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A GUIDE TO PREVENTING FINANCIAL AND NON-FINANCIAL CONFLICTS OF INTEREST IN HUMAN SUBJECTS RESEARCH AT NIH
February, 2007

Avoiding financial and other conflicts of interests is important for NIH, where the trust and protection of research subjects is vital to our mission to improve the public health. The number and complexity of laws and regulations in this area makes it difficult to know when there is a problem and what to do. This guide is intended to assist clinical investigators and NIH IRB members in avoiding real or perceived financial and non-financial conflicts of interest.

I. What are a clinical investigator's potential conflicts of interest?

All clinical investigators have primary obligations. These include obtaining knowledge that will promote health and health care and helping ensure the safety and health of research participants. Clinical investigators may also have other, personal or secondary interests, which could include teaching trainees, supporting a family, and earning income. These secondary interests are not, themselves, unethical, but in some circumstances they have the potential to compromise, or appear to compromise, the judgment of clinical researchers regarding their primary obligations. When these secondary interests compromise judgment, or appear to do so, there is a conflict between the secondary and primary interests.

This guide provides information to prevent financial and other conflict, thereby helping to ensure both the integrity of our research and the safety of participants.

II. To whom does the guide apply?

The restrictions discussed in this guide are based on the laws that apply to NIH employees.[1] Thus, all NIH employees who are listed as investigators[2] on the front sheet of a protocol because they substantively participate in the development, conduct, or analysis of clinical research protocols (both diagnostic and therapeutic) must adhere to the rules described below. These rules also apply to NIH employees who serve on NIH Institutional Review Boards (IRBs) and Data Safety and Monitoring Boards (DSMBs). It is expected that non-employees who serve as investigators and IRB and DSMB members will review this guide and adhere to rules set out to the extent practical. These non-employees should be mindful of real and potential conflicts and discuss such conflicts with the protocol's PI.

[1] NIH employees are those NIH staff with an appointment to the federal government pursuant to, for example, Title 5, 38 or 42, or the Commission Corps, and may include some fellows. Some IPA personnel may have federal government appointments as well.

[2] Investigators are those NIH employees who occupy the following positions: Principal Investigator; Co- Principal Investigator; Associate Investigator; Medical Advisory Investigator; and Research Contacts.

III. Examples of investigator and IRB and DSMB member financial conflicts of interest

As noted when applicable, some of these examples of financial conflicts of interest are prohibited by regulation for NIH employees. We list them, however, as guidance for non-employee investigators and IRB and DSMB members who are reviewing this guide. It should be noted that in addition to his or her own financial interests and outside interests, an NIH employee's financial interests also include the financial interests of others, such as his or her spouse, dependent children, or household members. Examples of such interests are:

- Serving as a director, officer or other decision-maker for a commercial sponsor of the human subjects research (prohibited activity for NIH employees);
- Holding stock or stock options in a commercial sponsor of the human subjects research (unless below the applicable de minimis amount or held within a diversified, independently managed mutual fund);
- Receiving compensation for service as consultant or advisor to a commercial sponsor of the human subjects research (excluding expenses) (prohibited activity for NIH employees);
- Receiving honoraria from a commercial sponsor of the human subjects research (prohibited activity for NIH employees);
- Personally accepting payment from the human subjects research sponsor for non-research travel or other gifts (for NIH employees, government receipt of in-kind, research-related travel is not included and other exceptions may apply);
- Obtaining royalties or being personally named as an inventor on patents (or invention reports) for the product(s) being evaluated in the human subjects research or products that could benefit from the human subjects research (special rules apply in this case when NIH holds the patent – see Section VII below);
- Receiving payments based on the research recruitment or outcomes (prohibited activity for NIH employees);
- Having other personal or outside relationships with the commercial sponsor of the human subjects research (prohibited activity for NIH employees);
- Having financial interest above the applicable de minimis in companies with similar products known to the investigator to be competing with the product under study (prohibited activity for NIH employees); or
- Participating in an IRB or DSMB decision that has the potential to affect your spouse's employer (prohibited activity for NIH employees).

IV. Examples of non-financial real or apparent conflicts of interest for IRB and DSMB members

- Voting on a protocol when a member of the IRB is the protocol's Principal Investigator, Associate Investigator or study coordinator;

- Voting on a protocol when a member of the IRB or DSMB is a spouse, child, household member or any other individual with whom the protocol's Principal Investigator, Associate Investigator or study coordinator has a close personal relationship[3]; or

- Voting on a protocol when the protocol's Principal Investigator is the IRB member's supervisor (up the chain of command to the Clinical Director).

V. NIH's system to assist in identifying and preventing financial conflicts for investigators in clinical research

The Principal Investigator is responsible for assuring that each investigator listed on the protocol front sheet receives a copy of this guide. The guide should be distributed to any new investigators added to a protocol while the protocol is active.

a. New Protocols

At the earliest point possible, the PI is responsible for providing his or her IC Deputy Ethics Counselor (DEC) with a list of all investigators. The Protocol COI Statement (see Appendix I) or an electronic equivalent should be used to provide this information. This submission date will be noted on the form 1195.

Upon receipt of the Protocol COI Statement, the IC DEC will verify that all investigators who are employees have a form 716/717 on file and that the personal investment information on the form 716/717 is current as of the date on the Protocol COI Statement. The IC DEC will then review file copies of each PI's and AI's 716 or 717 forms that enumerate stock holdings in all organizations that are significantly affected by the NIH (referred to as "SAOs").

For each protocol, the DEC will provide the PI with an anonymous list of AIs' holdings in SAOs reported on these forms so the PI can determine if any pose a conflict of interest for the protocol in question. Any investigator who has a potential conflict will be contacted by his or her DEC to determine how to resolve any actual or apparent conflict. The employee's supervisor and/or the Clinical Director will be consulted as necessary if a conflict exists. The conflicts review will occur in parallel to the IRB submission process.

At the completion of the conflicts review, the IC DEC will return a signed copy of the Protocol COI Statement to the PI. The PI will then note the date of DEC clearance on the Form 1195 and ensure that the Protocol COI Statement is included in the protocol packet.

The DEC clearance form will become part of the protocol packet forwarded to the IRB Chair for final approval. The IRB chair may not provide final approval by signing a protocol until the completed Protocol COI Statement is included in the protocol packet.

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[3] The IRB or DSMB member determines, in his/her own opinion, whether a close personal relationship with the protocol's Principal Investigator or another member of the research team exists. If such a determination is made, the IRB or DSMB member shall disqualify him or herself from the protocol to avoid any appearance of bias.

b. Continuing Review

A COI analysis will take place at the time of continuing review using the same process as described above. The Protocol COI Statement will be used for this process. For the conflicts analysis, the addition of new investigators, any changes related to the use of commercial products or any change to an IND/IDE will be evaluated by the IC DEC.

c. Amendment

A COI analysis will take place for amendments involving the addition of investigators to a protocol, any changes related to the use of commercial products or any change to an IND/IDE. The Protocol COI Statement will be used for this process following the procedure above.

Although government-wide regulations allow NIH employees to hold de minimis amounts of publicly-traded stock without triggering conflict of interest restrictions, there may be other factors to consider with respect to stock ownership. For example, new NIH policy will require that the informed consent document signed by protocol participants contain a statement that one or more investigators own a de minimis amount of stock in the company that makes the product being tested in the protocol. Also, if a publication should result from the protocol, most journals require the authors to disclose individual financial holdings within the text of the published paper. Such disclosures could raise at least the appearance of the conflict of interest. Thus, all investigators should consider these outside factors when making personal financial investments.

VI. IRB and DSMB Clearance for COI

- Before beginning protocol review activities, the Chair asks whether any member is aware of any real or apparent conflict of interest. The response of an individual who has a conflict of interest is noted in the minutes. No IRB or DSMB may have a member participate in the initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB or DSMB.

- When the Principal Investigator or Associate Investigator is the Institute Director, or Scientific Director, the protocol will be reviewed by an IRB not affiliated with that institute.

- When the Principal Investigator is the Clinical Director (CD) it shall be the prerogative of an IRB either to review such protocols or refer them to another Institute's IRB. IRBs reviewing protocols in which their CD is the PI must have a majority of members who are not employed by the CD's Institute otherwise any alternative plan must have prior approval by the Director, CC, and the Deputy Director for Intramural Research.

VII. NIH Intellectual Property and Royalties

In some instances, NIH clinical research protocols will evaluate or potentially advance product(s) in which NIH (i.e., the government) owns patents or has received invention reports. In such cases:

- An NIH investigator may participate in the clinical trial, even if the investigator is listed on the patent or invention report and/or may receive royalty payments from the NIH for the product(s) being tested.

- When such an investigator participates in a trial, there should be full disclosure of the relationship to the IRB and to the research subjects (i.e., information should appear in the consent form) with review and approval by the IRB.

- In the case of continuing review of current protocols where NIH has an intellectual property interest in the invention, investigators should provide a new human subjects consent form or correspondence outlining the relationship, for review and approval by the IRB.

- An independent entity, such as a DSMB, must review the results of all such human subjects research.

- These relationships must be reported to the DDIR as part of the quarterly report, without reference to specific individuals, but should not impede the pursuit of the trial.

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PROTOCOL CONFLICT OF INTEREST STATEMENT

(Appendix 1)

Date of Memo: **Date Received by Ethics Office____**

Date of IRB Meeting:

Date Protocol Expires:

_ New Protocol (attach **précis)**
_ Continuing Review
_ Amendment

To: _____
I.C. Deputy Ethics Counselor

From : _____
Principal Investigator
CC:

Re: Documentation of Discussion of Conflict of Interests with P.I.

Protocol #:
Type of Protocol:
Title:
Principal Investigator's IC:
Responsible IRB :

Product(s) made by commercial entity that is the subject of the study:
Manufacturer of study product(s) (drug or device):
IND/IDE # (if applicable):
IND/IDE Holder (if applicable):
Do you know of competitors for study drug or device manufacturer(s) for purposes related to this protocol?
Key words as per 1195:

Accountable Investigator :
Medical Advisory Investigator:
Research Contact:
Lead Associate Investigator :
List of Associate Investigators:

Name of Investigator	**NIH Employee's Institute or Non-NIH Affiliation**

___No conflicts identified

___ Conflicts if identified are resolved.
Explain:

_____ _____ _____
Deputy Ethics Counselor for IC of P.I. Date Signed Date Returned to P.I.