

APPENDIX A: A GUIDE TO AVOIDING FINANCIAL AND NON-FINANCIAL CONFLICTS OR PERCEIVED CONFLICTS OF INTEREST IN CLINICAL RESEARCH AT NIH

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Avoiding financial and other conflicts of interests is important for NIH, where the trust and protection of research participants 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 conflict or perceived conflict and what to do. This guide is intended to assist those engaged in clinical research and NIH IRB members in avoiding real or perceived financial and non-financial conflicts of interest.

I. What are potential conflicts of interest for those engaged in clinical research?

All NIH employees, including clinical researchers, when engaged in their NIH duties have an interest in advancing the public's health. For clinical researchers, these interests may include obtaining knowledge that will promote health and health care, and helping to ensure the safety and health of research participants. Employees often have other personal interests that could be affected by their NIH work such as a spouse's job, stock holdings and/or outside positions at universities and professional organizations. These outside interests are generally permissible, but in some circumstances they have the potential to compromise, or appear to compromise, the judgment of employees with respect to their NIH duties. When these outside interests have the potential to compromise the integrity of an employee's NIH work, a conflict of interests occurs between the employee's interest in his or her government work and his or her outside interests. Under the government rules, this conflict must be resolved before the employee can proceed to work on his or her NIH project.

This guide provides information to identify and prevent or mitigate financial and other conflicts, 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 employees¹. These financial disclosure rules apply to those NIH employees, Special Government Employees (SGEs), and individuals at NIH under an Intergovernmental Personnel Act (IPA) agreement who have key decisional roles in protocols that may lead to financial benefit, termed "covered individuals"² and "covered protocols"³. These rules also apply to NIH employees who serve on NIH Institutional Review Boards (IRBs) and Data and Safety Monitoring Boards (DSMBs).

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 Commissioned Corps, and may include some fellows. Personnel appointed through an Intergovernmental Personnel Act (IPA) agreement may have federal government appointments as well.

² Covered individuals are personnel who have independent decisional roles in conducting a specific covered research protocol. These individuals are influential in the design, direction, or conduct of a covered research protocol, or engaged in the analysis or interpretation of data. Individuals who participate only through isolated tasks that are incidental to the research (for example, scheduling patient tests), and those individuals who support research of many protocols through the performance of routine patient care tasks are not covered individuals. Covered Individuals include the principal investigator, personnel whose resume or CV is provided to a sponsor, personnel listed on a FDA 1572 Form, and personnel engaged in human subjects research, including but not limited to individuals who obtain informed consent or who make decisions about research eligibility. Others who have decisional responsibilities that meet the definition of a covered individual, e.g. as co-investigator, research nurse, associate investigators, or an individual who interprets or analyzes research data, are also covered individuals. The PI determines which individuals are "covered individuals" under this SOP. When protocols contain sub-studies that ask a research question about a product, it is possible that only those individuals involved in decisional roles in the sub-study are "covered individuals."

It is expected that non-NIH employees⁴ who are covered individuals or IRB or DSMB members⁵ will review this guide and adhere to the rules set out. Covered individuals who are not NIH employees should be mindful of real and potential conflicts and discuss such conflicts with the protocol's PI and their home institution, as applicable. Non-federal employees must certify that they have received this guide and will comply with its tenets. Please note that the National Institutes of Health expects that all non-NIH investigators will comply with the ethics and conflict of interest policies and procedures set forth by their institution or employer.

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

As noted below, some of these examples of financial conflicts of interest are prohibited by regulation for NIH employees. We list them, however, as guidance for non-NIH employee investigators, covered individuals, 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 clinical research (prohibited activity for NIH employees);
- Holding stock or stock options in a commercial sponsor of clinical 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 clinical research (excluding expenses) (prohibited activity for NIH employees);
- Receiving honoraria from a commercial sponsor of clinical research (prohibited activity for NIH employees);

³ Covered research protocols: For purposes of SOP 21, covered research protocols include: (1) studies of investigational drugs and devices, (2) studies with a research question about a commercially available drug or device, (3) studies involving collaborations with a substantially affected organization (SAO) or other for-profit entities when the entity is receiving data or specimens from the NIH for the purpose of developing a product, or (4) studies involving a technology/product not developed in an NIH lab which is evaluating the technology/product or comparing the technology/product to another technology/product or treatment. NIH research protocols that are categorized as Teaching and Training, or Natural History studies are not covered research protocols, unless they meet the criteria listed above. Most interventional protocols will be covered protocols unless the intervention does not involve the criteria listed above (e.g. a behavioral intervention might not meet the criteria for a covered research protocol).

⁴Non-NIH employees include Adjunct Principal Investigators, Guest Researchers, Special Volunteers, contractors, Intramural Research and Cancer Research Training Awardees, and collaborators from academia and industry, and employees of other federal agencies. Note: clinical investigators who are not NIH employees, but are Special Government Employees or IPA appointees, may serve as PIs on NIH clinical protocols.

⁵The IRB or DSMB member determines, in his/her own opinion, whether a 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 a conflict of interest.

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- Personally accepting payment from the clinical 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 clinical research or products that could benefit from the clinical 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 clinical 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 the member of the IRB is the protocol's Principal Investigator, Associate Investigator or study coordinator;
- Voting on a protocol when the member of the IRB or DSMB is or has a spouse, child, household member or any other individual with whom the protocol's Principal Investigator, Associate Investigator or study coordinator has the appearance of a conflict of interest; 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).

As noted in Section II - The National Institutes of Health expects that all non-NIH investigators are in compliance with their institutional/employer's conflict of interest policies.

CLEARANCE OF NIH EMPLOYEES ONLY – PERSONAL FINANCIAL HOLDINGS

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

The Principal Investigator of a covered protocol is responsible for assuring that each covered individual receives a copy of this guide. The guide should be distributed to any new covered individual added to a protocol while the protocol is active. All NIH employees, and individuals who are not federal employees, who are covered individuals shall acknowledge receipt of this guide via a written or electronic statement. Certain NIH employees (those who are Principal Investigators (PIs), accountable investigators, medical advisory investigators, associate investigators (AIs), or other subinvestigators, such as Lead Associate Investigators) on covered protocols are required to disclose the value of all interests in Substantially Affected Organizations⁶ (SAOs) held or acquired personally or by their spouses or minor children. This is done by filing Form **717-1**, Confidential Report of

Financial Interests in Substantially Affected Organizations for Employees of the National Institutes of Health (available at <http://ethics.od.nih.gov>), and/or a *Confidential Financial Disclosure Report (Form OGE-450)*. Non-federal employees, and NIH employees who do not file an OGE-450 or 717-1 form will provide the PI with a Conflict of Interest (COI) Certification form.

New Protocols

For any covered protocol, at the earliest point possible, the PI is responsible for providing his or her IC Deputy Ethics Counselor (DEC) with a completed copy of the "Clearance of NIH Investigator Personal Financial Holdings" (*PFH Clearance*) (see Appendix 1), which lists all covered individuals. Alternatively, an electronic equivalent could be used to provide this information. If applicable, the PI also will provide copies of the signed Conflict of Interest (COI) Certification for Non-Federal Employees, or the Conflict of Interest (COI) Certification for NIH Employees Who Do Not File form 450 or 717-1.

For each protocol:

1) The DEC will verify that all covered individuals have submitted a form 450 or 717-1 or one of the two COI certification forms, if appropriate. The DEC will verify that the personal investment information on the form 450 or 717-1 is current (within 6 months) as of the date on the PFH Clearance. The IC DEC will then review file copies of the 450 or 717-1 forms that enumerate stock holdings in Substantially Affected Organizations (SAOs).

2) If SAO holdings are above the de minimis values, the DEC will provide the PI with an anonymous list of the covered individual's holdings in SAOs as reported on these forms so the PI can determine if any pose a conflict of interest for the protocol in question. Any covered individual 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 personal financial holdings review, the IC DEC will return a signed copy of the Protocol PFH Clearance to the PI. The PI will then note the date of DEC clearance on the *Protocol Application* and ensure that the Protocol PFH Clearance 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 PFH Clearance is included in the protocol packet.

⁶Substantially Affected Organization (SAO): A biotechnology or pharmaceutical company, a medical device manufacturer; or a corporation, partnership, or other enterprise or entity significantly involved, directly or through subsidiaries, in the research, development, or manufacture of biotechnological, biostatistical, pharmaceutical, or medical devices, equipment, preparations, treatments, or products (5 CFR 5501.109(b)(10)).

The PFH form may be submitted, reviewed and returned using electronic systems for protocol submission.

Continuing Review

A COI analysis will take place at the time of continuing review using the same process as described above. The Protocol PFH Clearance will be used for this process. For the conflicts analysis, the IC DEC will evaluate the addition of new covered individuals, any changes related to the use of commercial products (as part of the scientific hypothesis) or any change to an IND/IDE.

Amendment

A COI analysis will take place for amendments involving the addition of covered individuals to a protocol, any changes related to the use of commercial products (as part of the scientific hypothesis), or any addition of an IND/IDE. The Protocol PFH Clearance will be used for this process following the procedure above. If just adding a new covered individual, only that individual needs to be cleared.

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. 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 minutes will reflect which individual(s) has a real or apparent conflict of interest. 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. The Deputy Director for Intramural Research may waive this requirement.

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 voting members present at the meeting who are not employed by the CD's Institute, otherwise an alternative plan must have prior approval by the Clinical Center Director 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 will 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. This is to ensure the quality and integrity of the data collected.

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

An independent entity or individual must review the integrity/accuracy of the results/quality of data to assure the safety of human subjects and to assess whether there is a change in the risk benefit ratio or introduction of possible bias.