates against an accusation of wrongful conduct; or (ii) to establish or collect a fee; or

(6) when permitted or required under these Rules or to comply with other law or court order.

(c) A lawyer make reasonable efforts to prevent the inadvertent or unauthorized disclosure or use of, or unauthorized access to, information protected by Rules 1.6, 1.9(c), or 1.18(b).

Conflicts of Interest Policies Under the Not-for-Profit Corporation Law

Charities Bureau
www.charitiesnys.com

Guidance Document
Issue date: September 2018

Conflicts of interest for board members are almost inevitable in not-for-profit corporations, and the existence of conflicts of interest should not disqualify board service. In fact, board members with significant community and business relationships are valuable because of the contacts and expertise they bring to the board, and more likely to have conflicts arising from those relations. An effective conflict of interest policy allows a not-for-profit entity to benefit from engaged and sophisticated board members, and to manage conflict of interest issues in ways that provide reassurance that the mission of the entity remains paramount.

This guidance has been drafted to assist not-for-profit corporations and trusts (hereafter collectively "nonprofits") that are drafting, reviewing, or revising their Conflict of Interest Policies and adopting and implementing those policies. It has been up-dated to reflect amendments to the Not-for-Profit Corporation Law ("N-PCL" that were enacted in November of 2016 and, with one exception, became effective on May 27, 2017[1]. The guidance is not intended to serve as a substitute for advice from a nonprofit's attorney, nor should it be construed to have anticipated or addressed every issue that a nonprofit should consider or address when drafting or implementing its policy.

[11] An amendment to Not-for-Profit Corporation Law § 713(f) that permits an employee to be the board chair under certain circumstances became effective on January 1, 2017.

The N-PCL follows both common law and best practices literature in requiring directors to make disclosures about potential conflicts of interest at the beginning of their service, and on an annual basis thereafter. It also requires directors, officers and key persons (called "key employees" prior to the 2016 amendments)[2] to disclose potential conflicts of interest in issues that come before the board and to refrain from participating in board deliberations and decisions on those issues. The N-PCL requires that a nonprofit's procedures for disclosing and resolving conflicts of interest be set forth in a Conflict of Interest Policy adopted by the board. The Conflict of Interest Policy adopted by the Board must reflect the minimum standards set forth in N-PCL Section 715-a.

Where a director, officer, or key person has a conflict of interest, as defined by a nonprofit's Conflict of Interest Policy, in an issue coming before the board, that individual must disclose the circumstances giving rise to the conflict, and the nonprofit has an obligation to make a record of the existence of the conflict and how it was addressed, both with respect to that individual and with respect to the transaction.

Director, officer, key person, related party and relative are all terms that are defined in the N-PCL. *See* N-PCL §§ 102(a)(6), 102(a)(22), 102(a)(23), 102(a)(25), 713(f). A 2016 amendment to the N-PCL replaced the term "Key employee" with the term "key person" and defined a key person as someone who is **not** an officer or director and who, whether or not employed by the corporation, has responsibilities or powers similar to those of officers and directors, manages the corporation of a substantial part of its activities, assets or finances, or has a role in controlling a substantial part of its capital expenditures or budget.

A key person might be

A founder who, although he or she has no title or official role, exercises apparent authority over the organization, or

A substantial donor who, although he or she has no official role or title in the organization, participated in setting the agenda and making employment decisions.

[2] The amendments changed the term "key employee" to key person and amended the definition of that term. An explanation of the change is included later in this guidance.

Conflict of Interest Policy: Minimum Statutory Requirements

The board of each nonprofit must adopt, implement and oversee compliance with a Conflict of Interest Policy "to ensure that its directors, officers, and key persons act in the [nonprofit's] best interest and comply with applicable legal requirements." The policy must cover conflicts and possible conflicts of interest, including related party transactions, which are defined by the N-PCL as transactions, agreements or arrangements in which a related party has a financial interest and in which the nonprofit or an affiliate is a participant. The policy may also cover other types of conflicts that may exist even though there is no financial interest at stake or the circumstances are otherwise outside the definition of a related party transaction.

The Conflict of Interest Policy must include:

1. A definition of the circumstances that constitute a conflict of interest (N-PCL § 715-a(b)(1)).

The statute gives the Board of Directors discretion to define the circumstances that constitute a conflict of interest, including the discretion to define exceptions for de minimis transactions and ordinary course of business transactions not covered by the policy. The board also has discretion to define the procedures that should be followed for different types of conflicts. This discretion includes the power to define additional restrictions on transactions between a board member and the corporation, or between the nonprofit's employees and third parties (for example, by articulating a no acceptance of gifts policy, a no nepotism policy, or by incorporating Food and Drug Administration or Public Health Service conflict standards into a university's conflict policy).

In addition, there may be circumstances specific to the organization that involve dual interests but do not present a significant risk of conflicting loyalties. For example, religious corporations in their charter or by-laws frequently will include directors who are members of religious orders, employees of sponsoring or related churches, or bishops who, by canon law, hold title to all property of related religious corporations and may be called upon to approve the disposition of that property. City-related nonprofits may define "circumstances that constitute a

conflict of interest" to exclude the responsibility of an ex-officio director to the electorate or the city appointing official, particularly where such *ex-officio* role is specifically set forth in the nonprofit's enabling legislation, charter or certificate of incorporation, since the role and definition of the *ex-officio* includes the responsibility of advocating a broader public interest in board discussions, and that role is clear to all non-city directors.

2. Procedures for disclosing a conflict of interest to the board or a committee or the board (N-PCL § 715-a(b)(2)).

These procedures may include expectations for each class of conflict reporters, forms, record-keeping, custodians; disclosure to other persons within the nonprofit or to third parties, timing, and committee review and action.

3. Requirement that the person with the conflict of interest not be present at or participate in board or committee deliberations or vote on the matter giving rise to such conflict. (N-PCL § 715-a(b)(3)).

The language of the statute refers only to board or committee deliberations and votes. It is recommended that the board adopt a more comprehensive policy that articulates standards of conduct for board members, officers and key persons regarding conflicts of interest, disclosure requirements, reporting requirements, and procedures for mitigation.

In the board or committee setting, however, the board may request that the person with the conflict of interest present information as background or answer questions at a committee or boards meeting prior to the commencement of deliberations or voting.

4. Prohibition of any attempt by the person with the conflict to influence improperly the deliberations or voting on the matter giving rise to such conflict. (N-PCL § 715-a(b)(4)).

"Improperly influence" in this context should have a meaning similar to that used by the Securities and Exchange Commission in addressing improperly influencing audits: "coercing, manipulating, misleading, or fraudulently influencing (collectively referred to herein as "improperly influencing") the "decision-making " when the officer, director or other person knew or should have known that the

action, if successful, could result " in the outcome which the officer or director could not deliberate or vote on directly. ("Improper Influence on Conduct of Audits," http://www.sec.gov/rules/final/34-47890.htm).

5. Requirement that existence and resolution of a conflict be properly documented, including in the minutes of any meeting at which the conflict was discussed or voted upon. (N-PCL § 715-a(b)(5)).

6. Procedures for disclosing, addressing, and documenting related party transactions pursuant to N-PCL § 715. Related party transactions include any transaction, agreement, or other arrangement in which a related party has a direct or indirect financial interest and in which the nonprofit or an affiliate participates. (N-PCL § 715-a(b)(6)).

A person has an indirect financial interest in an entity if a relative, as defined by the N-PCL, has an ownership interest in that entity or if the person has ownership in an entity that has ownership in a partnership or professional corporation. This is consistent with the definition of "indirect ownership interest" that is found in the instructions to Form 990, Schedule L.

A director, officer, or key person must disclose his or her interest in a transaction, agreement or arrangement *before* the board enters into that related party transaction.

Pursuant to N-PCL § 102(a)(24), the record-keeping requirements of N-PCL § 715 do not apply to the following three types of transactions: a) transactions in which the related party's financial interest is de minimis, b) transactions that are not customarily reviewed by the board or boards of similar organizations in the ordinary course of business and are available to others on similar terms, and c) provision of benefits provided to a related party solely as a member of a class that the corporation intends to benefit as part of the accomplishment of its mission.

While these transactions may not require the statutory process mandated by section 715 of the N-PCL, both the related party and the decision-maker have other obligations defined by governing law. The Board member or other related party in each of these cases may not intervene or seek to influence the decision-maker or reviewer in these transactions. The decision-maker, and those responsible for

reviewing or influencing these transactions, should not consider or be affected by a related party's involvement in decisions on matters that may affect the decision-maker or those who review or influence the decision.

- What constitutes a "de minimis" transaction will depend on the size of the corporation's budget and assets and the size of the transaction. A transaction that merits review by the Board of a smaller corporation might not merit review by the Board of a larger organization.

- A transaction or activity is in the ordinary course of business if it is consistent either with the corporation's past practices in similar transactions, or with common practices in the sector in which the corporation operates.

Examples of ordinary course of business transactions:

A. The library of a nonprofit university buys a book written by a member of the board, pursuant to a written library acquisitions policy.
B. A nonprofit hospital uses the local electric utility for its electrical service and supply, and a 35% shareholder of the local electric utility is a member of the board.
C. General counsel of a health system has a written, established, and enforced policy for the selection, retention, evaluation, and payment of outside counsel. A board member is a partner of and has a greater than 5% share in one of the firms retained by general counsel.
D. The curatorial department of a museum has a paid summer intern selection process involving resume review and evaluation and group interviews. The daughter of a board member is selected pursuant to the process as a summer intern.
E. The grandson of a board member of a hospital has just graduated from a university nursing school. He applies for and is selected by the Nursing Department of the hospital for a tuition repayment benefit and will receive a salary and overtime, consistent with the hospital's written policy regarding recruitment of new nursing graduates.
F. A board member is the sole owner of a fuel delivery company. In the ordinary course of business, the facilities department of a nonprofit housing

project puts out a written request for proposals for fuel supply for its properties, evaluates, and documents the selection of the board member's company based upon cost and service.

G. A university board member owns a 35% share of a restaurant conveniently located near the campus of the university. Some faculty members responsible for arranging staff holiday lunches buy food from this restaurant, using university credit cards. Each department has a modest authorized budget for these lunches, and faculty members have discretion about where to buy food for the lunches.

To qualify for the exception for benefits provided to a related party solely as a member of a class that the corporation intends to benefit as part of the accomplishment of its mission, the benefits must be provided in good faith and without unjustified favoritism towards the related party.

Example of a transaction in this category: A legal services program agrees to handle the eviction case of one of its board members who is eligible to be a client, and who is serving as one of the minimum number of client-eligible board members that is required by federal regulations. The decision to accept the case is made pursuant to the organization's established case acceptance policy, without regard to the client's status as a board member.

Transactions related to compensation of employees, officers or directors or reimbursement of reasonable expenses incurred by a related party on behalf of the corporation are not considered related party transactions, unless that individual is otherwise a related party based on some other status, such as being a relative of another related party . However, such transactions must be reasonable and commensurate with services performed, and the person who may benefit may not participate in any board or committee deliberation or vote concerning the compensation (although he or she may be present before deliberations at the request of the board in order to provide information).

7. The Policy must require that each officer, director and key employee submit to the Secretary prior to initial election to the board, and annually thereafter, a written statement identifying possible conflicts of interest. That statement should include, to the best of the individual's knowledge, any entity of

which the director is an officer, director, trustee, member, owner, or employee and with which the corporation has a relationship, and any transaction in which the corporation is a participant and in which the director has or might have a conflicting interest.

Disclosure of conflicts is required; the requirement of disclosure to the Secretary can be satisfied by disclosure to the Secretary's designee as custodian (e.g., the compliance officer), if set forth in the conflict of interest policy.

When initial election to the board is not reasonably foreseeable, for example when board candidates are nominated from the floor at an annual meeting of members held to elect directors, the written statement may be provided to the Secretary promptly after the initial election.

A conflict of interest disclosure statement is required from directors, officers, and key persons of nonprofits. All types of nonprofits are covered, including religious corporations.

The Secretary must provide a copy of the completed statements to the chair of the audit committee or the chair of the board. There is no statutory requirement that conflict of interest disclosure statements be shared with other members of the board, or members of the corporation, or with the public. Conflict of interest disclosures often contain sensitive personal financial information that could be harmful if disclosed.

The Secretary may direct his/her designee/custodian to provide a copy of the completed statements to the chair of the audit committee or the chair of the board. The Secretary should maintain a record of conflict of interest disclosures.

The N-PCL does not prescribe the method or content of assertions that a board member, officer, or key person's participation in deliberations or voting is barred by a conflict as defined by the policy. The N-PCL does require that the "existence and resolution of the conflict be documented in the corporation's records, including the minutes of any meeting in which the conflict was discussed or voted upon." The records or minutes do not need to reflect the specifics of a conflict of interest not "discussed or voted upon" so long as the records reflect that an

individual board member, officer, or key person did not participate in discussions or voting on the topic.

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Restoring Balance to Industry-Academia Relationships in an Era of Institutional Financial Conflicts of Interest

Promoting Research While Maintaining Trust

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Economic partnerships between industry and academia accelerate medical innovation and enhance patient access to medical advances, but such partnerships have sometimes eroded public trust in the research enterprise. There is particular risk for conflict of interest when economic partnerships extend beyond a university's corporate interests to involve institutional decision makers. Institutions and institutional decision makers should fully disclose industry-related financial interests and relationships. Without legitimate justification for such interests, individuals should divest themselves from these interests or recuse themselves from responsibility for research oversight. Management of institutional partnerships also might entail the physical separation of certain facilities, the placement of restrictions on information shared between investment and research staffs, and provision of oversight by independent review panels made up of persons who have expertise in intellectual property, finance, and research, but who are not financially or otherwise dependent on the institution. Through these means, it is possible to restore balance to industry-academia relationships, thereby promoting progress while maintaining public trust in research.

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IN MEDICINE, ACADEMIA IS NO longer as autonomous as it once was. Impelled by, among other things, the Bayh-Dole Act,[1] US academic centers have partnered with industry so that academic innovation can be rapidly and efficiently brought to market. Academic discoveries are often patented by universities and then licensed to industrial sponsors for commercialization. This translates into greater patient access to therapeutic advances, and ultimately serves the public good. Yet the nature and scope of this economic partnership have outpaced what was originally intended and have developed into a highly interwoven relationship extending to all levels of academia and the research enterprise. In addition to engaging in licensing agreements with private industry, academic institutions may own stock or options in the sponsors of research being conducted at the institution; incorporate start-up companies to develop faculty inventions in which they and their faculty members are major shareholders; accept cash compensation for granting preferred industry partners with first refusal rights on the discoveries of investigators or departments; and in some cases even develop their own brand-name products to be sold on the market.[2,3] Most universities have established technology-licensing offices to manage growing research-related business operations.

Academia's relationship with industry extends beyond the university's corporate interests. Researchers, institutional review board (IRB) members, and institutional decision makers (eg, trustees, presidents, chancellors, provosts, deans, department chairpersons) also have developed extensive financial ties with industry. These individuals may own stock or options in drug or device manufacturers or other industry sponsors of research; be beneficiaries of actual or expected royalty payments from the sale of industry products tested or developed at the institution; receive private research support through grants or contracts; be consultants to or directors of private research corporations; receive fees for serving as expert witnesses on behalf of industry in legal proceedings or for supporting industry lobbying or marketing activities; receive honoraria for speaking on behalf of industry at scientific conferences; or receive research-related gifts, such as dis-

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cretionary funds, biomaterials, or research equipment.[4-8]

While entrepreneurship in academia has accelerated scientific innovation, on occasion it has also marred academia's reputation as independent truth-seeker, reduced public trust in the research enterprise, and resulted in a burgeoning literature on conflicts of interest.[9-15] This literature is focused on the problems of investigator conflicts of interest and faculty conflicts of commitment, with little scholarship having been dedicated to institutional conflicts of interest.[16-18] Several empirical studies and anecdotal reports demonstrate that financial conflicts of interest can affect the professional judgment of physicians and researchers,[19-24] and there is growing concern within the research and regulatory communities that institutional financial conflicts of interest similarly may affect professional judgment. This concern has partly arisen from recent well-publicized research-related injuries or deaths in which the institutions hosting research, or noninvestigator officials within such institutions, reportedly had significant financial interests in the research.[18,25-27]

Some who have studied the conflict-of-interest issues raised by the ever-deepening academia-industry partnership have lost hope for the possibility of a middle ground in which financial incentives spur innovation without corrupting or appearing to corrupt academic and ethical values,[28] including protection of human participant safety and welfare, academic freedom, objectivity, data integrity, the right to publish, and scientific collaboration.[29,30] Doubtful of the prospect of a balanced alternative, physicians have been prompted to adopt positions at either end of the regulatory spectrum, some stressing the overreaching value of entrepreneurship in medical research while advocating a laissez-faire approach to financial conflicts of interest in research, and others highlighting the dangers to research and institutional integrity while emphasizing the need to reduce significantly or to eliminate industry-academia relationships.[31-33]

We suggest that, even in an era of institutional conflicts of interest, it is still possible to promote (and even accelerate) the progress of research while maintaining (and even enhancing) public trust in the research enterprise by restoring balance in, but not eliminating, industry-academia relationships. To that end, we (1) discuss the nature and operation of institutional financial conflicts of interest; (2) propose a test for determining when financial interests should be eliminated and when they should be tolerated with oversight; and (3) set forth practical strategies for dealing with institutional financial conflicts of interest.

Nature and Operation of Institutional Financial Conflicts of Interest

Unlike investigator financial conflicts of interest that are addressed by the Public Health Service, the National Science Foundation, and the US Food and Drug Administration,[34] no laws or regulations directly govern the financial conflicts of interest of institutions or institutional decision makers. A few regulatory agencies and professional associations have offered guidance on institutional conflicts of interest. Among the first were the Draft Interim Guidance issued by the federal Office of Human Research Protections in late 2000,[35] and commentary on that draft by the National Human Research Protections Advisory Committee in August 2001.[36] Additional guidance has been issued by the Association of American Universities,[37] the Pharmaceutical Research and Manufacturers of America,[38] and most recently by the Association of American Medical Colleges (AAMC).[39]

Institutional financial conflicts of interest may be understood as circumstances in which professional judgment regarding a primary interest (eg, patient welfare or research integrity) may be compromised by the actual or expected pecuniary corporate interests of the institution or its departments, the actual or expected individual economic interests of noninvestigator institutional decision makers, or the actual or expected individual economic interests of IRB members or the members of other institutional bodies responsible for research oversight. The research-related financial interests of institutional decision makers, IRB members, and members of other research oversight bodies are properly characterized as leading to institutional conflicts of interest when they threaten to compromise a primary interest because they arise from the individuals' authority and influence over research at the institution. Thus, institutional conflicts of interest can arise either from corporate or from individual financial holdings or relationships in research, and should be distinguished from investigator conflicts of interest.

Developing strategies for managing institutional conflicts of interest requires understanding the mechanisms through which such conflicts may operate and be expressed. Institutional conflicts typically involve institutional decision makers or IRB members. The institutional conflicts may inappropriately influence decisions of institutional decision makers or IRB members, or the conflicts may be transferred onto and then expressed through others at the institution, such as staff or investigators. Yet even when an institutional conflict is transferred onto and expressed through, for example, an investigator, the conflict remains institutional in nature since the financial interests that produced the conflict belong not to the investigator, but rather to the institution, an institutional decision maker, or IRB member. Therefore, conflict-of-interest policies should require investigators to disclose not only their personal financial interests in research, but also any information they may have regarding the financial interests of the institution, of an institutional decision maker, or of an IRB member in that same research. A conflict-of-interest oversight system thus may assess the need to manage any institutional interests that might inappropriately influence the investigator. Institutional conflicts may operate be-

fore, during, or after the review and performance of research.

First, institutional conflicts may result in inappropriate decision-making by institutional decision makers or IRB members. For example, an IRB member engaged in initial or continuing review of a research study may be improperly influenced by the fact that the IRB member, the institutional department with which he or she is affiliated, or the institution as a whole stands to profit significantly from US Food and Drug Administration marketing approval of the product under investigation. This may lead the IRB member to be more lenient or forgiving during initial review (eg, inadequate disclosure of study risks, insufficient description of eligibility and exclusion criteria, exaggeration of potential study benefits) or continuing review (eg, enrollment of subjects not meeting eligibility criteria, failure to exclude subjects meeting exclusion criteria, failure to report adverse events). The conflicted IRB member could even hesitate to suspend or terminate a study, based on awareness of institutional interests implicated.

Second, institutional conflicts may be transferred onto, and result in inappropriate decision-making by, others at the institution. For instance, an institutional decision maker may pressure support staff, IRB members, or investigators to achieve a research end point that is favorable to the pecuniary corporate interests of the institution or the personal economic interests of the institutional decision maker. This pressure may vary in the level of its directness and vigor. For example, while investigators who are informed of their department's significant economic interests in the outcome of their study may not be unduly influenced by this information alone, the conflict of interest that is created through such knowledge might be exacerbated to the point of affecting professional judgment if these investigators are also notified of their department's financial shortfalls or are notified of important upgrades that could be implemented within the department should additional funds become available. Moreover, depending on the manner and content of the information conveyed, investigators might assume that they are being implicitly or explicitly directed to exercise their discretion so as to favor the department's pecuniary interests. The risk, then, is that institutional support staff, IRB members, and/or researchers may act on the bias-generating information that is transmitted to them, directly or indirectly, by institutional decision makers.

Third, while institutional financial conflicts of interest that operate during the review or performance of research most commonly would be expressed through IRB members and investigators, those conflicts operating before or after the research process may be directly expressed through institutional decision makers and their support staff. Institutional decision makers may decide in advance, for example, preferentially to allocate institutional resources, including funds, equipment, or laboratory space toward industry-sponsored or clinically patentable work. After research has concluded, institutional pressure may, for example, delay publication or restrict oral communications of research results beyond what is reasonably necessary for the institution's office for technology licensing to secure patent rights to academic discoveries. However, the most worrisome institutional financial conflicts of interest are those that operate on IRB members, research administrators, and investigators during the review or conduct of research because these may directly jeopardize the health and safety of human research subjects or lead to inappropriate data manipulation.

The Justification Test

One means of restoring balance to industry-academia relationships that would reduce both the appearance of bias and the potential for actual bias, but would not eliminate the financial incentives that genuinely promote innovation in research, would be to require individual and corporate possessors of significant industry-related financial interests and relationships to have a legitimate justification for such interests and relationships. That is, possessing such interests and relationships would be a privilege and responsibility, rather than a right. Absent a legitimate justification, divestiture of significant industry-related financial interests and relationships or recusal from research oversight responsibilities would be expected.

The treatment of investigator conflicts of interest is the historical precedent for managing institutional conflicts. Most policies, including those suggested by the AAMC and the National Human Research Protections Advisory Committee (NHRPAC), would allow some exceptions to the general presumption that an investigator should hold no significant financial interests in research he or she is conducting. According to the AAMC and the NHRPAC, investigators should be allowed to maintain such interests in cases in which the researcher is the inventor of the device or drug under study and may be the best positioned to conduct research safely and competently. Such exceptions would also serve the social purpose of encouraging investigator-entrepreneurs to continue their interest and involvement in their own inventions, thus providing incentives for new inventions and ideas. In these contexts, the social purposes of encouraging entrepreneurship are greatest, even though dangers to data integrity also may be highest. Therefore, when inventors are allowed to conduct human participants research on their own ideas or inventions, independent oversight and tough management of the personal conflicts are indicated.

When institutional conflicts of interest arise from IRB members' or institutional officials' personal research-related holdings, the social purpose of tolerating conflicts to encourage entrepreneurship vanishes, and only a palpable risk to principled research oversight is left. There are no legitimate justifications for allowing IRB members to have significant financial interests related to studies they review.

Moreover, because these members have primary responsibility for protecting the safety and welfare of human research participants in trials at the institution, there are compelling reasons for requiring divestiture. The importance of distinguishing between persons responsible for overseeing biomedical research and those carrying out such research is gaining acceptance in both the legal and the biomedical communities. In general, a zero-tolerance policy regarding financial conflicts of interest typically is applied to the former category of persons. For example, the law has already instituted a zero-tolerance policy with respect to IRB members who may not hold any financial interests in the research they review.[40,41] Moreover, according to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals,[42] editors who make decisions about manuscripts must have no personal, professional, or financial involvement in any of the issues they might judge. Peer reviewers either should disqualify themselves from reviewing specific manuscripts or disclose any conflicts of interest that could bias their opinions of a manuscript.

This policy of zero tolerance regarding financial conflicts of interest should also be applied to institutional decision makers. At minimum, institutional decision makers should not be permitted to have any significant financial interests implicated in research being conducted at the institution. As with IRB members, there seem to be no legitimate justifications. Institutional decision makers are not usually the progenitors of academic discoveries, and technology transfer is not furthered when institutional decision makers have significant research-related financial interests. In those rare instances in which an individual is both inventor and institutional decision maker at the institution where the invention is being tested or developed—a recent example being the clinical drug trials of cetuximab at the M. D. Anderson Cancer Center at the University of Texas, where the conceiver of the drug serves as president[43]—the individual should be entitled to maintain his or her financial interests in the invention. However, removal of the study to an impartial institution should be considered. When decision makers are not also inventors, divestiture by institutional officials of personal significant industry-related financial interests vindicates their duty to uphold institutional integrity by ensuring compliance with laws, codes of ethics, and institutional policies.

The elimination of institutional financial conflicts of interest arising from the individual economic interests of institutional decision makers, IRB members, and any other persons at the institution who oversee clinical trials or safeguard the safety and welfare of human research participants will promote regulatory consistency and administrative simplification, enhance public confidence in the research enterprise by reducing the appearance of bias, and promote institutional integrity by reducing the likelihood that actual institutional bias affects research. Moreover, although such persons would be prohibited from maintaining any relevant research-related financial interests, they would remain free to invest in matters unrelated to research.[44]

Legitimate justifications exist for permitting institutions to derive income through licensing agreements with industry or to own equity in start-up companies aimed at developing faculty discoveries. Both types of interests serve the intent and purposes of the Bayh-Dole Act by promoting the commercialization of academic inventions. Moreover, the licensing and equity proceeds that are eventually received by the institution may be used to fund additional research at the institution.[45] Technology transfer is promoted through licensing because commercial entities have the resources to bring laboratory discoveries to market. Prior to the Bayh-Dole Act, the federal government retained ownership of technologies derived through federal research funding, which resulted in significant delays or total impasses in getting these technologies to market because "few companies were willing to take licenses on government-held patents."[45-47] By 1978 (the year Bayh-Dole was introduced), only 4% of the 28000 patents owned by the government had been licensed to the private sector for commercialization.[48] Congress enacted the Bayh-Dole Act to increase the speed with which innovations are brought to market, thus enhancing public access to these innovations and increasing the United States' world market competitiveness.[49] Commercialization of research and development has significantly accelerated after the Bayh-Dole Act. For example, between 1991 and 1995, licensing activity increased by 68%.[50] Between 1991 and 1999, licensing increased by 129%.[51]

In exchange for equity interests, academic institutions provide start-up companies with shareholder capital that then is used to finance the testing and development of one or more faculty discoveries. The nation's biotechnology industry and its continued world dominance have in fact been credited to the Bayh-Dole Act.[3] While few small or newly formed start-up companies (which are the bedrock of the biotechnology industry) had the resources to surmount the bureaucratic red tape associated with obtaining a license from the federal government, 66% of licenses issued by universities in the year 2000 were to small or newly formed corporations.[52] Nevertheless, the financial conflicts of interest created as a result of the pecuniary corporate interests of the institution should be subject to the oversight and management jurisdiction of a specially constituted conflict-of-interest committee.

Strategies for Dealing With Institutional Financial Conflicts of Interest

Because institutional conflicts of interest may arise from the research-related financial holdings of IRB members, institutional decision makers, or the hosting institution, a comprehensive policy on institutional conflicts of interest will address each of these sources of conflicts. There are no justifications for, and there are compel-

ling reasons against, allowing IRB members and institutional decision makers to maintain their research-related financial interests. Consequently, policies on institutional conflicts of interest should require IRB members to divest themselves completely of any financial interests they may have in any research they review or to recuse themselves from reviewing research in which they maintain an interest, and should require institutional decision makers to completely divest themselves, or to divest themselves beyond a threshold of significance, of any financial interests they may have in any research taking place at the institution. This could be effected by requiring IRB members and institutional decision makers to disclose annually their research-related financial interests to the institution's conflict-of-interest committee, and to update that committee when those interests materially change. This compliance strategy would build on that already existing for investigator conflicts. The conflict-of-interest committee could be charged with the responsibility for ensuring compliance with the policy on institutional conflicts of interest by IRB members and institutional decision makers. That committee then could be given the necessary powers to audit for the purpose of verifying the accuracy of financial disclosures and the power to impose sanctions for noncompliance. This single step would eliminate 2 of the 3 sources of institutional conflicts of interest.

Given the legitimate justifications for allowing institutions to maintain their significant financial interests in research, these interests should be managed rather than eliminated. The primary methods for controlling institutional conflicts of interest should include adequately separating research operations from institutional investment activities, and instituting oversight by an independent review panel (IRP).[17]

The separation method, which encompasses both physical separation and certain information-sharing restrictions regarding the institution's corporate holdings and relationships, can be used to control institutional conflicts of interest arising from the institution's research-related pecuniary corporate interests. Physical separation entails housing the institution's office for technology transfer in quarters that are set apart from faculties and departments whose members conduct research. Thus, the office might be attached to the provost's office or to other senior-level offices in the university, rather than to the faculties of medicine or science under the control and supervision of the deans of medicine or science.

Adequate separation also requires certain limitations on communication between those responsible for the institution's financial investment activities and those engaged in the performance or oversight of research at the institution. In general, information regarding the pecuniary assets and relationships of the institution should be considered the confidential information of the office for technology licensing, and should only be disseminated on a need-to-know basis in accordance with the formal policy of that office. The policy should describe the persons or categories of persons to whom disclosures may be made, the types of information that may be disclosed, and the purposes for which disclosures may be made. Additionally, technology licensing offices should ensure that bias-generating information, such as descriptions of research projects or start-up companies from which the institution stands to profit significantly, are not distributed within the university and among research faculty. Although this would not prevent all information regarding institutional financial interests from leaking to faculty, it at least would signify appropriate modesty and restraint about possible conflicts of interest arising from institutional interests.

Institutions increasingly satisfy their legal obligation of regulating investigator financial conflicts of interest through conflict-of-interest committees. This same method seems equally fitting to the oversight and management of conflicts originating from the financial interests of the institution. A significant difference, however, is that in the former case the institutional body oversees investigators (who are typically employees of the institution), whereas in the latter case the institutional body oversees the institution itself. This is not unlike the judiciary's role in supervising the actions of government. Judicial independence is fundamental to its ability to serve as watchdog, and the characteristics that secure such independence (eg, security of tenure for IRP members, removal for good cause only, documentation of removal and cause of removal for audit purposes, and immunity from retaliation) should be drawn on when structuring the IRP that will oversee conflicts emanating from the institution's financial interests in research.[17]

The IRP should have expertise in financial investments, the handling of intellectual property, bioethics, and the process of research involving human participants.[17] It also should be empowered to review and monitor research in which the institution has one or more significant financial interests, and to recommend strategies for managing institutional financial conflicts of interest to the institution's board or to its IRB.[17] The IRP could be a committee of the institution's board of directors, in recognition of the board's fiduciary duty to ensure integrity in all institutional operations, or could report to a board committee (eg, audit committee) while being composed of persons from the community who are independent from the board, but who have some moral affinity to the institution itself. The ideal member of such an IRP would be a community leader, not on the board of trustees, and not dependent, financially or otherwise, on the institution, but would have some financial and research expertise as well as sufficient loyalty to the institution to lead him or her to volunteer for this unique oversight role.

Conclusion

Our recommendations are designed to address institutional conflicts of interest in a real and meaningful way, without damaging the incentive structures

that have fostered so many scientific advances. Financial and nonfinancial incentives spur innovation. Industry-academia relationships are permitted only when there is a legitimate justification for them. In particular, no legitimate justification exists when a relationship with industry serves only the pecuniary interests of the holder, without directly and materially furthering scientific advancement. In these circumstances, elimination of the financial relationship seems appropriate. When industry-academia relationships promise to advance science, management of any potential conflicts of interest via independent and expert committees is necessary.

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Conflict of interest in human subjects research

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Conflict of interest (COI) has emerged as a dominant factor in the collapse of many American businesses. In health care, similarly, individual medical practitioners and large academic institutions are under increasing scrutiny for fear that financial COI have the potential to undermine the integrity of medical care and biomedical research in the United States. Nonfinancial conflicts might also be perceived as having an impact on the recruitment of research subjects or the reliability of data (1). Although nonfinancial, institutional policy, practices, and constraints imposed by the scientific method should be able to manage most COIs (2), universally accepted policy and standards to achieve such management do not exist (3–9). We present a brief overview of some of the issues that have brought COI front and center in our national healthcare debate, along with a review of the direction society is moving in resolving these issues.

In 1999, an 18-yr-old study subject, Jesse Gelsinger, died as a result of his participation in a phase I gene therapy study at the University of Pennsylvania. Covered extensively by the press (10), there were weaknesses in the oversight and development of the clinical investigation and a financial COI on the part of one of the investigators and the University of Pennsylvania. Succinctly stated by Jesse's father, "[w]hen lives are at stake, and my son's life was at stake, money and fame should take a back seat. The concern should not be on getting to the finish line first, but on making sure no unnecessary risks are taken, no lives filled with potential and promise are lost forever, no more fathers lose there sons (11)." In response to this incident, the American Society of Gene Therapy adopted a policy that:

> all investigators and team members directly responsible for patient selection, the informed consent process and/or clinical management in a trial must not have equity, stock options or comparable arrangements in companies sponsoring the trial. The American Society of Gene Therapy requests its members to abstain from or to discontinue any arrangement that is not consonant with this policy (12).

Further concern that the trust of the public is being jeopardized by the financial interests of investigators and institutions was heightened when it became known that there were additional problems with the review and monitoring of research at other leading medical centers (13). In a series of articles highlighting conflicts of interests by physicians and the pharmaceutical industry, patients were described as "commodities, bought and traded by testing companies and doctors" (14, 15). Concern over COI was also raised when patients entered into research trials were not told of an institution's stake in drug development (16) or of an investigator's interest in the use of "found material" for the development of diagnostic tests or potentially lucrative therapeutic advances (17, 18).

Little data exist describing the prevalence of COI, both financial and nonfinancial, among clinicians, institutions, or industry. Physicians and institutions stand to benefit greatly from the development of new drugs, biological agents, and medical equipment. These benefits may be financial, in the form new patents with consequent royalties, and nonfinancial, including personal gratification, academic promotion, added prestige, and community recognition of the institution. With so much at stake, reports abound on the changing relationship between industry and academia (6, 19), the influence pharmaceutical companies are exerting over academic freedom (20, 21), and on how research is moving away from the academic medical center setting into the community with the evolution of commercially oriented contract-research organizations and site-management organizations (22). This latter issue is likely to have a large impact on how COIs are regulated in the future (23).

Profits garnered from biomedical research can be enormous. In 1980, Congress enacted the Bayh-Dole Act (24), whose purpose was to reform national patent policy related to government-sponsored research and to create new incentives for research collaboration between the government, industry, and academia. The act had two purposes: to allow universities, not-for-profit corporations, and small businesses to patent and commercialize their federally funded inventions and to allow federal agencies to grant exclusive licenses for their technology to provide more incentive to businesses to deploy that technology. A report of the United States General Accounting Office in 1998 identified how, under the Bayh-Dole Act, universities identified inventions, approached licensing, and shared royalties with inventors, their academic departments, and their laboratories. In 1996, under the Bayh-Dole Act, select institutions derived millions of dollars from this technology transfer, and >$24.8 billion and 215,000 jobs were added to the U.S. economy (25).

In the 1980s, a landmark case was decided in the setting of the new frontier of biomedical research. In *Moore v. The Regents of the University of California* (3), John Moore was suffering from hairy cell leukemia and underwent splenectomy, which was medically necessary and even may have been life saving. Researchers at the University of California continued to render care to Moore, but without Moore's knowledge, they took blood spec-

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imens and splenic tissue, from which ultimately they developed and patented a permanent cell line, which liberated a number of cytokines. The physician researchers entered into agreements with industry to develop and market these proteins commercially for cash and stock offerings. In response to a suit filed by Moore contesting the unconsented use of his biological materials, the California Supreme Court suggested that Moore did have the right to be informed of the uses of his tissue, even if he lacked a clear ownership right in his biological material once it had been removed from him (3). The court specifically questioned the soundness of the physicians' allegedly altruistic research intentions and asked whether they were not simply rushing to patent for financial gain (18). These issues are now being revisited in Florida, where some families who provided their children's genetic material for research on Canavan disease have contested the uses of their children's materials. Their children's genetic material was patented by Miami Children's Hospital, which has developed a screening test, and where work on a cure for Canavan disease is in progress. The hospital has reportedly imposed strict controls on the screening tests and has demanded royalties for each test performed. According to the hospital, these royalties are necessary for it to recoup its research expenditures, and if it is not permitted to recoup these costs, future research endeavors will be stifled. The families are suing the hospital for alleged breach of informed consent (17, 26). Meanwhile, medical journals (27), specialty societies (28), and government agencies are debating appropriate courses of action to guarantee the integrity of future research. Among the options being covered are additional, stricter federal regulations of financial conflicts in human subjects research.

EXISTING FEDERAL REGULATIONS

Currently, in all research funded or authorized by the Public Health Service (PHS) of the United States Department of Health and Human Services (which includes the National Institutes of Health) and by the National Science Foundation, there are requirements for investigator disclosure of their financial conflicts of interest. The Food and Drug Administration (FDA) also maintains various regulations relating to study investigators' conflicts of interest. Current requirements seem mostly directed toward ensuring integrity of research data rather than toward protecting human research subjects.

PHS financial disclosure requirements apply only to human research funded by a PHS agency, or proposed for PHS funding, and do not apply to privately funded research (subject to some exceptions, the National Science Foundation regulations are similar to those of the PHS) (29, 30). The PHS basic requirement is that each investigator who participates in PHS-funded research (with investigator defined broadly as all research staff who exercise professional discretion regarding study data) must submit for review to an official at the research institution a listing of his or her "significant financial interests" 1) that would reasonably appear to be affected by the research for which PHS funding is sought and 2) in entities whose financial interests would reasonably appear to be affected by the research (31). The financial disclosure to the institution by investigators must be made by the time a grant application is submitted to the PHS and then updated either annually or as new reportable significant financial interests are obtained. The definition of "reasonably appear to be affected by the research" is not specific and provides little guidance on this issue. The result has been that individual institutions set their own individual guidelines or definitions.

Financial interests are defined as anything of monetary value, including cash; consulting fees or honoraria; stocks or other equitable interests, patents, copyrights, or other intellectual property rights; and royalties from intellectual property rights (32). Significant financial interests are payments received in 1 yr by the investigator, including payments to his or her spouse and dependent children, that are expected to be >$10,000 (32). If the relevant ownership interest of the investigator, spouse, and children is worth >$10,000 or constitutes >5% ownership interest in a single organization, it too must be reported (32). Notably, these financial interests do not include salary and other compensation from the research institution, income from seminars, teaching, or lectures sponsored by public or not-for-profit entities, and income from serving on advisory committees or review panels for public or not-for-profit entities, and they do not include holdings in mutual funds (32).

PHS regulations allow for management of conflicts through internal institutional policies. The institution must establish guidelines for its designated official to take action to ensure that the conflicts are managed, reduced, or eliminated (33). The institution must enforce these policies and sanction violators as appropriate (34).

Some of the potential methods and conditions that an institution may utilize to manage the conflicts of interest, include:

- Publicly disclosing the financial interest
- Having independent reviewers monitor the research
- Modifying the research plan
- Disqualifying certain investigators from participation in the research
- Requiring the investigator to divest the significant financial relationship
- Severing relationships that create actual or potential conflicts

Under the PHS regulations, institutions are also allowed to develop any "reasonable alternative solutions" for managing the conflicting interests (35).

FDA financial disclosure requirements apply to a pharmaceutical company, device manufacturer, or other party that has submitted a marketing application to the FDA for approval of a human drug, device, or biological product and that submits to the FDA the results of "covered clinical studies" as a proposed basis for FDA approval (36). These financial disclosures are retrospective, as they are submitted with the FDA application for marketing approval. Clinical investigators (broadly defined as in the PHS regulations) and their research institutions do not have a direct reporting obligation to the FDA, but investigators are obligated by the regulations to provide the research sponsor with sufficient financial information to enable the study sponsor to meet its disclosure obligations to the FDA. For every clinical investigator who participates in a "covered clinical study," the applicant (i.e., the research sponsor) must disclose to the FDA, using Form FDA 3455, the nature of the following financial interests of the clinical investigators:

1. Any financial arrangement between the sponsor and the clinical investigator in which the value of the com-

pensation to the investigator for conducting the study could be influenced by the outcome of the clinical studies, such as payments that are higher for a favorable study outcome, including royalty payments for sales of the product or an ownership interest in the sponsor of the study.

2. Any other compensation from the sponsor of the study to the investigator or the institution to support activities of the investigator that is worth >$25,000 (not including the costs of conducting the study), which is given while the clinical investigator is conducting the study or within 1 yr after completing the study. Examples of this type of compensation include grants for ongoing research, equipment and honoraria.
3. Any property or financial interest in the tested product held by the clinical investigator, including patents, copyrights, or licensing agreements.
4. Any ownership or other financial interest (including stock and stock options) in the sponsor held by the clinical investigator, the value of which cannot be easily determined by reference to public prices, or any ownership interest in a publicly traded company that exceeds $50,000 during the time that the investigator is conducting the study or within 1 yr after completion of such study.
5. Any steps taken to reduce the bias created by these disclosed financial relationships (37).

Notable differences exist between PHS and FDA financial reporting requirements. First, of course, PHS maintains a lower dollar threshold than the FDA. Second, whereas PHS requirements focus on financial interests that reasonably appear to be affected by the research, the FDA requirements focus on conflicts relating to the relationship between the investigator and the research sponsor. Third, disclosure/reporting to the FDA is retrospective (at the time an application is submitted to the FDA), whereas PHS requirements are prospective, when research is contemplated and PHS funds are sought to support that research. Of utmost importance is that neither agencies' requirements apply to privately funded "home-grown" or "institutionally sponsored" studies not used for FDA applications. Finally, neither the FDA nor PHS requirements mandate disclosure of the precise compensation flowing to the investigator or institution for a research study, and neither set of regulations imposes a "fair market value" standard for this research-related compensation.

A 2001 report of the United States General Accounting Office (38) revealed disparate policies and procedures regarding individual investigators' financial conflicts of interest in five universities studied. The universities' policies differed in their content, such as the kinds of financial relationships they considered to be manageable conflicts, and in their implementation. Although they used similar management strategies for conflicts, they differed in how they employed those strategies. The universities generally acknowledged a need for better coordination of information about investigators' financial relationships. They reported confusion regarding the conditions under which COI must be reported and what the universities themselves are required to report. All institutions had "firewalls" in place to isolate the universities' investments from academic and research affairs (a means of regulating institutional financial conflicts of interest).

DEBATE INTENSIFIES

Over the past few years, federal agencies, medical journals, and research institutions have developed guidelines by which conflicts of interest can be minimized. As a result of an August 2000 National Institutes of Health meeting, Health and Human Services' Office for Human Research Protection (OHRP) released the *Draft Interim Guidance: Financial Relationships in Clinical Research* (39), and expects to issue a final guidance in late 2002. Noting that many institutions have established a COI committee, the *Guidance* indicates that such a committee is useful in keeping the institutional review board (IRB) from bearing the burden of becoming the main group to consider these issues and that the COI committee's findings on how the institution should manage the conflicts should be shared with the IRB. The *Guidance* also recommends that institutions annually collect and review the financial interests in commercial sponsors of IRB staff, the IRB chair, and of IRB members, and it suggests that institutions educate and train investigators and IRB members on COI issues. Although not a mandate, the *Draft Guidance* introduces the concept of IRB consideration of disclosure of financial relationships/conflicts in informed consent forms. Although offering recommendations on identifying and managing individual investigator's conflicts, the *Draft Guidance* fails to offer detailed suggestions on how to identify and manage the institution's own COIs.

The role of the IRB in managing COIs is controversial. Health and Human Services regulations stipulate that no IRB member may participate in the IRB's initial or continuing review of a project in which the member has a conflicting interest, except to provide information requested by the IRB (40). COI is not precisely defined in these IRB regulations but would seem not to be solely financial. The potential for conflicts of interest should be considered when selecting IRB members. When IRB members frequently have conflicts (i.e., often serve as principal investigators) and must abstain from deliberation and voting, their contributions to group review processes may be diminished and could hinder review procedures. The problem is even more severe if the conflicted member is the IRB chair.

In mid-2001, the National Human Research Protection Advisory Committee (NHRPAC), having as part of its charter the responsibility and duty to advise OHRP, commented extensively on the OHRP *Draft Interim Guidance*. NHRPAC asked for clarification between financial relationships and COI, as the presence of a financial relationship may not represent any conflict. NHRPAC emphasized the need for confidentiality in the financial disclosure process. Lack of confidentiality might serve as a disincentive for researchers to disclose, especially in "close" cases where a potential COI is unclear. NHRPAC endorsed threshold amounts for disclosure policies (including honoraria, trips, and investments), below which a financial interest would be so minimal that it could not be interpreted as a COI. Noting the inconsistencies between PHS and FDA regulations, NHRPAC favored the stricter PHS standard of $10,000 (or <5% ownership interest) and recommended that this standard apply to all research, regardless of the source of funding (41). NHRPAC recommended analyzing research compensation to ensure that such compensation would fall within the variables of fair market value for services rendered. NHRPAC recognized,

however, that a COI analysis should take account of compelling and necessary exceptions in which a COI would be willingly tolerated. For example, when treating rare medical conditions with an innovative medical device, it may impose an undue burden on the patient if the investigator who developed the device were unable to render care. As others have agreed (7), NHRPAC would not leave the process of monitoring compliance with COI standards to the IRB. Noting that IRBs are already overburdened, NHRPAC suggested creation of an adjunct COI process. The COI committee would receive and analyze financial disclosures and report to the IRB its findings as necessary before IRB review. Yet how such a process could be implemented in community-based research with "freestanding" IRBs is speculative at the best, because these freestanding IRBs lack an overall institutional structure that could support a COI committee. Furthermore, such IRBs have an inherent conflict of their own when pharmaceutical companies or device manufacturers financially support the IRBs reviewing the company's protocol (42). NHRPAC guidance stated that if a financial COI on the part of the institution or clinical investigator had not been or could not be eliminated, what the financial arrangement is and how that conflict is being managed should be disclosed in the informed consent document. The document should explain what additional protections (such as COI management methods) have been put in place. NHRPAC suggested that the IRB consider special measures to modify the consent process when a potential COI exists. These could include having a nonbiased third party obtain consent, especially when the potential COI could influence the tone or presentation of information during the consent process. NHRPAC felt that disclosure should not be a cheap and easy substitute for actively identifying and managing conflicts. How precisely to make this disclosure to patients remains uncertain, but in the case of real conflict, NHRPAC thought that the conflict should be disclosed.

The Association of American Universities (AAU) (43) and the Association of American Medical Colleges (AAMC) (44, 45) each have each generated recommendations on individual and institutional conflicts of interest in clinical research. Both documents emphasize the need for high standards for institutional conflicts when human subjects are involved.

The AAU task force concluded that the problem is rarely a particular conflict itself but rather that the question is what should be done with the conflict. AAU emphasized robust campus-wide management systems in which institutions have adequate procedures for identifying potential conflicts through annual disclosure, along with rigorous and consistent review of such disclosures. These procedures should indicate how relevant officials are informed of conflicts and how the conflicts are to be managed. AAU endorsed the creation of COI committees and suggested that IRBs must develop disclosure thresholds to determine whether there has been adequate informed consent. The AAU document also addresses the significant potential of compromising the university's mission due to potential conflicts involving university equity holdings or royalty arrangements or in circumstances in which university officials make decisions with institution-wide implications. Questions are raised by the AAU regarding management of endowments and gift funds and regarding the roles of university officials when they are members of corporate boards.

The positions of the AAMC on individual conflicts are similar to those of NHRPAC. The AAMC, for example, also endorses a threshold for financial disclosures in keeping with the requirements of the PHS. An important aspect of the AAMC's position is that it recognizes that "in some cases, an official's position may convey an authority that is so pervasive or a responsibility for research programs or administration that is so direct that a conflict between the individual's financial interests and the institution's human subjects research should also be considered an 'institutional conflict of interest'" (44). To identify whether a particular institutional financial relationship may effect or reasonably seem to affect human subjects involved in research conducted at or under the auspices of an institution, the AAMC recommends a specific, fact-driven inquiry in the following circumstances:

A. When the institution is entitled to receive royalties from the sale of the investigational product that is the subject of the research.

B. When, through its technology licensing activities or investments related to such activities, the institution has obtained an equity interest or an entitlement to equity of any value (including options or warrants) in a *nonpublicly traded* sponsor of human subjects research at the institution.

C. When, through technology licensing activities or investments related to such activities, the institution has obtained an ownership interest or an entitlement to equity (including options or warrants) of >$100,000 in value in a *publicly-traded* sponsor of human subjects research at the institution.

D. When, with regard to a specific research project to be conducted at or under the auspices of the institution, institutional officials with direct responsibility for human subjects research hold a significant financial interest in the commercial research sponsor or the investigational product. Significant financial interest is defined for this purpose as one or more of the following:

1. An equity interest or entitlement to equity (including options or warrants) of any amount in a nonpublicly traded sponsor of human subjects research conducted at or under the auspices of the institution.
2. An equity interest or entitlement to equity (including options or warrants) in excess of the *de minimis* amount (and not including exceptions for certain mutual funds), as defined in the AAMC's 2001 guidelines (that of the PHS) for individual financial interests, in a publicly traded sponsor of human subjects research conducted at or under the auspices of the institution.
3. Consulting fees, honoraria, gifts or other emoluments, or "in kind" compensation from a sponsor of human subjects research conducted at or under the auspices of the institution that in the aggregate exceeded the *de minimis* amount as defined in the AAMC's 2001 guidelines for individual financial interests or are expected to exceed that amount in the next 12 months.
4. An appointment to serve, in either a personal or representative capacity, as an officer, director, or board member of a commercial sponsor of human subjects research conducted at or under the auspices of the in-

Integrity of our research relies on the development of a transparent system to identify, minimize, and manage conflict without stifling the scientific curiosity of investigators and on allowing investigators the personal and the financial rewards associated with their work.

stitution, regardless of whether remuneration is received for such service.

5. An appointment to serve on the scientific advisory board of a commercial sponsor of human subjects research conducted at or under the auspices of the institution, unless the official has no current significant financial interest in the sponsor or the investigational product and agrees not to hold such an interest for a period of no less than 3 yrs after completion of any related research conducted at or under the auspices of the institution (44).

In defining these standards for institutional conflicts of interest, the AAMC has gone far beyond current minimum federal legal requirements, which, as discussed earlier, relate only to investigators of PHS and National Science Foundation–funded research, IRB members, and investigators of studies that are later used to support FDA applications. However, as demonstrated by the Gelsinger case and by other cases (16, 46), great concerns may arise in regard to institutional conflicts in human subjects research. We may expect that even without federal regulations on these points, many academic medical centers and universities will begin to develop policies on institutional conflicts and that the pace of such internal regulation might be accelerated by any common law findings of liability in which institutional conflicts have been tolerated without management or disclosure to human subjects.

CONCLUSION

The premises for ethical conduct of interventional clinical research are well established. In clinical encounters, physicians are expected to attend solely to the welfare of the individual patient. When a patient is entered into a research protocol, there is no guarantee that the individual will benefit from the intervention. Entry must be voluntary and with the patient's informed consent. Before discussing the risks and benefits of participation in the research endeavor, the investigators must do all that is possible to identify, minimize, and articulate any actual or potential significant risks to the research subject. Articulation of risks must not be influenced by potential benefits to investigators, their institutions, or study sponsors. Study subjects must know, whether the researchers intentions' are purely scientific, that the investigation is not intended specifically to meet the healthcare needs of the subjects but that the study may ultimately lead to improved patient care. Although investigators and institutions may ultimately benefit financially or in stature, these potential end points must not compromise the well-being of the subject.

Federal regulations identify rudimentary conflicts of interest on the part of individual investigators, but these regulations have many gaps. The current debate over identification and management of conflicts has broadened our understanding of these conflicts and, rightfully, has identified institutional conflicts as a concern. The integrity of our research relies on the development of a transparent system to identify, minimize, and manage conflict without stifling the scientific curiosity of investigators and on allowing investigators the personal and the financial rewards associated with their work. Standards on how to identify, manage, and eradicate these conflicts are now rapidly evolving, with increased government oversight and stricter standards likely.

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Financial Conflicts of Interest in Human Subjects Research: The Problem of Institutional Conflicts

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Financial Conflicts of Interest in Human Subjects Research: The Problem of Institutional Conflicts

Mark Barnes and Patrik S. Florencio

In both academic literature and the media, financial conflicts of interest in human subjects research have come center-stage. The cover of a recent edition of *Time* magazine features a research subject in a cage with the caption "human guinea pigs,"[1] signifying perhaps that human research subjects are no more protected from research abuses than are laboratory animals.[2] That magazine issue highlights three well-publicized cases of human subjects research violations that occurred at the University of Oklahoma, the University of Pennsylvania, and Johns Hopkins University.

At St. John Medical Center in Tulsa, Oklahoma, a study that was co-sponsored by the University of Oklahoma Health Sciences Center investigated an experimental vaccine for malignant melanoma. In that case, the chair of the university's institutional review board (IRB) — the committee within each medical institution charged with ethics review of human research projects undertaken at that institution — and the dean of the University's College of Medicine allegedly concealed from both the IRB and the United States Food and Drug Administration (FDA) a report by an outside consulting firm that had found severe deficiencies with the melanoma vaccine study being conducted at the medical center. The outside consulting firm had been engaged by the IRB chair and dean of medicine after the research nurse of the investigator[3] in charge of the study reported to them substantial variations from the research protocol, such as improper storage of the melanoma vaccine, inadequate recordkeeping, and failure to report adverse side-effects to the IRB. In response to the outside report, the IRB chair and dean of medicine halted the trial, but the IRB chair stated in an annual report that there were no significant safety issues related to the melanoma vaccine. A letter was sent to all trial participants stating that the study was being halted because the sponsor had exceeded its capacity to supply the melanoma vaccine. When the research nurse read the letter, she thought the letter false, and notified the Office of Human Research Protections of the United States Department of Health and Human Services of the study deficiencies she had previously reported to the IRB chair and dean of medicine. Like the outside consulting firm, the Office of Human Research Protections found significant deficiencies associated with the trial, and shut down all federally funded human subjects research at the university.[4] This prompted the university to conduct it own investigation. Because the university investigation confirmed the Office of Human Research Protections findings, the IRB was disbanded, and the investigator, IRB chair, and dean of medicine left their positions.

The Oklahoma case is interesting because it shows how high-level, and presumptively neutral, institutional officials such as an IRB chair and dean of medicine can be led astray from their primary responsibilities of safeguarding human research subjects and of upholding the integrity of research. Clearly, secondary interests, whether financial or, in this case, nonfinancial, can exert significant pressures on institutional decision makers, and can sometimes overshadow their primary responsibilities. Concealing research data, and concealing adverse effects associated with a study medication or device, are significant offenses in academia generally, and in research particularly. The Oklahoma case may unfortunately be part of a trend in some quarters toward secrecy in medical research[5] that some reports indicate may be more common in industrially supported research than in publicly funded research.[6]

Another example of how secondary interests can sometimes overpower an institutional decision maker's primary responsibilities toward scientific and academic integrity occurred at the University of Toronto in Canada. In that case,

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the former president of the University of Toronto personally wrote a letter to the prime minister of Canada and four other federal cabinet ministers to warn them that the pharmaceutical giant, Apotex, would only provide the university with a multimillion-dollar donation toward the construction of a biomedical research center ($20 million for the University of Toronto and $10 million for its affiliated teaching hospitals) if proposed drug patent regulations were withdrawn; the university president urged them to do what was necessary to ensure that the university benefit from the sizeable pharmaceutical donation.[7] Thus, the university president was thought to have abused his position of privilege and responsibility by lending institutional prestige and influence to an unrelated commercial concern. This incident similarly demonstrates that compelling institutional financial interests can cloud the judgment of even the most high-ranking officials of an academic institution, notwithstanding that such persons have foremost responsibility for upholding academic values and for setting an appropriate example for others at the institution and in academia generally.

The University of Oklahoma and University of Toronto cases are evidence that conflicts of interest can influence behavior not only at the researcher and IRB level, but also at the institutional level. Despite this evidence, very little scholarship exists on the problem of institutional conflicts of interest. This article seeks to provide a preliminary framework from which to conceptualize and manage institutional conflicts of interest. To that end, we begin by reviewing evidence demonstrating that financial incentives can affect the professional judgment of physicians and researchers, and, by implication, that of other decision makers, including institutional decision makers. We then briefly comment on the regulatory regime that currently governs the financial conflicts of interest of researchers and IRB members. We discuss the nature of institutional conflicts of interest, how these conflicts might affect data integrity and/or subject safety, and whether oversight and management of institutional conflicts is necessary. Finally, we discuss strategies for managing the institutional conflicts of academic medical centers, hospitals, and other health-care facilities.

Do Financial Incentives Affect Professional Judgment?

That financial incentives exert significant influence over human behavior is evident from daily human experience. That these incentives can and do occasionally overpower professional judgment is illustrated by the University of Oklahoma and the University of Toronto cases described above, and by other cases discussed herein. What is not known is the frequency with which professional judgment and primary responsibilities are subverted in favor of secondary interests. What is probable is that secondary interests exert greater influence over the decision maker: (1) as the value of the secondary interest increases (e.g., more money at stake); (2) as the exercise of professional judgment becomes more specialized and thus less amenable to close supervision (e.g., a researcher's interpretation of data, or a university official's behind-the-scenes conversations with endowment officers or university contributors); (3) when the decision-making process is less transparent by virtue of wide discretion afforded to officials (e.g., wide discretion at the level of university president, dean, provost, department chair, IRB chair, or principal investigator); and (4) when there is a long-standing relationship between a particular manufacturer and the decision maker (i.e., over time the decision maker may develop loyalty to that manufacturer). While most articles in the literature on financial conflicts of interest in biomedical research typically offer a few references in support of the proposition that such conflicts can affect professional judgment, we have endeavored to provide a more comprehensive inventory of the empirical and anecdotal evidence in support of such a correlation.

The evidence comes from within and without the research environment. Beginning outside of the research context, numerous studies have shown, for example, that financial incentives and gifts from industry make physicians more likely to: (1) refer patients for tests, operations, or hospital admissions;[8] (2) recommend that the hospital pharmacy be stocked with drugs having no appreciable advantages over existing ones;[9] (3) prescribe newer, more expensive medications having no demonstrable advantage over older, generic medications;[10] and (4) engender positive attitudes of physicians toward pharmaceutical representatives.[11] Within the research context, there is mounting evidence that financial incentives affect the professional judgment of investigators. In general, studies have found researchers with industry funding to be more likely than researchers with nonprofit funding to conclude that industry drugs or devices are safe and effective.[12]

In one study, for example, 96 percent of authors supporting the safety of calcium channel blockers had financial relationships with manufacturers as compared to 60 percent of neutral authors and 37 percent of authors whose research did not support the drugs' safety.[13] Similarly, industry sponsored authors have been found more likely to conclude that the sponsoring manufacturer's "new" treatment is more efficacious and less toxic than standard or competing medications.[14] In another study, 38 percent of authors with nonprofit funding reached unfavorable results about certain oncology medications, whereas only 5 percent of industry sponsored authors reached similar conclusions.[15] In yet another study, multiple regression analyses revealed tobacco industry affiliation to be strongly correlated with an author's conclusion that passive smoking is not harmful to health; 75 percent of authors who concluded that passive smoking is not a health hazard were affiliated with a tobacco company.[16] There have also been reports of data tampering in cases where

the researcher owned large amounts of stock in the company whose product the researcher was testing in a clinical trial.[17]

Collectively, these data suggest that financial interests can affect the professional judgment of physicians and researchers. Likewise, there is no reason to assume that financial interests would not also affect the professional judgment of other health-care decision makers, such as an institution's senior management, department chairs, IRB members and/or IRB staff. As researchers and academic medical centers acquire greater financial interests in industry, and as the health-care industry and academic medical centers are increasingly short of discretionary funds, health-care entities may begin to operate less like objective fact-finders, and more like for-profit contract research organizations. Primarily to protect the scientific integrity of research data, but also to protect human research subjects from the harms that could befall them from biased judgment on the part of financially conflicted researchers engaged in human research trials and financially conflicted IRB members who oversee these trials, federal laws have been enacted to regulate the conflicts of researchers and IRB members. However, no such laws currently regulate the conflicts of institutions and/or their senior directors or trustees.

Regulation and oversight of researcher and IRB conflicts of interest

Current regulation of researcher and IRB member conflicts of interest is not based on the assumption that the secondary interests of researchers and IRB members will necessarily have an adverse effect on the conduct of research, but rather on the assumption that such secondary interests may potentially adversely effect research integrity. Moreover, it has been noted, it is "difficult if not impossible to distinguish cases in which financial gain does have improper influence from those in which it does not."[18] Thus, the response most often proffered to those who consider regulation of conflicts of interest to be a serious insult to the integrity of scientists and academic institutions[19] is that conflict of interest rules are not accusatory, and should therefore not be taken as an affront to those subject to the rules; conflicts of interest themselves represent only the *potential* for biased judgment, without indicating the likelihood or certainty that biased judgment will actually occur.[20] Consequently, the objective of regulations governing conflicts of interest is to "minimize conditions that would cause reasonable persons (patients, colleagues, and citizens) to believe that professional judgment has been improperly influenced, whether or not it has."[21] The legal regime that currently governs the financial conflicts of interest of researchers and IRB members has already been well-described in the literature[22] and a comprehensive review of existing reports and guidance by governmental agencies and professional organizations on that issue will soon be published.[23]

The laws that currently govern investigator financial conflicts of interest are rife with gaps. These laws cover only financial conflicts of interest, leaving nonfinancial conflicts (such as reputation and career advancement) for oversight through other established institutional mechanisms. Moreover, they apply only to research funded by the Public Health Service of the Department of Health and Human Services or the National Science Foundation, and to studies submitted to the FDA in support of sponsor applications. Investigator-initiated studies and industry-sponsored studies that won't be used in support of FDA applications are not covered. The Public Health Service, the National Science Foundation, and FDA regulations require reporting at inconsistent levels of financial interests, and of different categories of financial interests. Significantly, reporting under FDA requirements most likely occurs outside the ken of IRBs or other institutional officials, since report forms flow from investigators directly to sponsors. This regulatory regime is, therefore, far from seamless, and when considering institutional conflicts of interest, it is essential that one recognize that the more tangible, investigator-industry relationship is itself regulated in only an attenuated and imperfect fashion.[24]

What about institutional conflicts of interest?

It was previously noted that no laws or regulations currently govern the conflicts of interest of institutions and/or their senior directors or trustees. However, clear examples of biased judgment on the part of institutional decision makers, such as that which occurred at the University of Oklahoma and University of Toronto, lead one to wonder whether some type of formal (e.g., laws) or informal (e.g., voluntary guidance documents) oversight might be necessary to regulate institutional conflicts. But what other evidence is there that institutional conflicts exist and need to be managed? To answer this question one must first have a better understanding of what an institutional conflict is, and how this conflict might affect research outcomes or the health and safety of human research subjects participating in a trial at the institution. Notwithstanding the overall dearth of scholarship on the subject of institutional conflicts, some commentators and organizations have begun to address this issue.

Nature of institutional conflicts of interest

The Association of American Universities (AAU) has defined institutional financial conflicts of interest as situations in which:

> [T]he institution, any of its senior management or trustees, or a department, school, or other subunit, or an affiliated foundation or organization, has an external relationship or financial interest in a company that itself has a financial interest in

> a faculty research project. Senior managers or trustees may also have conflicts when they serve on the boards of (or otherwise have an official relationship with) organizations that have significant commercial transactions with the university. The existence (or appearance) of such conflicts can lead to actual bias, or suspicion about possible bias, in the review or conduct of research at the university. If they are not evaluated or managed, they may result in choices or actions that are incongruent with the missions, obligations, or the values of the university.[25]

What is central to the AAU's definition of institutional financial conflicts of interest is that: (1) the conflict can arise from corporate (i.e., the institution or a subdivision of the institution) or individual (i.e., senior management, trustees, department chairs) relationships with, or financial holdings in, industry; (2) there is no *de minimis* threshold below which the conflict will be considered insignificant (i.e., all relationships or financial interests are viewed as potential conflicts); (3) the appearance of bias is as important as actual bias; and (4) if conflicts are not managed, they can lead to improper decision-making.

Would the University of Oklahoma and the University of Toronto cases be captured by the AAU definition? The University of Oklahoma case would probably not be, because there is no evidence of any form of financial relationship between the IRB chair or the dean of medicine and the sponsor of the experimental melanoma vaccine; instead, the institutional conflict at issue appears to be nonfinancial. The University of Toronto case, however, would arguably be captured by the AAU definition since the university's financial expectation in the pharmaceutical company, Apotex, led to biased and improper decision-making on the part of the university's president. The University of Toronto case, therefore, can be regarded as a concrete example of the harms of institutional financial conflict of interest, albeit one that did not affect the welfare of human research subjects. The University of Oklahoma case, while not an example of an institutional financial conflict of interest, is nevertheless an example of a nonfinancial institutional conflict of interest. Moreover, because the IRB chair and dean of medicine, as part of the alleged concealment of risk data, did not notify the FDA of the side-effects associated with the melanoma vaccine, the institutional conflict could have led to subject injuries in future trials of the experimental vaccine.

The foregoing examples demonstrate that institutional conflicts of interest, like investigator conflicts of interest, may be financial or nonfinancial. Examples of nonfinancial institutional interests are the desire to enhance institutional reputation, originate innovative new technologies, develop safe and effective treatments for illnesses, and win prestigious research awards in order to be able to attract and maintain "star" faculty members and researchers to the institution, as well as to be able to compete successfully for sponsored research funding. These nonfinancial interests may generate conflicts through institutional pressure to achieve positive research results. Although nonfinancial interests have been widely acknowledged in the literature dealing with investigator conflicts of interest, nonfinancial conflicts of interest are generally thought to be effectively controlled through research oversight processes at institutions (e.g., IRB approval of only scientifically meritorious research protocols) and through the scientific method itself.[26] Moreover, nonfinancial interests are much less easily identified than are financial interests and are therefore harder to regulate. It is perhaps for these reasons that the federal government regulates financial, but not nonfinancial, investigator conflicts of interest. This article concentrates on institutional conflicts of interest that are financial in nature, even though a perfect regulatory structure would capture these other interests as well.

Potential effects of institutional conflicts of interest on human subjects research

How then might institutional financial conflicts of interest affect research outcomes or the health and safety of human research subjects participating in a trial at the institution? The issue of institutional financial conflicts of interest is premised on the assumption that institutional conflicts can influence researchers and institutional decision makers, including IRB members, IRB staff, and others employed by the institution. In its report to the Secretary of the Department of Health and Human Services, the National Human Research Protections Advisory Committee noted as follows:

> [O]ne risk here is that IRB members may often include department chairs, deans, mid- and high-level administrators from the entity, and researchers, any of whom may well understand the value of these investments to the institution, and their judgments on research approval and oversight could be altered by countervailing concerns for patent value, stock price, or related financial interests.... Closely related to this is the risk that the researchers themselves who are amassing and analyzing data could be influenced by an awareness that their own institution's financial health may be affected by the results of their research, if their institution holds a significant stake in the drug or device being tested.[27]

Researchers and institutional decision makers may thus be influenced not only by their own direct financial incentives, but also by those of the institution. The risk is that their professional judgment may be affected by institutional

pressure to achieve a research end point that is favorable to the institution's reputation or financial interests. The institutional pressure may be indirect (e.g., researcher or institutional decision maker obliquely learns that the institution is heavily invested in the trial being conducted) or direct (e.g., he or she is notified by an institutional administrator or department chair of the institution's interest in the outcome of the trial). This institutional pressure may lead researchers and/or administrators to compromise their primary responsibilities toward assuring human subject welfare, scientific integrity, and institutional integrity. Examples of compromised primary responsibilities may include, among others: (1) the inadequate disclosure of study risks and exaggeration of potential study benefits in order to enhance subject enrollment; (2) enrollment of subjects not meeting eligibility criteria; (3) failure to exclude subjects meeting exclusion criteria; (4) failure to report adverse events to the IRB charged with overseeing the trial; (5) improper data manipulation; (6) failure to conduct rigorous initial and continuing review; and (7) failure to suspend or terminate trials when indicated.

Evidence that institutional conflicts of interest can affect human subjects research

What other evidence is there, besides the direct evidence of biased judgment in the University of Oklahoma and University of Toronto cases, that institutional conflicts of interest, especially financial interests, can affect research outcomes or subject safety? Some of the evidence is circumstantial and comes from a variety of cases where *ex post facto* investigation of human subjects research violations has revealed that the institution and researcher have had financial ties with, or investments in, the sponsor of the research. One of these cases took place at the University of Pennsylvania, where a young volunteer, Jesse Gelsinger, died in a gene therapy trial.[28] Investigation of the death revealed that the researchers responsible for the gene therapy trial had violated several federal rules designed to protect the safety of human research subjects, including the rule that investigators must notify the FDA of any significant side-effects associated with the drug or device under investigation (i.e., prior to the enrollment of Jesse Gelsinger, other research subjects in the trial had experienced significant liver toxicity from the adenovirus being studied in the trial).[29] The investigation also revealed that the principal investigator of the gene therapy trial held a 30 percent equity interest, and the University of Pennsylvania a 3.2 percent equity interest, in the sponsor of the trial; when another corporation acquired the sponsor, the principal investigator reportedly made a return of $13.5 million, and the University of Pennsylvania reportedly earned $1.4 million.[30]

The Gelsinger case provides only circumstantial evidence of the potential influence of institutional financial conflicts of interest (i.e., the institutional conflict and research violations happen to coincide in the same case) because there is no direct evidence that the breach by researchers of federal rules governing human subject safety was in any way caused by the researchers' and/or institutions' financial interests in the outcome of the trial. Nevertheless, the death of Jesse Gelsinger from his participation in the gene therapy trial led the American Society of Gene Therapy — an organization representing 2,500 professionals involved in conducting gene therapy research — to issue a voluntary guidance suggesting that gene therapy researchers refrain from owning any equity, stock options, or other interests in companies whose products they are testing in clinical trials.[31] If adhered to, this guidance would subject American Society of Gene Therapy members to the same "zero tolerance" policy regarding financial conflicts of interest that now applies to IRB members under federal rules.[32]

Another example suggesting a possible correlation between institutional financial conflicts of interests and wrongful decision-making during the conduct of a research trial involves the Fred Hutchinson Cancer Center.[33] As in the Gelsinger case, researchers at the Cancer Center allegedly continued the study, and failed to notify the FDA, despite the occurrence of numerous adverse events of which the researchers were apparently aware. Subsequent investigation reportedly revealed financial ties between the sponsor of the trial, the investigators, and the Cancer Center. Hutchinson has rigorously denied these allegations and reports, but the allegations themselves have created enormous publicity precisely because of the alleged financial conflicts involved — including alleged institutional conflicts.

In any event, if financial interests can affect the professional judgment of physicians and researchers, it would appear to be a straightforward and reasonable assumption that such interests could also affect institutional decision makers; there is, after all, no principled reason for believing that institutional officials are somehow impermeable to direct or indirect financial incentives. Thus, biased institutional decision makers may pass on their bias to IRB members and/or researchers who may act upon that bias. Before the late 1980s, little evidence had been accumulated on the correlation between researcher financial conflicts of interest and the outcome of clinical trials, and yet we know today that such a correlation exists. We should not, however, simply assume a correlation to exist between institutional financial interests and research outcomes until sufficient evidence for such a conclusion has been collected. Yet the difficulty with conducting studies on institutional financial conflicts of interest is that such studies would require the collection of detailed information on the financial holdings of academic medical centers and hospitals that host clinical trials, information that trustees and senior administrators of such institutions are unlikely to be willing to share. Moreover, conclusively demonstrating causation between identified institutional interests and inappropriate decision-making in clinical research oversight may be, by its very

nature, impossible. In short, all the evidence we may ever have in this regard may be anecdotal and/or intuitional.

Additional rationales for regulating institutional conflicts of interest

Quite apart from the risk that institutional financial conflicts of interest may adversely influence researchers, other rationales have been put forth as to why such conflicts should be managed. The first rationale is that there is no reason for treating institutional financial conflicts of interest any differently than we treat researcher or IRB member conflicts (i.e., equality of treatment). Since these latter types of conflicts are regulated, so too should institutional conflicts.[34] Moreover, as discussed above, institutional conflicts are, at base, individual conflicts in that the individual's personal financial well-being is closely connected to the institution's financial well-being (e.g., individual's salary and bonus are derived from institutional proceeds and contingent upon institutional solvency), and the individual's personal moral interests are closely tied to the institution's reputation or prestige. The second rationale is that since institutions are responsible for policing the conflicts of interest of researchers employed by the institution, institutions should set an example by disclosing and managing their own conflicts of interest. The third rationale is that institutions (and all those involved in the research enterprise) should avoid even the appearance of bias that is created when they are invested in the sponsors of research being conducted at the institution, or in the technology being tested, whether or not such investments actually affect the outcome of research trials. This rationale is based on the argument that public trust in biomedical research and in the institutions that host such research is eroded when institutions merely appear biased.[35] The fourth rationale is that research institutions that invest in the sponsors of research being conducted at the institution are essentially engaging in what would otherwise be regarded as insider trading.[36] Finally, the fifth rationale is that if research institutions do not adequately self-regulate themselves, government agencies will develop external regulations governing institutions, which may be more draconian and imprecise than needed to address these issues.[37]

The Management of Institutional Financial Conflicts of Interest

While most scholars are likely to agree that some oversight and regulation of institutional financial conflicts of interest are necessary, opinions diverge when it comes to deciding the quantum of regulation to impose. One approach to addressing institutional financial conflicts has been put forth by the AAU in its Report on Individual and Institutional Financial Conflicts of Interest. In that report, the AAU summarized its approach as consisting of the following three steps: "(1) disclose always; (2) manage the conflict in most cases; and (3) prohibit the activity when necessary to protect the public interest or the interest of the university."[38] The AAU report is, however, general in nature, and leaves to universities the tasks of both developing specific policies that address institutional conflicts, and of developing administrative processes for implementing these specific policies. Other than the AAU, few other organizations have issued guidance on how to deal with institutional conflicts.[39] In fact, even when one canvases other industries, guidance on institutional conflicts seems only to exist in the securities and financial services sector, where the suggested management strategies consist primarily of disclosure, and the implementation of "firewalls" between research operations and investment banking.[40]

In the material that follows, we propose management strategies for dealing with institutional financial conflicts of interest. Disclosure of institutional conflicts to an independent review committee, and perhaps to the subjects taking part in the trial for which an institutional conflict has been identified, must be a first step in any management strategy. Disclosure, by itself, however, only identifies a problem without proposing solutions to minimize that problem. Consequently, disclosure of institutional financial conflicts of interest must always be accompanied by proactive measures that are undertaken to eliminate or reduce any institutional conflicts identified through the disclosure process.

Disclosure of institutional financial conflicts of interests

The AAU's first recommended step to address institutional conflicts is disclosure, and the AAU report notes that university policies on institutional conflicts should address the issue of "who discloses what to whom."[41] However, the AAU does not detail how or by whom these disclosures should be made.

Applying the AAU's disclosure standard[42] would lead an institution to identify with specificity: (1) the institutional officials responsible for disclosing the institution's financial interests in all sponsors whose products are being investigated at the institution (e.g., by way of employment titles or functions); (2) the types of financial information that must be disclosed (e.g., equity, royalty agreements); and (3) the individuals to whom such disclosure must be made (e.g., independent conflicts of interest review committee, research subjects). Institutional financial conflicts of interest can arise not only when the institution itself or a subdivision of the institution (i.e., the corporate entity) has financial holdings in, or financial relationships with, industry sponsors of research, but also when the directors, trustees, or department chairs of institutions have such financial holdings or relationships. Consequently, the institution's policy should address whether these institutional officials are subject to the disclosure requirement. If so, then the institution's policy should

specify: (1) the categories of institutional officials who must disclose; (2) the types of financial information that must be disclosed (e.g., equity interests, directorships, board memberships); and (3) the individuals to whom such disclosure must be made (e.g., independent conflicts of interest review committee, research subjects).

Regarding the conflicts of institutional officials, the institution's policy also must take into account the regulations on intermediate sanctions that prevent "disqualified persons" from profiting from "excess benefit transactions" with an applicable tax-exempt organization, such as not-for-profit hospitals and academic medical centers.[43] The regulations, in other words, would prevent institutional officials and IRB members who meet the definition of "disqualified person" (i.e., persons in a position to exercise "substantial influence" over the organization's affairs) from exercising their decision-making authority in a manner that is personally profitable and inconsistent with the institution's best interests. This would occur, for example, where institutional officials or IRB members exercise their decision-making discretion so as to approve research projects that would not otherwise be allowed to proceed at the institution and that cost the institution in staff time and/or resources. Another example would be a case in which institutional officials or IRB members approve research projects that are more costly, but no more worthy, than alternative projects because those persons have a financial interest in a particular drug or device being studied or in the sponsor of the research project.

The policy should therefore reflect federal regulations governing "excess benefit transactions."[44] An appropriate institutional policy should also specify that the obligation to disclose institutional conflicts, whether corporate or personal, does not consist of a one-time event at the initiation of each new trial, but rather is an ongoing obligation to disclose any new conflicts that might arise during the course of the trial, just as intermediate sanction rules impose on institutional decision makers the obligation of avoiding "excess benefit transactions."

The disclosure process might consist of a series of "trigger" questions throughout the research review and approval process, so that all institutional staff and administrators think broadly in their identification of possible institutional conflicts. More specifically, all research approval and conflict of interest forms, including those sent to investigators and those to be signed or approved by an IRB or an institutional official, could contain appropriate questions regarding the possibility of an institutional conflict in the proposed study (or approved study in the case of continuing review forms). Because the failure to protect the confidentiality of financial information will serve as a disincentive for researchers, IRB members, IRB staff, and any other person involved in the research review and approval process, to disclose their personal financial information or that of the institution, the policy on institutional conflicts should impose on reviewers the obligation of maintaining the disclosed information in strict confidence, even in the form of written pledges of nondisclosure.

Institutions must decide whether disclosure will be made only to a review committee or set of reviewers charged with managing the institution's conflicts, and/or will be made to research subjects enrolled in a trial at the institution for which there is an institutional financial conflict of interest. The purpose of disclosing the financial incentives of institutions (and researchers) to research subjects is to allow the subjects to make an informed decision about whether to participate in the clinical trial. Unless financial incentives are made apparent through disclosure, they will remain hidden from subjects and are unlikely to form part of the informed consent process.[45] One leading court has been willing to conclude that failure of researchers to disclose their financial incentives in the research during the informed consent process constitutes a breach of that consent process.[46] Similarly, in the managed care context, failure of physicians to notify patients of their financial incentives in prescribing a particular medication or course of medical treatment has been held to constitute a violation of informed consent.[47] While the current informed consent doctrine may not be broad enough to encompass institutional financial conflicts of interest, institutions should consider whether it is nevertheless in the best interests of research subjects to be informed of the institution's financial incentives in the research it is hosting.

There is evidence in the literature to suggest, however, that disclosure of financial conflicts of interest to research subjects is not in their best interests, unless the researcher can also inform the subjects of how the financial conflicts have been, or will be, managed.[48] In the managed care context, for example, where financial incentives are sometimes used to discourage physicians from using particular treatment options, it has been suggested that patients who are informed of their physician's financial conflicts of interest may not understand the relevance of the information to their health-care choices and treatment, and may not in any case have reasonable alternative courses of action in the circumstances.[49] This may be particularly true in the research context, where access to an innovative treatment may only be offered to patients through participation in a specific research trial (in which the researcher may be conflicted).

Another danger of disclosing financial incentives to research subjects without informing them of how these incentives have been, or will be, managed, is that such disclosure may lead to feelings of anxiety and/or mistrust on the part of the subjects. This anxiety and mistrust is likely to be greatest when both the researcher and the hosting institution are conflicted. Where the institution is conflicted, but the researcher is not, there may be less erosion of trust because the subject may perceive the researcher to be a patient advocate responsible for protecting the subject from any potential bias the institution may try to exert during the course of the research trial. For these reasons, institutions should not disclose to

research subjects their financial conflicts, nor should they require researchers to reveal their own financial conflicts, unless such conflicts have been, or will be, managed. In other words, disclosure of interests should not be regarded as a panacea for financial conflicts, as it only foists on research subjects information whose implications they are unlikely to understand.

Disclosure should, of course, always be made to the reviewers charged with deciding how the institution's conflicts will be managed or which research should not proceed at the institution due to conflicts. When disclosure to research subjects is indicated because financial incentives have been managed, the institution should give thought to the appropriate timing, content, and scope of the disclosure. Disclosure of financial incentives to research subjects should in no way be thought to absolve researchers and institutions from their primary obligation of protecting the welfare of research subjects taking part in trials at the institution, not only through active management of conflicts, but also by close adherence to research ethics.

Management of institutional financial conflicts of interests

Managing institutional financial conflicts of interest is no simple task. At every major research center, complex networks of financial ties and relationships may exist between industry sponsors of research and the hosting institution or its directors, trustees, department chairs, and others. In recent times, industry-academia relationships have intensified, resulting in a dramatic increase in the introduction of new drugs and devices.[50] In 2000 alone, the for-profit industry invested approximately $55 to $60 billion in research and development, over twice as much spent by the federal government.[51] Seventy percent of that funding reportedly went for clinical drug trials in the United States.[52] Pharmaceutical companies also spend over $11 billion each year in promotion and marketing,[53] $5 billion of which goes to sales representatives.[54] Because the average cost of developing a new drug is estimated to be $300 million to $600 million,[55] drug manufacturers must aggressively market their products to recoup their development costs. For each day's delay in gaining FDA approval of a drug, the manufacturer reportedly loses, on average, $1.3 million.[56]

While the close partnership between academia and for-profit industry has led to a surge in the rapidity with which scientific innovations are brought to market, this partnership has also led to a number of practices that are incompatible with academic values. For instance, clinical trial agreements between investigators and sponsors have sometimes contained "gag clauses" permitting the sponsor to delay publication of research findings for significant periods of time, or to outrightly prohibit publication when research results are unfavorable to the sponsor's product.[57] In some cases, industry sponsors have taken legal action to enforce such clauses, even where the withholding of data could lead to research injuries.[58] While "gag clauses" are simple to regulate in that they are usually easy to identify, and can then be modified or altogether negotiated out of clinical trial agreements, the nature and extent of the steps that should be taken to manage other problems associated with the growing nexus between academia and industry, such as the problem of institutional financial conflicts of interest, are less clear.

It is recommended that the primary methods for controlling institutional financial conflicts of interest should focus on assuring adequate separation of research activities from institutional investment activities, and instituting independent monitoring of clinical trials. While the erection of "firewalls" to assure adequate separation between researchers and those institutional officials responsible for the institution's corporate investments and relationships should be feasible to implement, isolating researchers from, for example, conflicted department chairs will be more difficult to achieve. For instance, in an academic medical center where the head of the department of cardiology has financially invested in a sponsor whose cardiac device is being tested by a faculty member of the department of cardiology, it may not be feasible, or even desirable, to largely restrict communication between the head of a cardiology department and the faculty member for the duration of the trial. First, regular interaction between department chairs and faculty members, for example, during faculty meetings, is necessary to the efficient operation of academic medical centers. Second, most clinical trials continue at least for months, and many carry on for years. Thus, while "firewalls" are an appropriate mechanism for managing institutional conflicts that arise from the institution's corporate investments and relationships, this mechanism may be less reasonable or practical in the case of certain institutional conflicts that arise from the personal investments and relationships of senior managers. In these cases, management of institutional conflicts ought to occur at various stages of the research process — for example, during trial enrollment, eligibility determinations, informed consent, physical examinations, data interpretation, and analysis — by outside, independent professionals.

The question arises, therefore, as to what persons or entity, within or outside the institution, ought to be vested with the responsibility and authority for making monitoring and risk-reduction recommendations appropriate to each trial. One recommendation would be to vest such responsibility and authority in an independent review panel (IRP) that would receive information about potential institutional conflicts. Some of the issues that institutions would be faced with regarding the characteristics of their IRP include the composition of the IRP's membership, the nature and extent of the IRP's powers, appointment of IRP members, tenure of IRP membership, removal of IRP members for cause, and IRP reporting. When addressing these particular issues, in-

stitutions may appropriately differ, depending on the needs and resources of the particular institution, as long as minimum safeguards assure the IRP's independence and accountability. To substantiate this need for independence, the IRP should naturally not be composed solely of institutional administrators.

Moreover, it seems unwise to allocate to IRBs the responsibilities of an IRP. IRBs are already overburdened,[59] do not necessarily have the technical expertise to evaluate and recommend corrective actions to remedy institutional financial conflicts of interest, and may not be perceived as being sufficiently independent from the institution.[60] The IRP should, however, report its findings and conclusions to the IRB charged with reviewing the study for which an institutional conflict has been identified. For largely the same reasons, it would be inappropriate for institutions to agree to review institutional conflicts through one another's IRBs. While review by a sister IRB (or IRP) would help create the appearance of independence, trustees and senior administrators of institutions are unlikely to disclose fully their institution's financial holdings to the IRB (or IRP) of a sister institution. Moreover, the IRP should be composed of persons having some affinity for, and/or loyalty to, the institution so that IRP recommendations are consistent with the institution's long-term interests while assuring subject safety and research integrity. Additionally, sister IRBs (or IRPs) are unlikely to be any less burdened, or have any more technical expertise, than the institution's own IRB, thus making them an inappropriate choice.

The IRP should ideally be composed of members having expertise in financial investments, the handling of intellectual property, and the process of human subjects research. These members could be drawn partly from within the institution, such as from the faculties of business, law, and bioethics in the case of academic medical centers, and partly from outside the institution, such as from expert or lay members of the community whose personal livelihood and financial interests are not dependent on the institution. No member of the IRP should have responsibility for the institution's financial well-being, nor should any member be associated with any research that could benefit directly from the financial investments or relationships under review. Moreover, as with IRB members, a "zero tolerance" policy should exist with respect to the IRP member's own financial connections to a research sponsor. The IRP members could be appointed by the institution's board of trustees, or a designated committee of the board (such as an audit or finance committee), but the appointment would be tenured for a period of time specified in the policy on institutional conflicts, and removal of an IRP member could only occur for good cause, which cause would need to be formally documented for audit purposes.

The IRP could report in a formal sense to the board, but the IRP would also share its findings and recommendations with the IRB charged with reviewing the trial associated with the institutional conflict, the relevant conflict of interest committee charged with reviewing any individual researcher conflicts associated with that same trial, and to the designated institutional official who is responsible for making the disclosure under the policy. The IRP should be given the authority to require meaningful modifications of institution-industry relationships. The IRP's recommendations should, however, be commensurate with the seriousness of the conflict, and the likelihood that the conflict could in fact be transmitted to researchers and exert undue influence on them during the course of the trial.

In addition, consistent with National Human Research Protection Advisory Committee's recommendation that is also espoused by the Association of American Medical Colleges, the IRP should be able to consider "compelling and necessary" exceptions that would allow a conflicted institution to conduct the trial with oversight where that institution's staff has special expertise regarding a particular drug or device under investigation.[61] The IRP should therefore be able to consider such exceptions when a conflicted institution has staff members with special expertise, or has special facilities or equipment that are unavailable at most other institutions. In these cases, the IRP should consider whether the benefits of conducting the trial at the conflicted institution outweigh the possible risks of bias. The IRP's management recommendations might include: (1) eliminating the conflict by referring the study to another site that has no institutional conflicts at work, or by requiring complete divestiture of the conflicting financial interest; (2) reducing the conflict by requiring partial divestiture of the conflicting financial interest, or by establishing "freeze" periods during which institutional investments cannot be traded or sold; (3) disclosing the financial conflict to sponsors[62] or biomedical journals[63]; (4) requiring independent monitoring and oversight of subject-researcher interactions, data gathering, data analysis, and/or data reporting; and (5) arranging for independent review of all adverse events, including review of subject records on a comprehensive, periodic or sampled basis to assure that reports of adverse events have been timely and properly made.

Drafting policies for the disclosure and management of institutional financial conflicts of interest should be among the first steps undertaken by institutions as they prepare to confront such conflicts. When drafting these policies, institutions should build upon the research compliance structures already in place at the institution, such as those governing IRB review and oversight of research trials and/or those governing individual researchers' financial conflicts of interest. Institutions should also revise all research forms that investigators, IRB members, IRB staff, and other institutional administrators complete during the research review and approval process. As discussed above, these forms should be amended to incorporate "trigger" questions regarding possible institutional financial conflicts of interest. The "trigger"

questions should be designed to elicit information regarding the personal financial conflicts of the individual completing the form, as well as information concerning the individual's knowledge or awareness of any corporate financial holdings or interests of the institution in the sponsor of the trial or that may be affected by the trial, or any relationships that the institution or that institutional decision makers may have with that sponsor.

Finally, the policies on institutional financial conflicts of interest should require all those involved in the research approval and oversight process to be educated about institutional conflicts, the undue influence these conflicts may bring to bear on research, and generally about the importance of professional integrity and trust in research. While education may not reduce the appearance of institutional bias, it may help to prevent actual bias from affecting research results or from compromising subject safety. Some commentators, in fact, view professional integrity as being central to a prevention strategy aimed at reducing the unwanted effects of financial conflicts of interest.[64] Moreover, education regarding financial conflicts of interest may be necessary. Studies have shown, for example, that while 85 percent of medical students believe that it is improper for politicians to accept a gift, only 46 percent think it improper for themselves to accept a gift of similar value from a pharmaceutical company.[65] Researchers, IRB members, IRB staff, and other research administrators should be trained to identify institutional conflicts that might influence them, and should be instructed to report these conflicts to the IRP, and potentially also to the IRB and/or individual conflicts of interest committee. Education might even help to prevent some of the more subtle influences of industry-academia relationships about which some commentators have expressed concern, such as the potential influence these relationships may have over the direction of research conducted at the institution (i.e., industry-sponsored researchers may tend to put more emphasis on commercially useful research than on basic research).[66] Education regarding this concern may reduce the likelihood that researchers alter the scope or direction of their research at the institution (or that of their graduate students) so as to materially benefit the corporate sponsor.

Conclusion

As industry-academia partnerships are likely to continue to intensify, it will be paramount that the public perceives these sectors as operating independently from one another under appropriate standards of integrity. To maintain public trust, academia will need to prove that it values the advancement of human knowledge more than short-term profit. To that end, institutions should adopt formal policies and procedures for dealing with researcher and institutional financial conflicts of interest. To be effective, these policies will need to prescribe more than the mere disclosure of financial conflicts. Particularly, institutional policies should document the specific steps that will be undertaken by the institution to eliminate or reduce institutional financial conflicts that are identified through the disclosure process. Institutions should establish a duly constituted independent review panel that is sufficiently autonomous from the institution so as to not itself be conflicted and so as to act reliably to protect human subject safety and research integrity; and yet, the committee must be sufficiently loyal to the institution, so that management strategies for reducing the potential ill-effects of financial conflicts of interest are, to the extent possible, devised according to the long-term interests of the institution.

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55. See Bodenheimer, *supra* note 52.

56. See *id.*

57. D. Blumenthal et al., "Withholding Research Results in Academic Life Sciences: Evidence From a National Survey of Faculty," *JAMA*, 277 (1997): 1224–28; I. Chalmers, "Underreporting Research is Scientific Misconduct," *JAMA*, 263 (1990): 1405–08.

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59. E.E. Slater, "IRB Reform," *N. Engl. J. Med.*, 346 (2002): 1402–04 at 1403 (noting that "... the increasing number and complexity of protocols are taxing the capability of local IRBs.").

60. E.J. Emanuel and D. Steiner, "Institutional Conflict of Interest," *N. Engl. J. Med.*, 332 (1995): 262–67 at 265 ("... some members of the [IRB] might work for the department that stood to benefit financially from the clinical research, and others might benefit indirectly from the institution's royalties. Finally, the public perceives these boards as internal rather than external bodies. Just as citizens may be suspicious of the thoroughness of a government agency's review of its own behavior, there may be little confidence in an [IRB's] judgment when the institution has a financial interest in the research").

61. See National Human Research Protections Advisory Committee, *supra* note 27, at 6 ("[c]onflict of interest analysis should take account of, and contain 'compelling and necessary' exceptions for, situations in which physicians who treat unusual conditions invent new devices or develop other interventions, and yet have significant financial interests in those techniques, interventions, or devices. In these cases, guidance should not discourage these physicians from inventing new devices and developing new interventions and therapies, and should not prohibit these physicians from acting as clinical investigators, particularly in the initial stages of investigation, since they may be in the best position to undertake critical research with a high assurance of safety for research subjects"). See 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* (December 2001): 1–25, at 7, *available at* <http://www.aamc.org/members/coitf/firstreport.pdf>,("[i]n 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").

62. It has been recommended that pharmaceutical companies, device manufacturers, biotechnology companies, and other research sponsors maintain a "searchable web-based registry of researchers and practicing physicians with whom they have an established financial relationship." See Kassirer, *supra* note 50, at 151. This searchable registry could be extended to also list corporate and personal institutional financial conflicts of interest when disclosure to the sponsor is recommended by the IRP.

63. As we noted above, the editors of many leading biomedical journals have adopted the position that they must reveal to readers the financial incentives underlying the articles they publish so that readers can interpret the findings presented in the articles in light of the financial incentives. When recommended by the independent review panel, significant institutional financial incentives might also be disclosed to journal editors who could then publish this information alongside the article.

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65. P. Palmisano and J. Edelstein, "Teaching Drug Promotion Abuses to Health Care Profession Students," *Journal of Medical Education*, 55 (1980): 453–55.

66. See Blumenthal et al., *supra* note 6.