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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of Public Health and Science

[Docket No. 02N-0475]

AGENCY: Office of Public Health and Science, HHS

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

ACTION: Notice

SUMMARY: The Office of Public Health and Science, Department of Health and Human Services (HHS) is soliciting public comment on a draft guidance document for Institutional Review Boards (IRBs), investigators, research institutions, and other interested parties, entitled "Draft Guidance Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection." This draft guidance document raises points to consider in determining whether specific financial interests in research affect the rights and welfare of human subjects, and if so,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 Food and Drug Administration. Persons with access to the Internet also may obtain the document at http://www.fda.gov/ohrms/dockets/GUIDANCES/DGUIDES.HTM.

DATES: Submit written or electronic comments on the draft guidance on or before 4:305:00 p.m. on [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. General cComments on HHS guidance documents are welcome at any time.

ADDRESS: Submit written comments to the Dockets Management Branch (HFA-305), Docket Number 02N-0475, Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. All comments submitted should be identified with the docket number found in brackets in the heading of this notice. Comments received may be viewed on the Food and Drug Administration (FDA) website at http://www.fda.gov/ohrms/dockets/default.htm or may be seen in the FDA Docket Management Branch at 5630 Fishers Lane, Room 1061, Rockville, MD 20852 between

9 a.m. and 4 p.m., Monday through Friday.

Submit requests for single copies of the draft guidance document to the address identified below for further information. Requests may be made by mail or e-mail. Persons with access to the Internet also may obtain the document at http://www.fda.gov/ohrms/dockets/GUIDANCES/DGUIDES.HTM.

FOR FURTHER INFORMATION CONTACT: Glen Drew, Office for Human Research Protections, Office of Public Health and Science, The Tower Building, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852, (301) 402-4994, facsimile (301) 402-2071; e-mail gdrew@osophs.dhhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

OPHS is seeking comments on the HHS draft guidance for IRBs, investigators, and research institutions, entitled "Draft Guidance Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection." 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 conflicts 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. This document will replace that draft interim guidance.

The draft guidance recommends consideration of approaches and methods for dealing with issues of financial interests under the HHS human research subject protections regulations, 45 CFR part 46 and 21 CFR parts 50 and 56. The draft guidance expressly does not address regulatory requirements designed to enhance data integrity and objectivity in research found inof 42 CFR part 50, subpart F, and 45 CFR part 94, andor 21 CFR part 54, related to financial interests of investigators.

The draft guidance identifies specifically applicable sections of the regulations, and recommends that, in particular, IRBs, institutions engaged in research, and investigators consider whether specific financial relationships create financial interests in research studies that may adversely affect the rights and welfare of subjects. The guidance poses general considerations in evaluatingSeveral possible questions regarding financial relationships andt their possible effects on human subjectsresulting

interests are offered. Some mMore detailed points for consideration are also offered, as are specific issues for institutions, IRBs operations, IRB review of proposed research, and investigators.

II. Request for Comments

OPHS is distributing this draft guidance document for public comment. The Secretary is interested not only in reactions to the Guidance in general, and specifically the Points for Consideration, but also wishes to solicit views and ideas as to how to best assess any impacts of this guidance, as well as related non-Federal recommendations on enhancing the protection of human subjects. HHS guidance on consideration of financial interests in human subjects research will be issued after the public comments have been considered.

III. Draft Guidance Document

Department of Health and Human Services

DRAFT GUIDANCE DOCUMENT

(DATE)

FINANCIAL RELATIONSHIPS AND INTERESTS IN RESEARCH INVOLVING HUMAN SUBJECTS:

GUIDANCE FOR HUMAN SUBJECT PROTECTION[1]

This document will replace 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.

I. Introduction

A. Purpose

[1] **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 HHS, including FDA, or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.**

In this draft guidance document the Department of Health and Human Services (HHS, or the Department) raises points to consider in determining whether specific financial interests in research affect the rights and welfare of human subjects[2] and if so, what actions could be considered to protect those subjects. This draft guidance applies to human subjects research conducted or supported by HHS or regulated by the Food and Drug Administration (FDA). This document addresses only requirements for human subject protection (45 CFR Part 46, 21 CFR Parts 50, 56)[3] This document is

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[2] 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.

[3] This document does not address HHS Public Health Service regulatory requirements that cover institutional management of the financial interests of individual investigators who conduct 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 NIH that involve human subjects are available at http://grants.nihgov/grants/guide/notice-files/NOT-OD-00-040.html. Guidance interpreting the provisions of the FDA regulations appears at http://www.fda.gov/oc/guidance/financialdis.html.

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

nonbinding and does not change any existing regulations or requirements, and does not impose any new requirements.

Institutions and individuals involved in human 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 if it will, or may be reasonably expected to, create a bias stemming from that financial interest. Furthermore, the Department recognizes that some financial interests in research may potentially or actually affect the rights and welfare of subjects, and this document provides some possible approaches to consider in assuring that subjects are adequately protected. Institutional review boards (IRBs), institutions, and investigators engaged in human subjects research may each have appropriate roles in ensuring that financial interests do not compromise the protection of research subjects.

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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.nsf.gov/bfa/cpo/gpm95/ch5.htm#ch5.

B. Target Audiences

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

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. Financial relationships in human research should not compromise any of these principles. 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 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 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));**

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

- **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)).**

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Ffor 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) directlyPart 46 Subpart A addresses conflicts of interest by requiringexplicitly in the requirement of section '46.107(e) 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 research subjects. Financial interests are not prohibited, and not all financial interests cause conflicts of interest or harm to 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**

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[5] **http://ohrp.osophs.dhhs.gov/humansubjects/finreltn/finguid.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 AEthical 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 (NHRPC) 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 2001and 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/issues/v287n1/abs/jsc10070.html), the American Society of Gene Therapy, April 2000 (http://www.asgt.org/policy/index.html), 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

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 engaged in research, and investigators consider whether specific financial relationships create financial interests in research studies that may adversely affect the rights and welfare

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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/vahrpapfinstds.pdf).

Internationally, the World Medical Association's revision in 2000 of the Declaration of Helsinki, (http://www.wma.net/e/policy/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.gov/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.

of subjects. These entities may elect to include the following questions in their deliberations:

- **What financial relationships and resulting financial interests cause potential or actual conflicts?**
- **At what levels could those interests cause potential or actual conflicts?**
- **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,**
    - **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 may be managed by eliminating them or mitigating their potentially negative 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. 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 for protection of the rights and welfare of the human research subjects.

- **Does the research involve financial relationships that could create 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, and licensing agreements?**
  - **have an equity interest in the research sponsor and is it 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, and honoraria)**
  - **receive payment per participant or incentive payments, and are those payments within the norm?**

- **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 Issues for Consideration Regarding:

1. Institutions

The Department recommends that institutions engaged in federally conducted or supported human subjects research consider the following actions or other actions regarding financial conflicts of interest:

- **Separate responsibilities for financial decisions and research decisions.**
- **Establish conflict of interest committees (COICs) or identify other bodies or persons [7] or identify other bodies or persons to deal with individuals' financial interests in research or verify their absence.**
- **Extend the responsibility of the COIC to address institutional financial interests in research or establish a separate COIC to address institutional financial interests in research.**

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

- **Establish 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.**
- **Establish clear channels of communication between COICs and IRBs.**
- **Establish policies on providing information, recommendations, or findings from COIC deliberations to IRBs.**
- **Establish measures to foster the independence of IRBs and COICs.**
- **Include IRB members and staff and appropriate officials of the institution, along with investigators, among the individuals who report financial interests to COICs.**
- **Establish procedures for disclosure of institutional financial relationships to COICs.**
- **Provide training to appropriate individuals regarding financial interest requirements.**
- **Use independent organizations to hold or administer the institution's financial interest.**
- **Include individuals from outside the institution in the review and oversight of financial interests in research.**
- **Establish policies regarding the types of relationships that may be held by parties involved in the research, and circumstances under which, those**

financial relationships and interests may be held by parties involved in the research.

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 establishing policies and procedures addressing IRB member potential and actual conflicts of interest as part of overall IRB policies and procedures. These might include:

- **Reminding members of conflict of interest policies at the start of each meeting.**
- **Polling members to verify that no conflicts of interest exist regarding any protocols to be considered during the meeting.**
- **Recording the polling results in the meeting minutes.**
- **Recording in the meeting minutes verification for each protocol that any conflicted members did not participate in discussion or voteing on protocols involving their conflict of interest, except to provide information as requested by the IRB (45 CFR 46.107(e), 21 CFR 56.107(e)).**
- **Developing educational materials about the regulations' requirements for IRB members.**

3. IRB Review

The Department recommends that IRBs reviewing HHS conducted or supported human subjects research or FDA regulated human subjects research consider the following actions, or other actions related to conduct or oversight of research, based on particular situations:

- **Determine whether methods being considered or used for management of financial interests of parties involved in the research adequately protect the rights and welfare of human subjects.**
- **Determine when an IRB needs additional information to decide whether the financial interests of parties involved in research could affect the rights and welfare of subjects as well as mechanisms for obtaining the additional information.**
- **Determine what actions are necessary to minimize risks to subjects.**
- **Determine 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 consider the potential effect that a financial relationship of any kind might have on a clinical trial, including interactions with research subjects, and whether to take any of the following actions:

- **Including information in the 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 consent process when a potential or actual financial conflict exists, such as**
  - **having a non-biased third party obtain consent, especially when a potential or actual conflict of interest could influence the tone, presentation, or type of information presented during the consent process.**
- **Considering independent monitoring of the research, e.g., using a data and safety monitoring committee.**

Dated:

Tommy G. Thompson

Secretary

U.S. Department of Health and Human Services