

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

The Public Health Service has had regulations concerning Financial Conflict of Interest since 1995 and FDA has had regulations requiring financial disclosure for clinical investigators since 1998. Neither PHS nor FDA requirements are prescriptive regarding the types of financial interests that may be held and neither mentions the role and responsibilities of IRBs in this area, nor disclosure of financial arrangements to the research subject via the Consent document. Further, both the "Common Rule" which sets out requirements for IRBs at institutions receiving PHS funds, and FDA's equivalent regulations governing IRBs and Informed Consent, are mostly silent in this area.

Despite these PHS and FDA regulations, there is currently no uniform, comprehensive approach to consideration of potential financial conflict of interest in human research. The HHS Inspector General found that about one-quarter of IRBs are considering financial arrangements with sponsors of research to varying extents in their review of protocols. Some include disclosures about financial relationships in consent forms. In August 2000 HHS held a conference on Human Subject Protection and Financial Conflict of Interest. The presentations and the comments received before, during, and after the conference shed further light on current policies, as well as practical approaches to management and resolution of conflicts.

At this time, there is much discussion on the topic of financial conflict of interest and clinical research. Recent issues of the *New England Journal of Medicine* and the *Journal of the American Medical Association* have devoted major sections entirely to this topic. Many professional societies have developed or are developing policies on this topic, most addressed to clinical investigators, but more recently to cover institutions as well. There is, however, little policy guidance for IRB members and staff that is easily available, although a number of organizations and universities have policies and procedures for IRB deliberations available on their websites.

Recognizing that policies and procedures are evolving in this area in the private sector and that there are as yet no "best practices", and that there is little consensus on what is "right" and what is "wrong" at this time, HHS is offering this guidance to assist Institutions, Clinical Investigators, and IRBs in their deliberations concerning potential and real conflicts of interest, and to facilitate disclosure, where appropriate, in consent forms.

Five new initiatives to strengthen human subject protection in clinical research were announced by Secretary Shalala in May, 2000. One of these was to develop guidance on financial conflict of interest that would serve to further protect research participants. As part of the information gathering process to assist

HHS in developing guidance, HHS held a conference on the topic of human subject protection and financial conflict of interest on August 15-16, 2000. This guidance is based on presentations made at that conference and public comments received, and related documents and, to a lesser extent, the medical literature.

As above, HHS agencies (Public Health Service agencies include NIH, CDC, FDA, AHRQ, HRSA, IHS, etc.) have regulations, policies, and guidance covering financial conflict of interest and financial disclosure in effect. This guidance is not meant to replace or modify any of the above, but to help IRBs, Clinical Investigators, and Institutions in carrying out their responsibilities to protect human subjects in research that they have under the "Common Rule" and the equivalent FDA regulations governing IRBs and Informed Consent. It is also intended to stimulate further development of policies and approaches in this area.

Much has been written on this subject. While some policies and financial reporting requirements, some with thresholds for reporting financial holdings, are in place, there is as yet no consensus as to the nature or magnitude of a financial interest that warrants attention and, possibly, action to mitigate the fact or appearance of a financial conflict of interest. FDA, in fact, does not even use the term "conflict of interest" in its regulations requiring financial disclosure by investigators (through the sponsor) of FDA-regulated research. This document emphasizes financial arrangements and financial disclosure issues that, hopefully, will assist IRBs to function in a way that will facilitate informed, unbiased discussion and properly informed research subjects. Thus, the sections on the Institution and Clinical Investigators focus on those areas and activities that would seem to impact most on the role and activities of IRBs in carrying out this mission.

Clear demonstration by sponsors, institutions and investigators to potential subjects that conflicts are being eliminated when possible and effectively managed when they cannot be eliminated, can help to develop a stronger bond of trust that can actually facilitate enrollment and the conduct of research. Openness and honesty are indicators of integrity and responsibility, characteristics that promote quality research and can only strengthen the research process.

1. THE INSTITUTION: INSTITUTIONAL CONSIDERATIONS

1.1 A conflict of interest exists, according to PHS regulations, when a "designated Institutional official(s) reasonably determines that a Significant Financial Interest could directly and significantly affect the design, conduct, or reporting of PHS-funded research." Consequently, such conflicts may bear directly on issues of human subject protection. Under the regulations, Conflict of Interest information should be obtained from all clinical investigators according to institutional policies and procedures. The flow of the information should be clear, including who makes the determination about whether there is a "significant" financial conflict of interest.

Many Institutions have established a Conflict of Interest Committee. This is a useful body for an institution to have and is helpful in keeping the IRB from bearing the burden of becoming the main group for considering such issues at an institution. The Chair of that committee generally shares the results of the Committee's reviews that relate to specific problematic protocols with the IRB Chair/Staff. The latter should be aware of how potential or actual financial conflicts of interest are managed, reduced or eliminated. Specifically, the Institution should share information about how it has dealt with the Clinical Investigator in terms of Financial Conflict of Interest—including how it has managed, reduced, or eliminated any conflict of interest—with the Conflict of Interest Committee and the IRB.

1.2 If the Institution does not already collect such information, the Institutional official might wish to request that Clinical Investigators conducting studies of FDA regulated articles, submit to that official the same information that the Investigators must submit to the sponsors of the studies (that will in turn be submitted to FDA by the sponsors on either

FDA Financial Disclosure Form 3454 or 3455.) This information should be shared with the Conflict of Interest Committee and, if appropriate, the IRB.

Similarly, the Institutional official may wish to distribute copies of letters relating to the management of significant financial conflict of interest that are submitted to PHS Grants Management by the Institution to the IRB, when appropriate.

1.3 Concerns have also been expressed that IRBs may be subject to institutional pressures, whether implicit or explicit, to approve research activities in which the institution has either a financial stake or other interest in the outcome of the research. Institutions engaged in human research should take great care to ensure that the composition of the membership of an affiliated IRB and its positioning within or relative to the administrative structure of the institution ensures that the review board is free to make its decisions and conduct its oversight activities in an autonomous manner, free from institutional pressures to follow a preferred course of action. Broad participation of members from outside the institution, who will have no interest in the outcome of the research or the business interests of the institution, is considered to be one of the most effective means of protecting the integrity of the IRB process.

1.4 The Institution should collect and review information from IRB staff, Chair, and all members on their financial interests with commercial sponsors, at least on an annual basis. Institutional policies and procedures should include specific guidance for all of the above regarding potential and actual financial conflicts and their management.

1.5 Institutions should establish educational programs on financial conflict of interest as part of their educational requirements for clinical investigators and IRB members. Institutions should make their financial conflict of interest policies and related documents, forms, etc. available online.

On December 1, 2000, the Public Health Service announced a new "PHS Policy on Instruction in the Responsible Conduct of Research (RCR)" which requires institutions to establish an education program on certain core areas of instruction for responsible research (including conflict of interest and commitment) for research staff at the institution who have direct and substantive involvement in proposing, performing, reviewing, or reporting research, or who receive research training, supported by PHS funds or who otherwise work on the PHS-supported research project even if the individual does not receive PHS support. The research institution may make reasonable determinations regarding which research staff fall within this definition. For more information on the RCR policy, including the full text and commonly asked questions and answers, see the ORI website <http://ori.hhs.gov> under "news."

1.6 While institutions clearly need to have policies and procedures for managing conflicts of interest among their employees, they should not lose sight of the need to manage their own conflicts of interest as well. Increasingly, academic institutions and corporate entities are entering into agreements that are mutually beneficial, and which may also bring the institution's interests into direct conflict with those of research participants. For example, an institution may accept a principal equity interest in a biotechnology company as part of a cooperative endeavor to develop a new medical device. Clearly, in such a situation, both the institution and the corporate partner would stand to gain financially if the device proves to be safe and effective. Accordingly, the institution should carefully consider whether a clinical trial to evaluate safety and efficacy should be performed at that site, and if it should, what special protections would be needed. The financial interest of the institution in the successful outcome of the trial could directly influence the conduct of the trial, including enrollment of subjects, adverse event reporting or evaluation of efficacy data. In such cases, the integrity of the research, as well as the integrity of the institution and its corporate partner, and the well-being of the research participants, may be best protected by having the clinical trial performed and evaluated by independent investigators at sites that do not have a financial stake in the outcome of the trial, or carried out at the institution but with special safeguards to maximally protect the scientific integrity of the study and the research participants.

1.7 When institutions consider entering into such business agreements, they should consider establishing an independent advisory and oversight committee (institutional conflicts of interest committee), if one does not already exist, to determine whether the financial arrangements pose a conflict of interest, and if so, how those conflicts should be managed.

1.8 Any financial relationships that the institution has with the commercial sponsor of a study should be documented and the specific relationships submitted to the Chair/Staff of the IRB as described above. Items to be identified include: any equity interest in the commercial sponsor; any "up front" payments to the Institution beyond those payments directly applicable to carrying out a particular protocol; any funds given to the Institution (or an entity within the Institution, e.g. an Institute); any equity ownership in the commercial sponsor that was transferred to the Institution,

including the percentage ownership of any patents related to articles under study in the protocol; any royalties; any licenses granted to the commercial sponsor by the Institution; whether or not the Institution stands to gain financially if the study shows the “article” to be successful for its proposed use.

2. CLINICAL INVESTIGATORS

2.1 Clinical Investigators should consider the potential effect that having a financial relationship of any kind with a commercial sponsor of a study might have on his or her conduct of a clinical trial or interactions with research subjects. Relationships that lead an investigator to prefer one outcome to another may influence an investigator's judgment and behavior. Influenced by a financial incentive, an investigator may, even if unwittingly, color the consent discussion in a manner that encourages participation by subtly minimizing the presentation of risks or overstating the benefits. Additionally, the above and so-called “recruitment bonuses” paid per participant, or for reaching an accrual goal within a specific time-frame, and being paid or paying a “finders fee” for referral of potential participants, might affect one's judgment, or willingness to report adverse reactions possibly related to the study article, or the analysis and interpretation of data. All aspects and types of relationships need to be considered, including such clear-cut issues as commitments of financial support unrelated to the study in question, financial incentives, serving as a paid consultant or speaker on behalf of a commercial sponsor, to less obvious ones such as non-monetary inducements or rewards to investigators or their family members.

2.2 Any agreements between Investigators and a sponsor should be reviewed by the Institution's Conflict of Interest Committee or equivalent body. It is desirable to avoid conflicts of interest whenever possible. If a potential conflict cannot be eliminated, the committee's determination of how the potential conflict is to be managed/reduced should be shared with the IRB for consideration during its discussion of the protocol.

2.3 Clinical Investigators should participate in educational and training programs concerned with financial conflict of interest issues including those that are required by their institutions.

3. IRB MEMBERS AND STAFF

3.1 The IRB Chair should ask the IRB members about whether they have any potential financial conflict of interest related to any of the protocols that the IRB is about to consider. The IRB should have clear procedures for recusal of IRB members, including the Chair, from deliberating/voting on all protocols for which there is a potential or actual financial conflict of interest. Many IRBs remind their members of these policies at the outset of each meeting and incorporate this reminder in the minutes of the meeting. The IRB minutes should also specifically reflect such recusals as they occur during meetings.

3.2 IRB members and staff should participate in education and training activities related to financial conflict of interest issues including those required by their institution.

3.3 The IRB policy and Procedures Manual should contain Institutional/ IRB Financial Conflict of Interest/financial relationship policies. Additionally, the manual might contain references to Conflict of Interest medical literature and the HHS August 2000 conference website (OHRP) where PHS/FDA policies, requirements, guidelines, and guidance may be found. <http://ohrp.osophs.dhhs.gov/coi/index.htm>

4. IRB REVIEW OF PROTOCOLS AND APPROVAL OF CONSENT DOCUMENTS

4.1 When an Institutional official or Conflict of Interest Committee or its equivalent determines that a potential Institutional conflict is problematic, the IRB should review the Institution's financial relationship to the Sponsor of a specific trial and determine whether the trial should be permitted to be carried out at the Institution. If so, the IRB should consider how this should best be managed, including what modifications might need to be made to the protocol or to the Consent form.

4.2 All IRBs (Institutionally based and non-Institutionally based) should be cognizant of the source of funding and funding arrangement for each protocol they review, and the source and arrangement for the funding the IRB's review of each protocol.

4.3 When the Institutional official or Conflict of Interest Committee or equivalent determines that a Clinical Investigator has potential conflict of interest that cannot be eliminated, and must be reduced or managed in some way, IRBs should consider not only what modifications might need to be made to the protocol or Consent, but other approaches as appropriate. To assist the IRB in this:

The IRB should consider all the categories in the PHS regulations on Financial Conflict of Interest and the FDA Financial Disclosure Regulations (per the PHS policy for grantees and the FDA regulations on Financial Disclosure). That is, it should consider all the elements that a designated Institutional official would need to consider under PHS policies, requirements, guidelines and guidance as well as FDA Financial Disclosure requirements that are the basis for submissions to sponsors and then to FDA, and then decide if the protocols and Consent documents should be modified accordingly.

In addition, the IRB might wish to consider the answers to the following questions in its deliberations:

- Who is the sponsor?
- Who designed the clinical trial?
- Who will analyze the safety and efficacy data?
- Is there a Data Safety Monitoring Board (DSMB)?
- What are the financial relationships between the Clinical Investigator and the commercial sponsor?
- Is there any compensation that is affected by the study outcome?
- Does the Investigator have any proprietary interests in the product including patents, trademarks, copyrights, and licensing agreements?
- Does the Investigator have equity interest in the company-- publicly held company or non-publicly held company?
- Does the Investigator receive significant payments of other sorts? (e.g. grants, compensation in the form of equipment, retainers for ongoing consultation, and honoraria)
- What are the specific arrangements for payment?
- Where does the payment go? To the Institution? To the Investigator?
- What is the payment per participant? Are there other arrangements?

(Note: Some Institutions and IRBs use special forms to facilitate collection and consideration of the type of information listed above in special situations or as a routine)

4.4 IRBs should carefully consider the specific mechanisms proposed to minimize the potential adverse consequences of the conflict in an effort to optimally protect the interests of the research subjects. In general, if there are any financial conflict of interest issues on the part of the Clinical Investigator, he or she should not be directly engaged in aspects of the trial that could be influenced inappropriately by that conflict. These could include: the design of the trial, monitoring the trial, obtaining the informed consent, adverse event reporting, or analyzing the data.

In all cases, good judgment, openness of process and reliance upon objective, third party oversight can effectively minimize the potential for harm to subjects and safeguard the integrity of the research.

5. CONSENT

5.1 IRBs (Institutionally based and non-Institutionally based) should consider including in the Consent document the source of funding and funding arrangements for performing the IRB review of that protocol.

5.2 IRBs should take steps to ensure that the potential research participants are apprised of the source of funding for the study and the payment arrangements for Investigators during the consent process and in the Consent Form, whenever that information is considered to be material to the potential subjects' decision-making process.

5.3 If a financial conflict of interest on the part of the Institution and/or Clinical Investigator has not been or cannot be eliminated, what the financial arrangement is and how that conflict is being managed should be disclosed in the Consent document. The document should explain what additional protections have been put in place. An IRB should consider taking special measures to modify the consent process when a potential financial conflicts exists. These could include having a non-biased third party obtain Consent, especially when potential conflicts could influence the tone or presentation of information during the consent process.

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