Conflicts of Interest: Clinical Research

Policy

1. Investigator Conflicts of Interest

All Children's Hospital investigators are required to disclose to Harvard Medical School (HMS), on an annul basis, any potential conflicts of interest. All investigators are required to adhere to HMS guidelines for managing or eliminating specified categories of conflicts of interest.

In addition, to fulfill its obligations, the Committee on Clinical Investigation (CCI) must address the impact of the investigator's financial interests and other relationships on human subject protection. In many cases, such interests and relationships will be barred or managed independently of CCI review through institutional policies of Children's Hospital or Harvard Medical School. However, in certain situations, regulations or other standards that govern human subject protection may treat a financial interest or relationship as potentially affecting human subjects, even though Children's Hospital and HMS institutional policies do not prohibit it.

For example, compensation for serving as a company consultant to design a protocol, particularly where company payments to the investigator will depend on the outcome of the clinical research, raises special concerns for the protection of human subjects. Those concerns require CCI attention even though such consulting may be permitted under Harvard Medical School conflict of interest guidelines.

Similarly, from time to time, the CCI reviews protocols in which an investigator wishes to test, in children, a device the investigator has invented. In some of these cases the device is not licensed to any company, the investigator owns all or some of the patent rights, and the investigator wishes to collect data that might ultimately support licensing and development. This does not violate Harvard Medical School guidelines, which are instead directed to regulating the financial and equity relationships between the investigator and a company that is sponsoring research or to which the device is licensed or "contractually committed." Nonetheless, this is an issue for CCI review, since the design, conduct, and results of the research protocol, and its effect on children, are intertwined with the investigator's interest in developing and licensing the invention, its regulatory approval, and (if the results of the trial are favorable) the financial terms a company would offer the investigator to license his or her patent rights.
Consistently, the Food and Drug Administration regulations list both types of interest described above -- investigators' intellectual property interests, and payments dependent on research outcome -- as conflicts of interest, and require that they be disclosed and managed. Recent draft guidance by the federal Office of Human Research Protections also lists these interests as among those that IRBs should understand, evaluate, and manage in connection with review and approval of a protocol.

In the interests of protecting human subjects, the Committee on Clinical Investigation requires that certain steps be taken to address such potential conflicts of interest in clinical research.

As part of the current protocol application, an investigator must submit a conflict of interest disclosure. As most recently revised, that form now requires the investigator to disclose financial relationships or investment interests in a research sponsor. It also requires disclosure of any intellectual property interest in technology that is the subject of the research (whether or not the technology is licensed), certain positions of responsibility with the sponsor, and certain other interests that could affect the research.

The CCI anticipates that an investigator's disclosures on the disclosure form will generally be sufficient for the CCI to conduct its review without further inquiries, and that investigator conflicts of interest may then be addressed or managed concurrently with the CCI's review of the rest of the protocol application.

When necessary, the Chair of the CCI or the Director of Clinical Research Compliance (in consultation with CCI members and other clinicians, where appropriate), will request the Vice President of Research Administration and/or the Office of General Counsel to make further inquiries. Responsive details will be provided to the Chair of the CCI and the Director of Clinical Research Compliance for distillation or discussion with the CCI as necessary. The sensitive nature of such information will be emphasized to all those who review the material.

The Vice President of Research Administration in collaboration with General Counsel will resolve any issues raised by Harvard Medical School or other institutional conflict of interest policies not subject to CCI jurisdiction.

It is not the purview of the CCI to reinterpret or second-guess institutional conflict of interest policies or their implementation. Rather its function is to ensure that subjects and patients, the integrity of IRB review, and the conduct of a trial are not jeopardized by an unidentified and unmanaged conflict of interest. **The CCI will therefore concentrate its efforts on the elimination and management of those aspects of any conflict of interest that may reasonably affect human subject protection.**

As proposed in these guidelines, the sequence of steps to be taken by the CCI to address a conflict of interest is as follows:

a. Where the investigator, as an interested party, is also the primary source of information contained in the protocol (for example, concerning the risks and benefits to subjects of a drug or device to be tested) and in other circumstances as appropriate**, the CCI may require that independent scientific review verify the investigator's representations of risks and benefits, assess the impact of the research design on subject burdens and benefits, and identify any critical points in the protocol in which the conflict of interest, if acted upon, could have a material adverse impact on the clinical care of the subject.** The precise form of scientific review may vary. The independent review may occur as part of the departmental review, if the reviewers are appropriately aware of the nature of the conflict, or it may occur in other ways, including referral to the clinical research support office.

b. Where the investigator, as an interested party, also has significant clinical involvement in the care of subjects under the protocol**, the CCI may require that an independent data safety monitoring process be established for reviewing adverse events, validating the application of inclusion and exclusion criteria, performing interim analyses of the integrity of the data, and assessing any potential effects on the clinical care of subjects.** In this context, or for purposes of later reporting on continuing review, the CCI may consider requiring the collection of additional data that would document whether a conflict of interest has had any effect on subjects or the research.

c. **Where applicable, the informed consent must disclose that the investigator is the inventor of or has an interest in a related patent, that the investigator and /or Children's Hospital, as applicable, may receive financial benefits from development of the invented technology, and that the financial benefit may depend on the outcome of the trial.**
The following language is recommended for cases in which an investigator has an intellectual property interest:

> *As [an inventor of the technology], Dr. Z has a financial interest in _____ technology that is used in this research study. In the future it is possible that this technology will be sold commercially, and that the results of this trial will be important in securing government approval or contracting with a business to manufacture or develop the technology. If this were to occur, Children's Hospital and/or the investigator might receive financial benefits in the form of royalties or other compensation. As in all research studies, the Hospital has taken steps designed to ensure that this potential for financial gain does not endanger research subjects, or undercut the validity and integrity of the information learned by this research.*

In other cases, the CCI may require the informed consent to state the general nature of the interest.

d. **The CCI may require that someone other than an investigator who has a financial relationship, intellectual property interest, or investment interest, serve as the principal investigator (PI), perform certain of the functions otherwise designated for the investigator** (such as enrollment), or engage in supplementary oversight roles, particularly where subject safety would otherwise depend solely on clinical judgments made by an investigator with a conflict of interest.

e. In treatment protocols where the risks are significant and medical circumstances warrant, **the CCI may request that the investigator, the sponsor, or the department provide a mechanism for the ongoing monitoring of the clinical care of the subjects against the effects of any potential conflict of interest, through peer reviewed or other concurrent clinical processes not triggered simply by reported adverse events**, and may condition approval on implementation of such a process as approved by the pertinent Chief. This may take the form of an enhanced data safety monitoring plan, which includes broader review of clinical data pertinent to risks; or, where the conflict may raise or appear to raise significant questions about whether clinical care of subjects may be subordinated to research objectives to the detriment of patients, the CCI may condition its approval on periodic reporting of the results, or sufficiently concurrent departmental or other clinical review.

f. As part of the CCI deliberations, the committee will consider the particular protocol, associated risks, and the potential for risks and benefits, and determine whether any or all of the above mentioned safeguards, or any others appropriate under the particular circumstances, should be required as part of the approval process**. The CCI may, for example, consider any other remedies it would ordinarily have available, such as conditioning approval on a process to manage or eliminate other effects of a conflict, requiring consent monitoring, or requesting information about how sponsors or their agents will mitigate or monitor for risks presented.**

This protocol has been (1) approved for submission to the Committee on Clinical Investigation, and (2) **the PI has completed and submitted a Research Disclosure Form to me that I have reviewed and determined that no actual or potential conflict of interest exists.**

_____ _____
Signature of department Chairperson/Division Chief Date

2. Definitions of Terms used in Financial Disclosure Forms

Protocol is defined as the protocol submitted with the disclosure form and includes the study to be conducted under the protocol.

You is defined to include the investigator and members of his or her immediate family (i.e., spouse, children, persons with whom he or she maintains living arrangements that approximate a family relationship).

Person affiliated with is defined to include all personnel who will work on research under the protocol and members of their immediate families.

Proprietary interest is defined to include inventions, discoveries, patents, copyrights, and licenses. Investigators are asked to include these interests even if they are assigned to someone else (e.g., an academic employer; subject to a royalty-sharing policy). Such interests should also be included whether they are licensed or unlicensed, and whether their ownership is direct or indirect (e.g., through a development partnership or small corporation).

The form asks about **investments, financial relationships, advisory roles, and appointments**. While these are not defined, they should be understood broadly, and in a "common sense" way.

For example, questions that ask about investments are seeking information about stocks, options, and any kind of security in which the investigator has a direct or indirect interest. **Investigators can exclude only publicly traded mutual funds.** Similarly, questions about financial relationships are directed towards any arrangement under which the investigator receives any form of compensation.

3. Procedures when the Hospital owns Equity

Children's Hospital will not generally participate in clinical trials of a test article sponsored by a licensee in which the Hospital holds license-related equity except in extraordinary situations, as demonstrated by the presence of *all* of the following circumstances: (1) there is no other venue that is appropriate for the study, or there are other compelling reasons why Children's Hospital must be a possible venue, such as ensuring access for vulnerable or affected populations; (2) the test article, whether a drug or device, is of significant potential benefit for the public or Hospital patients; (3) there is independent verification and monitoring of all significant aspects of the study relevant to human subject protection and scientific integrity, including protocol design, description of risks and benefits, implementation of exclusion and inclusion criteria, securing informed consent, criteria and procedures for subject withdrawal, reporting and addressing adverse events, maintaining research subjects' awareness of their rights, and reporting of data; and (4) the Hospital Institutional Review Board, in its sole discretion, has approved the study, and whatever additional conditions the Hospital Institutional Review Board has imposed are satisfied.

In deciding whether to participate in a clinical trial sponsored by a company in which Children's Hospital owns such licensee equity, the Committee on Clinical Investigation will independently evaluate whether the criteria above have been met; the requirements and standards of regulatory and accrediting bodies, and its own policies; the adequacy of the Hospital's and the clinical department's steps to ensure that impacts of a potential conflict have been and will be effectively mitigated; the conflict's impact on the validity and integrity of the data generated from the clinical trial, to the extent such data contributes to the potential benefit of the study; how to implement full disclosure of the Hospital's equity interest to subject patients and others; and how to ensure that there is no inappropriate preferential access to patient populations for companies in which the Hospital owns equity.

Under no circumstances may any clinical trial be overseen solely by an inventor of a test article that is the subject of the trial. Except in extraordinary circumstances in which the inventor's involvement is necessary to assure the safety of subjects because of the inventor's unique knowledge of a device or other test article, an inventor should not be the principal investigator in the clinical trial concerning that test article, nor should the principal investigator be directly or indirectly supervised by an inventor.

It is expected that confirmatory clinical trials (typically Phase II and Phase III studies) will be conducted as multi-center studies and directed by principal investigators who have no affiliation with the hospital.

> ***Informed Consent Statement if Children's Hospital Owns Equity****:*
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> *Children's Hospital licenses certain of its research discoveries to companies for research and/or commercial development. From time to time, Children's Hospital receives equity, either as capital stock or as options to buy capital stock, as partial consideration for a license. In keeping with Children's Hospital policy, you are advised that Children' s Hospital has equity in the company that is sponsoring this research and may gain financial (monetary) benefits if the drug/device/technology being studied in this trial proves to be of benefit. As in all research studies, the Hospital confirms that it has taken, and will continue to take, all necessary steps to ensure research subject safety, and the validity and integrity of the information obtained by this research.*

4. IRB Member Conflicts of Interest

As part of new member orientation, all new members are informed about the policy on conflicts of interest. The members are informed that any IRB member, voting or nonvoting, with a conflict of interest in a study, must leave the room during the final discussion and vote on the protocol. A member with a conflict may be asked questions about the content of the protocol, and issues concerning the study, but must not be present beyond the questions and answers, and, other than to provide information, must not seek, inside or outside the meeting, to influence or affect the voting of no conflicted members. Any individual member with a conflict of interest must leave the room for the final discussion and vote. The minutes must document the fact that the member left the meeting room during the final discussion and vote because of a conflict of interest. Members are expected to advise the Director of Clinical Research Compliance if they are assigned a protocol, continuing review or amendment as a reviewer so that the protocol may be reassigned. Members are also expected to notify the Chair during a meeting if they have a conflict of interest for an initial review, continuing review, modification, adverse event, unanticipated problem or review of non-compliance.

A conflict of interest for an IRB member is defined to include the member and his or her immediate family (i.e., spouse, children, persons with whom he or she maintains living arrangements that approximate a family relationship).

Conflicts include

- Service as an investigator, co investigator, or consultant to the study before the IRB;
- Financial relationships or investment interests in the study's commercial sponsor that would trigger a disclosure under Harvard Medical School guidelines
- Any pending or anticipated negotiation or agreement with the same commercial sponsor for clinical research, consulting services, speeches, or any other matter; and current receipt of a substantial portion of their own research monies (greater than 20%) from the same commercial sponsor.
- Ownership interest (equity or stock options) of $10,000 or greater value when aggregated for the immediate family and when referenced to publicly traded prices or other measure of fair market value.
- Ownership interest (equity or stock options) whose value when aggregated for the immediate family represented 5% or more interest in any one single entity.
- Compensation of $10,000 or more in the past year when aggregated for the immediate family.
- Compensation of any amount when the value of the interest would be affected by the outcome of the research.
- Proprietary interest related to the research of any value including, but not limited to, a patent, trademark, copyright or licensing agreement.

- Board or executive relationship related to the research, regardless of compensation

Document Attributes

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Author	**Susan Kornetsky**	**Dates Reviewed/ Revised**	04/01/05, 6/20/05 07/17/07 02/22/08
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Approved	Susan Kornetsky Director of Clinical Research Compliance Carleen Brunelli, MBA, PhD Vice President for Research Administration		