

Section 32: Principal Investigators (PIs)

The Principal Investigator (PI) has ultimate responsibility for the conduct of the research trial. The duties of a PI are outlined in the [FDA form 1572](#) in section 9 entitled “Commitments.”

32.1 General Responsibilities of the PI

The PI is responsible for:

- Conducting the trial in accordance with the relevant, current protocol and only making changes to the protocol after notifying the sponsor (if applicable) and the IRB, except when a delay to notify the sponsor might compromise the safety, rights, or welfare of participants
- Conducting the trial in accordance with the investigational plan, institutional policies, and all applicable regulations
- Personally conducting or supervising the trial
- Informing trial participants that the drugs/devices are being used for investigational purposes and ensuring that the requirements relating to obtaining informed consent and IRB review are met
- Reporting to the sponsor and the IRB any adverse events (AEs) that occur in the course of the trial
- Reading and understanding the information in the investigator’s brochure, including the potential risks and side effects of the drugs/devices
- Ensuring that all associates, colleagues, and employees assisting in the conduct of the trial are informed about their obligations in meeting these commitments
- Maintaining adequate and accurate records in accordance with all regulations and requirements and making those records available for inspection
- Maintaining a record of accreditation for all laboratories used during the trial

PIs must be active staff members (non-trainees) of the DF/HCC. The PI assumes responsibility for the overall review and conduct of the research across the DF/HCC. In addition to the overall PI, a Site PI must be designated for each institution for trials conducted across the DF/HCC.

The regulations require that the IRB have a policy for responding to serious and continuing non-compliance. The IRB and the institutions take these issues very seriously. It is imperative that investigators understand their role and responsibilities.

32.2 Financial Disclosure by Clinical Investigators

Please see Section 32.3 Conflict of Interest Policy, for relevant policies and the review practices.

The DFCI IRB requires all research staff to indicate, at the time a protocol is submitted for review, if they,

their spouse or dependent children have any financial interests that might be affected by the research, or in entities whose financial interest might be affected by the research. If so, the research staff member must indicate whether the financial interest is income, equity (including ownership of stock, stock options, or any other ownership interest), or intellectual property rights. In addition, if the financial interest is income, the reporting individual must indicate whether the income is >\$0-\$10,000, >\$10,000-\$20,000 or >\$20,000. If the financial interest is equity, the reporting individual must indicate whether the equity ownership is >\$0-\$10,000, >\$10,000-\$30,000, or >\$30,000 in value and if the % ownership in the Business is >0-5% ownership or >5% ownership interest.

Potential Conflicts of Interest are reviewed as described in the next section.

32.3 CONFLICT OF INTEREST POLICY

There are two policies that the DF/HCC applies to address potential conflicts of interest of Investigators in Human Subject Research, the Harvard Faculty of Medicine Policy on Conflicts of Interest and Commitment (“HMS Policy”) and PHS Regulation 45 CFR Part 50, subpart F, “Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought” (“PHS Regulation”). These policies apply to all research involving human subjects that is subject to review by the DFCI IRB, acting on behalf of DF/HCC, regardless of primary funding source. In addition, each Investigator participating in DF/HCC research project involving human participants must abide by the Conflict of Interest policy of his/her primary institution, and when applicable, by FDA Regulation 21 CFR Part 54 “Financial Disclosure by Clinical Investigators” for investigational drug, biologic and device studies.

HMS Policy

Under the HMS Policy, any Financial Interest of the Faculty Member, his/her Family Members or Associated Entities, in a Business that owns or has licensed a Technology under study must be reported. Investigators, their Family Members, and Associated Entities may *not* have a financial interest in a business that owns or licenses (including an option to license) the technology under study unless the financial interest does not exceed specific income or equity limits. According to the HMS Policy, under exceptional circumstances the HMS Committee on Conflicts of Interest and Commitment could permit a faculty member to conduct human subject research while having a financial interest that exceeds these limits, with a management plan established to protect the patient safety and the validity of the data. In practice, such exemptions are almost never permitted.

HMS De Minimis levels

Income: The income limit is defined as **not more than \$20,000** per 12-month period, including any compensation or gift from the Business, either directly or through an agent. Excluded from this restriction is the receipt of Income that results from the institution’s supervised sponsored research or royalties under an institutional royalty-sharing plan.

Equity: This includes any ownership in the business, be it stock, stock options, or in any other form that exceeds \$30,000 in a Business that owns or has licensed the Technology under study. Excluded from this restriction is ownership of a mutual, pension, or other institutional investment fund over which the Participant does not exercise control.

When the investigator, including **Family Members** or **Associated Entities**, own **Equity** in the **Business**, additional conditions must be met, no matter what the value of the ownership. The **Equity** must be:

- Publicly traded (sold on a stock market)
- Widely held (owned in significant part by individuals who are not/have not been employed by the **Business** or **Family Members**, or by individuals who supported the **Business** before it became public)
- Acquired independently of the research (for example, it was inherited from parent(s), or the **Equity** was purchased before the investigator had, or contemplated having, a professional relationship with the **Business**)

Note: As of September 2009, the HMS Policy is under review by a Harvard faculty of medicine committee, which will make recommendations to the dean. Should these de minimis levels be reduced, the change in policy will be disseminated to the faculty and will be applicable to Investigators in human subject research at the time it takes effect at HMS.

PHS Regulation

According to the PHS Regulation, Investigators in research submitted for PHS funding must report whether or not he/she (including his/her spouse and dependent children) has a known Significant Financial Interests that would reasonably appear to be affected by the research, and/or in entities whose financial interests would reasonably appear to be affected by the research. The Institution then must make a reasonable determination as to whether the financial interest could directly and significantly affect the design, conduct or reporting of the proposed research. If a Conflict of Interest is determined to be present, the Institution may, at its discretion, require that the financial interest be reduced or eliminated, or might require a management plan. A Significant Financial Interest is defined in the regulations (included below).

Institutional Review and Oversight

Each participant (member of the study team or “Participant”) in the clinical trial must indicate in the protocol and the protocol cover sheet any **Financial Interest** in the **Business that owns or has licensed the Technology under study, or that is the study sponsor. If the Participant indicates that he/she has such a Financial Interest, he/she must indicate** what range the financial interest fall into. The absence of **Financial Interest** must be positively noted as indicated on the coversheet.

When a Financial Interest is reported that requires institutional review, the Institutional Official and Conflict of Interest Committee at the institution with which the Investigator is primarily affiliated (“Relevant IO” and “Relevant COI Committee”) will review the circumstances of the financial interest and the research and make recommendation to the DFCI IRB.

If the Participant answers as indicated, the following responses are required. If a Participant indicates that he/she has more than one relevant financial interest, each financial interest will be addressed according to the relevant algorithm.

No Financial Interest: If there is no financial interest, then no further action is required.

Income:

1. None: No further action
2. >\$0-\$10,000: Allowable by HMS Policy and PHS Regulation-
 - a. No further evaluation by the Institutional Official (IO*) is required. However, IO/COI Committee may review the circumstances if there is heightened concern, such as if the

study is unusually high risk, or at the request of the IRB. IRB informed by disclosure on the cover sheet of the protocol. Although the financial interest is allowed by HMS Policy and PHS Regulation, the IRB may determine that the financial interest is not permissible if the study is unusually high risk or if there are circumstances that they deem make the Conflict of Interest impermissible. In addition, the IRB must determine whether or not patients need to be informed of this financial interest in the consent document.

3. >\$10,000-\$20,000: Allowable by HMS Policy, requires review by PHS Regulation-
 - a. Relevant IO and COI Committee will review the circumstances, according to the policies of the institution with which the Participant is primarily affiliated (“Relevant Institution”), and reasonably determine whether the financial interest could directly and significantly affect the design, conduct or reporting of the research
 - i. If No: Relevant IO/COI Committee will provide a report to the IRB outlining their analysis, and recommend that the Investigator be permitted to participate in the research, subject to IRB approval
 - ii. If Yes: the Relevant IO/COI Committee will consider options with the Investigator. Possible outcomes:
 1. Financial Interest can be reduced/eliminated-IO/COI Committee will recommend that the Investigator be permitted to Participate in the research-according the new income range
 2. Conflict of Interest cannot be reduced/eliminated- Relevant IO/COI Committee will determine whether the COI can be managed based upon an analysis of the risks/benefits of the Investigators participation, whether there are compelling circumstances for permitting the investigators participation, whether there are strategies that could mitigate the risk, and other relevant factors. The IO will provide to the IRB a report that outlines the COI review, conclusions and recommendations:
 - a. IO recommends approval with management plan: IRB may, at its sole discretion:
 - i. accept the assessment/recommendation,
 - ii. require more stringent management or
 - iii. may conclude that the COI is not permissible-
 - b. IO recommends that the COI is not permissible-the Investigator is not permitted to Participate.
4. >\$20,000: The COI is not permissible. If the Investigator appeals this decision, arguing that their participation is essential for the study, then the COI must be approved by the Relevant Institution’s IO and COI Committee and the Relevant Harvard Committee on Conflicts of Interest and Committee.

Equity

1. None: No further Action
2. \$>0-10,000 AND the equity is widely held, publicly traded and acquired independently of the

research, AND the equity interest does not exceed 5% of the overall value of the Business

- a. Allowable according to HMS Policy and PHS Regulation. IO and COI Committee will review only if there are unusual circumstances that prompt concern about the COI, such as an unusually high risk study, or at the request of the IRB.
3. $\$>10,000$ - $\$30,000$ AND the equity is widely held, publicly traded and acquired independently of the research
 - a. See the process for Income that $>\$10,000$ - $\$20,000$ (above)
 4. $>5\%$ ownership ownership in the Business AND condition 5 does not apply.
 - a. See the process for Income that $10,000$ - $\$20,000$ (above)
 5. $>\$30,000$ OR the equity is not widely held and publicly traded OR the equity was acquired such that it might appear to be related to the research
 - a. The COI is not permissible. If the Investigator appeals this decision, arguing that their participation is essential for the study, then the COI must be approved by the Relevant Institution's IO and COI Committee and the Relevant Harvard Committee on Conflicts of Interest and Committee.

Intellectual Property

1. None: No action is required
2. See the process for Income $>\$10,000$ - $\$20,000$ (#3)

Role of the IRB

Whenever IO/COI Committee review is required, the DFCI IRB will receive a memo from the appropriate IO indicating the evaluation of the conflict of interest at all required levels of approval, with any requirements for management of the conflict that are conditions of the approval. The PI will include the management plan and the approval memo with the protocol, for consideration/concurrence by the IRB. If the Financial Interest exceeds the de minimis levels set by HMS Policy, the HMS Standing Committee on Conflict of Interest also must have approved this management plan as appropriate and adequate for assuring the integrity of the study and safeguarding the welfare of the human subjects of the study.

The IRB will then determine whether it concurs with the recommended assessment of the conflict, and the appropriateness of the management plan to assure objective oversight of the clinical trial. The IRB may concur with the recommendations, or may choose not to accept the approval and management plan, instead determining that the financial interest could jeopardize the objectivity of the study.

If the IRB approves the plan for management of the conflict, then the IRB should determine what information should be disclosed to the patient and determine the appropriate language for disclosure of this financial interest to study subjects in the consent document.

If the study team includes an investigator with a potential conflict of interest who is not the PI, the protocol

may be approved without the participation of that study team member (unless that individual is critical to the performance of the study). If the protocol has been submitted before the conflict of interest review process has been completed, the investigator may not participate in the study until all required levels of review have been completed and any plan for management and disclosure of the conflict receives concurrence by the IRB. Upon completion of the appropriate levels of review, with concurrence of the IRB, the investigator may be added to the protocol via an amendment.

If an individual other than the PI is not permitted to participate in the clinical trial, he or she still can provide assistance for the clinical trial if he or she is purely advisory, with no direct access to the data (either control over its collection or analysis) or to the individuals who are study subjects, and is not in a position to influence the study's results or to have privileged information as to the outcome of the study.

If the PI has a financial interest that is not acceptable to the IRB for any reason, the trial cannot be approved until the financial interest is:

1. Reduced or eliminated;
2. A more stringent management plan is submitted; or
3. Alternatively, another PI is named.

Definitions

Associated Entities: Trusts, organizations, or enterprises over which you or a family member exercise(s) control (e.g. revocable trusts, trusts for the benefit of your child(ren), membership in an investment club or a venture capital group).

Exclusion: The University and any affiliated hospital (e.g., - if the business sponsoring the trial provides funds to the DFCI/HCC or an affiliate to support a portion of your salary, that income is not considered a financial interest in the Business)

Business: Any corporation, partnership, sole proprietorship, firm, franchise, association, organization, holding company, joint stock company, receivership, business or real estate trust, or any other legal entity organized for profit or charitable purposes, but excluding the University, any affiliated Hospital, any Private Medical Practice, or any other entity controlled by, controlling, or under common control with the University or an affiliated Hospital.

Faculty Member: Any person possessing either a full- or part-time academic or fellowship appointment in the Faculty of Medicine.

Family Members: Includes spouse, minor children, other persons living in the same household,

Financial interests (HMS) include:

- Ownership of Equity (such as stock, stock options, or other mechanisms of ownership; and
- Income, including monetary or non-monetary forms of compensation or gift(s) that you have or expect to receive from the business or an agent of the business. Non-monetary forms of compensation include:
 - Allowance/forbearance/forgiveness (such as when the business reduces the price of an item you plan to buy, or delays collection or chooses not to collect on a debt that you owe.

- Interest in property,
- Dividends
- Royalty derived from licensing of the Technology,
- Rent
- Capital gain
- Any other form of compensation

Institutional Official: The senior official at each research institution who has the responsibility for assuring institutional compliance with applicable federal policies, rules and regulations.

Investigator: The principal investigator and any other person who is responsible for the design, conduct or reporting of the proposed research. For the purposes of the requirements of this section, "Investigator" includes the Investigator's spouse and dependent children.

Participant: An individual who is participating in the proposed research

Relevant Institution: The institution at which the disclosing Investigator or Participant has his/her primary affiliation.

Technology: A drug, compound, device, diagnostic, or procedure intended for use in health care or health care delivery.

Significant Financial Interest (PHS): A Significant Financial Interest is means anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees for honoraria); equity interests (e.g., stocks, stock options or other ownership interests); and intellectual property rights (e.g., patents, copyrights and royalties from such rights). The term does not include:

- (1) Salary, royalties, or other remuneration from the applicant institution;
- (2) Any ownership interests in the institution, if the institution is an applicant under the SBIR Program;
- (3) Income from seminars, lectures, or teaching engagements sponsored by public or nonprofit entities;
- (4) Income from service on advisory committees or review panels for public or nonprofit entities;
- (5) An equity interest that when aggregated for the Investigator and the Investigator's spouse and dependent children, meets both of the following tests: Does not exceed \$10,000 in value as determined through reference to public prices or other reasonable measures of fair market value, and does not represent more than a five percent ownership interest in any single entity; or
- (6) Salary, royalties or other payments that when aggregated for the Investigator and the Investigator's spouse and dependent children over the next twelve months, are not expected to exceed \$10,000.

Sponsored Research: Research, training and instructional projects involving funds, materials, or other compensation from outside sources under agreements that contain any of the following:

1. The agreement binds the University or Hospital to a line of scholarly or scientific inquiry specified to a substantial level of detail. Such specificity may be indicated by a plan, by the stipulation of requirements for orderly testing or validation of particular approaches, or by the designation of performance targets.
2. A line-item budget is involved. A line-item budget details expenses by activity, function or project period. The designation of overhead (or indirect costs) qualifies a budget as "line item".

3. Financial reports are required.
4. The award is subject to external audit.
5. Unexpended funds must be returned to the sponsor at the conclusion of the project.
6. The agreement provides for the disposition of either tangible or intangible properties that may result from the activity. Tangible properties include equipment, records, technical reports, theses or dissertations. Intangible properties include rights in data, copyrights or inventions.