

III. Draft Guidance Document

Department of Health and Human Services

Draft Guidance Document

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Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection¹

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

In this draft guidance document the Department of Health and Human Services (HHS, or the Department) raises points to consider in determining whether specific financial interests in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 subjects² 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 This draft guidance applies to human subjects research conducted or supported by HHS or regulated by the Food and Drug Administration (FDA).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 nonbinding

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.

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.nih.gov/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>.

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 each have appropriate roles in ensuring that financial interests do not compromise the protection of research subjects.

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.nsf.gov/bja/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));
- 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

⁴ <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm>.