Intramural Research Program
Our Research Changes Lives

Management of real or apparent financial and other conflicts of interests or royalty payments for investigators conducting research being reviewed by the NIH IRB.

All investigators, whether NIH or non-NIH employees, who are conducting research on behalf of the NIH IRP, must follow the applicable laws and NIH policies that govern financial and other conflicts of interests (COI).

All NIH investigators who are working on a covered research protocol and who are either engaged in human subjects research, or involved in the statistical analysis of primary endpoint data obtained from human subjects research, and whose role has the potential to bias the research results, even if they are not otherwise engaged in human subjects research, must be cleared by the IC Deputy Ethics Counselor (DEC). This process assures that there are no individuals involved in the research who have a disqualifying financial or other COI.

In general, federal law and NIH policies do not permit any investigator to work on a protocol in which they have a disqualifying financial or other interest. However, there are 2 circumstances that arise in which a real or apparent financial COI may exist. In exceptional circumstances, the NIH Director may approve a waiver to permit participation of an individual with a financial COI in all or a portion of the research project; an agency designee may authorize participation in cases involving other sources of bias. Second, although not legally considered a financial conflict of interest, some NIH investigators may have intellectual property rights that may lead to payment of government royalties related to the research under review.

The NIH IRB may serve as the reviewing IRB for other institutions, including non-governmental institutions. These institutions have COI policies that differ from NIH, and non-NIH investigators may have financial or other COI that would not be permitted under NIH policies. At times, such conflicts require management plans to ensure the safety of human subjects and the integrity of the data. While the determination of whether there is a financial or other conflict of interest generally lies with the investigator's home institution, when the NIH IRB is the reviewing IRB, it has certain obligations that must be met.

Financial and other conflicts of interest can result in incentives that are not aligned with the best interests of human subjects or the unbiased analysis and presentation of data. The rights, welfare and safety of human subjects may be compromised when a conflicted investigators bias (whether conscious or unconscious) leads to an informed consent process that does not fairly present the risks and benefits, when eligibility requirements are interpreted in a way to allow enrollment of an ineligible subject or when causality of adverse events is not properly attributed. Overall study integrity can be undermined if the data is not analyzed in a completely unbiased manner.

Guidance issued by the Office of Human Research Protections (OHRP) advises that IRBs consider whether investigators have financial or other interests that may impact the rights and welfare of research participants. In addition, the Association for the Accreditation of Human Research Protection Programs (AAHRPP) requires that IRBs review any COI management plans to assure they are sufficient to protect human subjects.

For these reasons, the Office of Human Subjects Research Protections has instituted the following processes.

Required Disclosures to the IRB

Consistent with *Policy 102-Investigator Conflict of Interest and Government Royalties;*

1. For research being reviewed by the NIH IRB,
    a. OHSRP or the NIH IRB may request from the PIs DEC whether the NIH Director has approved the issuance of a waiver for any NIH Investigator to allow participation in the research
    b. Investigators must disclose in the NIH electronic IRB application whether they are listed as an inventor for any intellectual property that is being evaluated in the research study under review.
2. For research being reviewed by a non-NIH IRB, the COI outcome letter will be provided to the reviewing IRB.
    a. NIH Investigators may NOT disclose the issuance of a waiver outside the NIH.
    b. If an NIH investigator is entitled to receive licensing fees or royalty payments for any intellectual property being evaluated in the study, this should be disclosed to the reviewing IRB.
    c. No other financial details or disclosures should be provided to the reviewing IRB.
3. For research in which the NIH IRB is serving as a reviewing IRB for non-NIH institutions:
    a. Non-NIH investigators must inform the NIH IRB if they have been determined by their home institutional policies to have a financial conflict of interest and to provide a summary of the management plan to the IRB for review, consistent with the terms of any reliance agreement.
    b. NIH site consents must include required COI paragraph for non-NIH investigators, as appropriate.

Review Process

The OHSRP Protocol Royalty Analysis Committee (PRAC) review process is triggered when the NIH IRB is the reviewing IRB and has been informed that any of the following circumstances exist

1. the NIH Director has approved the issuance of a waiver,
2. an investigator engaged in the research is identified as an inventor on intellectual property that is being evaluated in the research,
3. a non-NIH investigator has been determined to have a COI by their home institution

OHSRP's PRAC, described below, will review and determine if additional management strategies are needed to ensure the protection of human subjects in the research. This review may happen concurrent with other review processes.

In some cases, the review may be conducted by a single individual authorized by the full committee to conduct the review such as when the IP is unlicensed, or when the value of the payments for the prior 12 months is less than $5000 or when the value of the royalty payments cannot be influenced by the outcome of the research. If the study is assessed to be particularly high risk to subjects, or the research may have a very large impact on the financial value of the IP, the PRAC will be consulted about whether committee review should be conducted.

The committee will consist of the following members:

1. Director OHSRP (PRAC Chair)
2. IRB Executive Chair
3. Director IRBO
4. Representative of the Deputy Director for Intramural Research
5. Representative of the NIH Ethics Office
6. Representative of the NIH Ethics Advisory Committee
7. Two Clinical Investigators nominated by the Medical Executive Committee
8. Representative of the Office of Technology Transfer and Development

The committee or designee will review the research study and the nature of the conflict, and consistent with 45 CFR 46.111(a)(1) to determine that risks to subjects are minimized, will consider if management strategies to mitigate any risks to human subjects are required. The committee or designee may consult with the NIH Office of Technology Transfer to obtain additional information as to the nature of the intellectual property, the nature and status of any associated patents or license arrangements (including running royalties or milestone payments), and whether any payments are being made to investigators.

When the conflicted individual is a non-NIH investigator for which the NIH IRB is the reviewing IRB, if a management plan has been provided by the investigator's home institution, the committee or its designee will review this to determine if it is sufficient or if additional measures may be needed. If it determines changes are needed to the plan, it will consult with the investigator's home institution before requiring any such changes. Management plans will be submitted to the NIH IRB for acceptance, either during initial review or as an amendment.

Appeals of any decisions related to NIH investigators will be considered by the Deputy Director for Intramural Research.

Factors to be considered when determining the need for management strategies.

This committee is responsible for determining if measures are needed to protect human subjects. The management strategies advised should be limited to measures directly involving human subjects, and the committee will consult with the Office of the General Counsel, NIH Branch and Ethics Division as needed. The responsibility for ensuring that adequate processes are in place to protect data integrity lies within the NIH Institute or Center.

Several factors can influence the need for the imposition of specific measures to manage a conflict of interest or the receipt of royalties. However, the committee should be careful not to overmanage any particular situation. Overly restricting an investigator's involvement in a study can be a disincentive to conducting research. Furthermore, the conflicted investigator may be the most knowledgeable and qualified individual to conduct aspects of the research.

In the case of government royalties, the government is required by law to make these payments. Unlike a private institution where an investigator can choose to eliminate a potential conflict by not accepting the payments, this is not an option available to NIH investigators. In addition, when technology is licensed by the NIH and government royalties are paid to the investigator, the payment information does not include the source of those payments, further distancing the investigator from the financial interest.

Single site vs multi-site: Single site research poses a greater risk that an individual investigator's actions could influence the outcome of the research. In multi-site research, as any given site enrolls only a fraction of the subjects, a single investigator's actions have less overall impact. Given this, the IRB should consider imposing management strategies for single site research.

Overall risk of the research: Management strategies should be tiered to the potential for the research to cause harm to human subjects. In a minimal risk study, such as one in which the only interaction with a human subject is the collection of a blood sample, or other non- or minimally-invasive procedures, a disclosure in the consent document may be all that is required, as it is unlikely that any harm will come to human subjects. On the other end of the spectrum, studies with investigational drugs with serious adverse effect profiles, or significant risk devices such as an implantable device, pose greater risk to subjects and may require more stringent management strategies.

Extent of the conflicted individuals' ability to directly influence the design, conduct or reporting of research. The ability to influence the outcome of the research depends on the conflicted individual's role. Management plans should consider the potential impact the individual has and be tailored appropriately.

Extent to which the research outcome can influence the financial or other interest. The likelihood that the research will influence the financial value of the conflicted individuals financial interest depends on the nature of the interest and the research study itself. For example, an investigator holds a royalty interest in a new drug and is conducting research directly evaluating the drug's safety and efficacy and the results are intended to be used to support a marketing application to the FDA. In this case, the research has a high potential to impact the value of the financial interest.

Potential Management strategies

The table below lists several possible management strategies and for what types of studies they might be considered. However, this table is not meant to imply that these measures must be used in any given situation. Each situation should be evaluated individually, and the requirements tailored appropriately.

Management strategy	Research study	Responsibility
Disclosure (if legally permissible) of the conflict in the informed consent document.	All studies	PRAC
Informed consent must be obtained by a non-conflicted investigator. If the conflicted investigator is the PI of the protocol, they may discuss the protocol with the subject and answer questions, but not obtain final documentation of consent.	Consider for greater than minimal risk studies, for single site studies	PRAC
Restrictions on the conflicted investigator from independently determining eligibility status of prospective subjects.	Consider for greater than minimal risk studies, for single site studies	PRAC
Restrictions on the conflicted investigator from adjudicating AEs/SAEs, and/or requiring a group adjudication process involving non-conflicted investigators.	Consider for greater than minimal risk studies, for studies evaluating safety/efficacy investigational drugs/devices, and/or for single site studies	PRAC

Management strategy	Research study	Responsibility
Restrictions on the conflicted investigator being independently or largely responsible for data analysis	Consider for greater than minimal risk studies Consider for studies evaluating safety/efficacy investigational drugs/devices	Institute/Center
Requirement for independent review of study data prior to publication or submission to FDA in support of a marketing application.	Consider for greater than minimal risk studies Consider for studies evaluating safety/efficacy investigational drugs/devices	Institute/Center

OHSRP PRAC staff will conduct an annual re-review of open studies with invention disclosures to ascertain whether changes have occurred that may warrant additional review by the PRAC.