Department of Health and Human Services

Final Guidance Document

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

This document replaces the "HHS Draft Interim Guidance: 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" 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 the Department), including the Food and Drug Administration (FDA), or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and 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 subjects[1] 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]

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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 at http://ohrp.osophs.dhhs.gov/humansubjects/assurance/engage.htm. 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://era.nih.gov/services_for_applicants/other/fcoi.cfm. 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

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

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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] http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm

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

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[5] http://www.hhs.gov/ohrp/archive/humansubjects/finreltn/finmain.htm.

[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 one-quarter 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,

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

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(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.

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.

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

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.

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Tommy G. Thompson
Secretary
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