Potential Bias and Risk to Subjects Related to Conflict of Interest

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Federal agencies, including the VA, have recognized the need to insure that clinical trials, particularly those involved with determining the safety and efficacy of drugs or treatments, are free from any bias related to the financial interests of the institution or the investigators. In addition, potential human research subjects need to be confident that conflicts are being eliminated when possible and effectively managed when they cannot be eliminated. A critical component of Federal policies now in place or under development, is a need for education and training activities concerned with financial conflict of interest. The material presented herein is meant to help fulfill that need.

Recent History
In September, 1999, a relatively fit 18-year-old male volunteer with an inherited enzyme-deficiency, died 4 days after doctors at the University of Pennsylvania injected a genetically altered virus into his liver. This was the first case of a patient in a gene therapy trial to die of the therapy itself. The subject was injected with a massive dose of the vector in an attempt to get sufficient functioning genes into his liver. Within hours, his temperature increased to over 104 degrees (F). On the second day, he was put on dialysis and then a ventilator. His lungs filled with fluid and, when it became impossible to oxygenate his blood, he died. On post-mortem examination, traces of the vector were found in multiple tissues outside the target organ. Only 1% of the transferred genes reached the target cells in the liver. In fact, none of the patients in the trial showed significant gene expression.

The unexpected death triggered a flood of publicity and extensive investigations by officials of the university as well as the FDA and NIH. Congressional hearings on the safety of gene therapy were announced. The FDA stopped all seven clinical trials run by Penn’s Institute for Human Gene Therapy. The university decreed that the institute could no longer conduct any clinical trials, but must focus on basic science and animal studies.

The FDA report on the death uncovered 18 problems with the clinical study. It found, for example, that none of the physicians had filled out volunteer eligibility forms in advance. Undated forms were completed only after the death of the volunteer. It also found that the consent process for 9 of the 18 patients was not adequately documented, that the FDA was not promptly informed of the deaths of two monkeys in a similarly designed experiment and that standard operating procedures had not been developed for the clinical trials.

The findings suggest that the clinical trials may have been started too soon and allowed to proceed too rapidly. Why might this have happened? Could there have been a financial incentive? Further investigation revealed that both the university and the director of the institute had an equity stake in a company that supplied reagents for the clinical trial in question. An outside panel established to investigate the incident recommended, among other things, that Penn review its policies on conflict of

Jesse Gelsinger, the first case of a patient in a gene therapy trial to die of the therapy itself.
interest, noting that "equity positions by an investigator and/or university may be ill-advised" because of the perception of a conflict of interest, whether or not it is real. In response, the American Society of Gene Therapy and the American Society of Human Genetics both asked members to avoid holding equity in companies that sponsor clinical trials they oversee.

In situations where professional judgment concerning a primary interest tends to be unduly influenced by a secondary interest, a conflict of interest exists. Conflicts of interest in research are nearly universal and unavoidable. Whenever academic promotions and grant renewals are contingent on the demonstrated scientific productivity, a conflict of interest exists. So all investigators need to be able to identify conflicts of interest and deal with them appropriately.
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Conflicts of interest are not always financial in nature. When a physician enrolls a patient in a research study, for example, a potential conflict occurs in the doctor-patient relationship. The physician's primary interest in the patient is now in conflict with the secondary interest in obtaining useful scientific data. The physician's focus on the general wellbeing of the patient may now become focused on that aspect of the patient's condition specifically under study. The treatments offered to the patient become experimental rather than conventional and may be less effective and more risky.

The focus of the information presented here is financial conflict of interest, one potential source of bias in clinical studies.

Reality versus Perception
Evaluating the reality of undue influence in clinical studies is extremely difficult. The rules dealing with conflict of interest therefore focus on the perception of conflict of interest. A perceived conflict of interest, whether or not it does exist, can as easily serve to undermine the public trust and thwart the acceptance of a medical treatment that may be, in fact, both safe and effective.

An effective strategy in tempering the appearance of conflict of interest is to increase the researcher's and the public's awareness of the potential for bias. Several factors are critical in this regard:

- the openness of the investigator in disclosing potential conflicts,
- the amount of oversight incorporated into the study design,
- the value of the financial arrangement.

Each of these factors will be considered in more detail.

Open Disclosure
Dr. Jackson has been instrumental in the development of a new drug for treating heart disease and will serve as the principal investigator for the clinical trials. Let's assume the drug, in fact, is both safe and effective. Dr. Jackson owns a considerable amount of stock in the pharmaceutical company that holds the rights for the drug. Assume his stock ownership, in fact, will not have any influence on his participation in the study. Both assumptions presented above need to be demonstrated. It will likely be easier to demonstrate that the drug is effective than that Dr. Jackson's work has not been influenced by a conflict of interest. So it becomes the perception of conflict of interest that needs to be dealt with.

Consider the following scenarios:

Scenario 1: Dr. Jackson fails to disclose his stock ownership. A reporter working on a story related to the new drug inadvertently discovers the financial interest. In response to the reporter's concerns, Dr. Johnson states that his stock holdings had no influence on his work and that as a professional, his motives should not be challenged. He defends non-disclosure on the grounds that his financial affairs should not be a matter of public record.
Scenario 2: Dr. Jackson makes a full disclosure of his financial interests in the company in advance of his participation in the clinical trials, making sure the sponsors are fully informed.

Scenario 3: Dr. Jackson makes a full disclosure of his financial interests in the company and details specific procedures that will be followed to minimize any risk of bias in the outcome of the trials. He indicates, for example, that he will not participate in the selection of patients to be included in the study.

In which of the three scenarios presented above would you perceive that biased results related to a financial conflict of interest would be least likely to occur? The scenarios presented are meant to illustrate the point that the public acceptance of the investigator's claims concerning the safety and efficacy of the drug will be directly related to the openness of the investigator concerning his or her financial interest.

**Independent Oversight**

The more opportunities for participation by co-investigators with no conflict of interest, the less likely the chance a financial interest will unduly affect the outcome of the study. As an example, the decision of an investigator with a financial interest to assign the duties of subject selection to a co-investigator helps to minimize not only the perception of conflict of interest, but also the possibility of obtaining biased results.

The more possibilities for scrutiny from persons not involved in the research, the less likely the chance a financial interest will unduly affect the outcome of the study. Research performed in an academic medical setting falls under the scrutiny of the Institutional Review Board (IRB) and colleagues in the institution. Financial arrangements are subject to institution rules limiting, for example, the acceptance of gifts. Similarly, government sponsored research involves public funds with regulations aimed at maintaining the public trust. In contrast, a private clinician under contract to a pharmaceutical company financed with private funds is subject to considerably less oversight.

**Financial Value**

An important consideration used to evaluate the potential inadequacy of a study due to conflict of interest is the value of the financial interest. The public will reason that the greater the value, the greater is the temptation to bias the results so as not to jeopardize the financial gain. There is a difference between being treated to an occasional free lunch and having unlimited access to a vacation home owned by a pharmaceutical company. In order to maintain the public trust, it may become necessary to forgo some of the financial perks offered by the sponsor.

Defining significant financial value is, of course, arbitrary and somewhat relative. To help provide some guidance in determining financial value, a summary of both the current FDA and PHS policies follows. In comparing the policies, it is apparent that there is, at present, no uniform standard.
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Investigator Responsibilities
Clinical investigators need to consider the potential effect that having a financial relationship of any kind with a sponsor of a study might have on his or her conduct of a clinical trial or interactions with research subjects. All aspects and types of relationships need to be considered, including clear-cut issues such as financial incentives to less obvious ones such a non-monetary inducements to investigators or their families. Relationships that lead an investigator to prefer one outcome to another may influence an investigator's judgment and behavior:

- The consent discussion may subtly minimize the presentation of risks or overstate the benefits.
- The willingness to report adverse reactions possibly related to the study may be diminished.
- Data analysis or interpretation may be biased.

Any agreements between investigators and sponsors should be fully disclosed by the investigator and reviewed by the appropriate institutional committees, including the Institutional Review Board. It is desirable to avoid conflicts of interest whenever possible. But if a potential conflict cannot be eliminated, the disclosure should include strategies to be implemented to manage or reduce the conflict.

Disclosure should be made to the sponsor, the appropriate Federal agencies, the institution, appropriate institutional committees (including the IRB) as well as the human studies participants.

Clinical investigators should participate in educational and training programs concerned with financial conflict of interest issues including those of their institution. This tutorial complies with that requirement.

IRB Responsibilities
The IRB should have clear procedures for recusal of IRB members, including the Chair, from deliberating or voting on protocols for which there is a potential or actual financial conflict of interest. The Chair should ask IRB members if they have any potential financial conflict of interest related to any of the protocols that the IRB is about to consider. The minutes should reflect such recusals as they occur during the meetings.

IRB members and staff should participate in education and training activities related to financial conflict of interest. This tutorial complies with that requirement.

The IRB Standard Operating Procedures manual should contain the institutional/IRB policies related to conflict of interest.

In evaluating protocols, particularly those for which a potential conflict of interest has been identified, the IRB should consider:
the source of funding and funding arrangements for the protocol,
the appropriateness of modifications made in the protocol and consent procedures to reduce or manage conflict of interest in situations where the conflict can't be eliminated,
the extent to which the conflict of interest is disclosed to the study participants (in the consent document, for example),
the prudence of placing limits on the investigator's role in certain aspects of the study including trial design and monitoring, obtaining informed consent, reporting of adverse events or data analysis,
any institutional conflict of interest related to the institutions financial relationship with a sponsor and how that might be addressed.
IRB and R&D Committee Members
The following procedures have been established for recusal of its IRB and R&D Committee members, including the Chairs, from deliberating or voting on protocols sponsored by a non-governmental entity for which they have a potential or actual financial conflict of interest:

- IRB or R&D Committee members will not serve as primary or secondary reviewers of protocols sponsored by entities for which they have declared a financial interest. Should they receive such a protocol, they will notify the IRB Coordinator.
- Prior to deliberations of a submitted protocol at a convened committee meeting, the Chair will ask members if they have a financial conflict of interest with the protocol sponsor.
- Members identifying themselves as having a financial conflict of interest with the sponsor of a submitted protocol:
  o will be allowed to participate in discussions of the protocol, having advised the committee of their potential or actual conflict of interest,
  o will recuse themselves from final discussion and voting on the protocol.

Human Studies Investigators
A Research Conflict of Interest Officer has been appointed to deal with financial conflict issues at this medical center. The COI officer will disclose potential conflict of interest by human studies investigators and co-investigators to the appropriate reviewing committees.

By local policy, the term “investigator” includes principal investigator, co-principal investigator, investigator (including a collaborator who has a VA appointment), study chair or site principal investigator (herein referred to as “Investigators”).

For each human studies research proposal performed at this medical center, which has been or will be funded in whole or in part, through a contract or grant with a non-governmental entity for which a conflict of interest has been disclosed, the Committee will:

- Receive disclosures of financial conflict of interest between investigators and/or co-investigators and the sponsor of the proposal. (Disclosures will be provided by the investigator at the time of protocol submission. A Research Financial Conflict of Interest Statement form is used for disclosure.)
- Review steps taken by the investigator(s) to eliminate, reduce or manage conflict of interest in clinical studies whose purpose is to evaluate the safety or effectiveness of a drug, medical device or treatment. The investigator proposes steps to be taken by submitting a Research Financial Conflict of Interest Supplement form.
• Advise the IRB of any potential financial conflict of interest between investigators and/or co-investigators and the sponsor of the proposal and steps recommended for eliminating, reducing or managing the conflict.
• Verify that disclosure of potential financial conflict of interest, and steps taken to eliminate, reduce or manage the conflict, have been made by the investigator to the sponsor of the study.

The convened IRB has the final authority to decide whether the interest and its management, if any, allows the research to be approved or to specify other measures to be taken to manage a financial conflict.

Local Criteria for Conflict of Interest
As defined by local policy, significant real or potential financial conflicts of interest include:

a. INCOME AND COMPENSATION
   An investigator, investigator’s spouse, dependent child or general partner receiving income or other compensation (including non-Federal salary, consulting fees, honoraria, gifts, and in-kind compensation) from an entity (including the university affiliate) whose financial interests could be affected by the study.

b. BUSINESS RELATIONSHIPS.
   – Current Relationships: An investigator, investigator’s spouse or dependent child, general partner or parent serving, or seeking to serve, as officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee (paid or unpaid) with any entity (other than the Federal Government, but including the university affiliate) whose financial interest could be affected by the study.
   – Covered Relationships: A study affecting the financial interest of the investigator, investigator’s spouse, close relative, household member or general partner.
   – Relationships in the Past Year: An investigator who, within the last year, served as an officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee for any entity whose financial interest could be affected by the study.
   – Business Arrangement or Agreements: An investigator seeking, negotiating for, or having, any business arrangement or agreement, such as a future employment agreement, re-employment rights, consultant agreement, pending severance arrangement or retirement plan, with any entity whose financial interest could be affected by the study.

c. INTELLECTUAL PROPERTY.
   With respect to intellectual property that could be affected by the study, an investigator, investigator’s spouse, dependent child, general partner, or outside employer who is:
   (i) listed as the inventor on an invention disclosure or a patent application;
   (ii) the owner of any intellectual property;
   (iii) the holder of a license of a patent, copyright, software or other intellectual property;
   (iv) entitled to earn royalties now or in the future;
   (v) the author of written materials that are, or are going to be, commercialized;
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(vi) otherwise earning compensation from, or having a financial interest in, intellectual property; OR
(vii) holding any other financial relationship.

d. NON - PUBLICLY TRADED COMPANIES.
An investigator, investigator’s spouse, dependent child, or general partner having any stock, stock options, or other equity interest in a non-publicly traded company whose financial interest could be affected by the study.

e. SPECIFIC TYPES OF FINANCIAL INTERESTS.
  – Publicly-Traded Companies: An investigator, investigator’s spouse, or dependent child (in the aggregate) who owns or has an equity interest (stock ownership, stock options, etc.) valued at more than $15,000 in a publicly-traded company or companies (aggregate value of all stocks in all such companies) whose financial interest could be affected by the study. This does not include stock controlled through a diversified mutual fund or a blind trust.
  – Sector Mutual Funds: An investigator, investigator’s spouse or dependent child (in the aggregate) having equity holdings valued at more than $50,000 in any sector mutual fund (or funds that concentrate in the same sector) whose holdings could be affected by the study. A sector mutual fund concentrates its investments in an industry, business, single country other than the United States, or bonds of a single State within the United States.

Significant financial conflicts of interest do NOT include:
  a. Salary, royalties or other remuneration from the applicant’s home institution.
  b. Income from seminars, lectures, or teaching engagements sponsored by public or nonprofit entities.
  c. Income from service on advisory committees or review panels for public or nonprofit entities.

Non-financial Conflict of Interest
Ensuring disclosure and management of non-financial conflict of interest is the responsibility of the IRB. Non-financial conflicts of interest include:
  a. Investigators serving a dual role (e.g. investigator/health care provider, student/teacher, employee/supervisor); or
  b. Other interests (e.g. publication, promotion, tenure).
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Public Health Service
To address the increasing complexities of the financial interests held by biomedical and behavioral researchers and the resulting interactions among Government, research Institutions, and the private sector, the Public Health Service (PHS) and the Office of the Secretary of the U.S. Department of Health and Human Services (HHS) published revised regulations (42 CFR Part 50 Subpart F) on the Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought and Responsible Prospective Contractors (commonly known as the Financial Conflict of Interest (FCOI) regulations). In the regulations, a Financial Conflict of Interest exists when the Institution, through its designated official(s), reasonably determines that an Investigator’s Significant Financial Interest (SFI) is related to a NIH-funded research project and could directly and significantly affect the design, conduct or reporting of the NIH-funded research. The regulation covers all financial interests that have monetary value, whether or not the value is readily ascertainable.

At this facility, VA Investigators apply for non-VA Federal research grants through the academic affiliate and funds awarded are administered by the academic affiliate. Therefore, it is the responsibility of the academic affiliate to ensure that Investigators meet all PHS FCOI requirements.

For the Medical College of Wisconsin, the current regulation requires an investigator or key personnel to disclose to MCW any SFIs equaling $5,000 or more that could reasonably appear to be related to that persons professional responsibilities at MCW. These SFI(s) must be disclosed by the Covered Person to MCW:

- Each time a person is an investigator on a new PHS funded grant, cooperative agreement or contract application OR is named as a ‘key personnel’ on such an award,
- At least annually during the Medical College of Wisconsin’s Annual Conflicts of Interest and Outside Professional Activities process, and
- Within 30 days of a Covered Person discovering or acquiring any new SFI.

The MCW Financial Conflicts of Interest in Research Committee will determine if any disclosed SFIs could reasonably be considered to be a conflict of interest with PHS funded research activities that the Covered Person is participating in.

The PHS regulations also require all MCW Covered Persons to receive training on the PHS rule and MCW policy. Training for investigators/key personnel must be taken prior to engaging in any MCW PHS funded research and every four years thereafter.

Investigators receiving PHS research funds through other academic affiliates must comply with the FCOI policy of that institution.
Food and Drug Administration

Food and Drug Administration (FDA) regulations dealing with conflict of interest are set forth in 21 CFR 54 (Code of Federal Regulations) and summarized below.

A clinical study may be inadequate and the data inadequate if appropriate steps have not been taken in the design, conduct, reporting, and analysis of the studies to minimize bias. One potential source of bias in clinical studies is a financial interest of the clinical investigator in the outcome of the study because of the way payment is arranged - a financial conflict of interest. Examples include:

- Compensation that could be higher for a favorable outcome than for an unfavorable outcome (e.g. tied to the sales of the product, such as a royalty interest).
- Equity interest in the sponsor of a covered study including ownership interest, stock options, or other financial interest that exceeds $50,000 during and for one year following the study.
- Proprietary interest in the tested product including, but not limited to, a patent, trademark, copyright or licensing agreement.
- Significant payments of other sorts that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study.

According to 21 CFR 54, clinical studies of concern would be those designed to study the efficacy or safety of a drug or device in humans. In general, studies in which financial conflict of interest is NOT of concern include:

- Phase 1 tolerance studies or pharmacokinetic studies
- Most clinical pharmacology studies (unless critical to efficacy determination)
- Large open safety studies conducted at multiple sites
- Treatment protocols
- Parallel track protocols

Conflict of interest refers not only to the financial interests of the investigators or sub-investigators directly involved in the study, but those of their spouses and dependent children as well.

The FDA requires that an applicant that relies in whole or in part on clinical studies shall submit, for each clinical investigator participating in the study, either a certification or a disclosure statement. Certification: FDA form 3454 attesting to the absence of financial interests and arrangements, dated and signed by the chief financial officer or other responsible corporate official or representative. If the certification covers less than all clinical data, the applicant shall include in the certification a list of studies covered.

Disclosure Statement: FDA form 3455 disclosing completely and accurately the following:

- Any financial arrangements entered into between the sponsor and the clinical investigator whereby the value of the compensation to the investigator for conducting the study could be influenced by the outcome.
- Any significant payments of other sorts from the sponsor, such as grants to fund ongoing research, compensation in the form of equipment, consultation retainer or honoraria.
• Any proprietary interest in the tested product.
• Any significant equity interest in the sponsor of the covered study.
• Any steps taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests or payments.

Information provided must be promptly updated if any relevant changes occur in the course of the investigation or for one year following the completion of the study. Financial records pertaining to financial interests described above must be maintained for two years following the approval of the application and must be made available to authorized officials of the FDA.

If, based on the information provided, the FDA determines that the financial interest of any investigator raises a serious question about the integrity of the data, action will be taken to ensure the reliability of the data including:

• Initiating agency audits of the data derived from the clinical investigator in question.
• Requesting that the applicant submit further analyses of the data to evaluate the effect of the clinical investigator's data on the overall study outcome.
• Requesting the applicant to conduct additional independent studies to confirm the results of the study.
• Refusing to treat the covered clinical study as providing data that can be the basis for an agency action.