HCCA: Compliance in Conducting Clinical Research: Conflict of Interest

Prepared jointly by
Kendra Dimond, Esq.
Epstein, Becker & Green, P.C.
Washington, DC
202-861-4186
kdimond@ebglaw.com

F. Lisa Murtha, J.D.
The Children’s Hospital of Philadelphia
Philadelphia, PA
267-426-6914
murtha@email.CHOP.edu
Why Are Conflicts A Problem for Universities?

- May endanger human subjects’ safety
- May jeopardize public’s faith in findings and/or lead them to question whether the investigator is acting in their best interest or merely using them as a vehicle for conducting research
- May reduce the public’s willingness to participate in studies
- May inhibit future discoveries if less support for research
Definition of Conflicts of Interest

A Conflict of Interest is a situation in which financial or other personal considerations have the potential to compromise or bias professional judgment and objectivity.

Conflicts of Interest always involve the use of a person’s authority for personal and/or financial gain.

Conflicts may involve both individuals and institutions.
Examples of Recent Conflicts of Interest Problems


University sued after 18 year old with rare metabolic disorder died while volunteering for a gene transfer clinical trial. The principal investigator failed to disclose the relationship between the investigator, the University of Pennsylvania and Genovo, Inc., maker of the therapy.
Problems (continued)

Wright v. Fred Hutchinson Cancer Center (March 2001)

Patients in two separate studies brought suit against the Center for research improprieties, much of which grew out of researchers’ and the institution’s failure to disclose their financial interests in a collaborating research company
Problems (continued)

House of Representatives Investigation

Rep. Billy Tauzin (R-La.) and James Greenwood (R-Pa.) launched a broad investigation into NIH grant-making decisions after discovering alleged improprieties in how grants were distributed by former NCI Director. House Committee now wants full accounting of industry payment to NIH employees.
The Bayh-Dole Act (1980)

- Permits recipients of federal funds to obtain the title to the inventions they develop under their federally funded projects, and to transfer the technology to the private sector.
- Requires federally funded researchers to obtain a patent for products developed, to seek commercial opportunities, and to report to the NIH on the use of discoveries.
- There is a downside to this Act. Financial arrangements with sponsors are having effects on publication practices, on prescribing patterns and even on assignments of trainees on work. This is a trend that must be watched.
Who Can Have a Conflict of Interest?

- **Individuals**
  - Clinical Investigators
  - Study Coordinators
  - Research technicians
  - IRB members
  - Anyone else involved in technology transfer

- **Institutions**
  - Financial holdings of the institution
  - Allocation of resources for research
Types of Conflict of Interest

Scientific/Academic: The potential for personal gain must not jeopardize or appear to jeopardize the integrity of the research process including the choice of research, its design, the interpretation of results, and the reporting of results.
Types of Conflict of Interest

Conflict of Financial Commitment: A financial Conflict of Interest involves some type of financial payment, such as a consulting fee, equity in a company, or other monetary reward, which influences an individual to prefer one outcome over another one.
Types of Conflicts of Interest

Conflict of Commitment: Faculty and research staff owe their primary commitment to their institution. Examples of conflict of commitment include: involvement with commercial ventures in roles such as serving on the board of directors or on the scientific advisory board, acting as a manager or scientific director, consulting, etc.

Penn Policy: Faculty may not engage in non-academic commitments that, in the aggregate, exceed one day in seven during the academic year.
Types of Conflict of Interest

Conflict of Educational Mission: Students and post doctoral fellows must be assured of an educationally appropriate training program. Hence, it is inappropriate to support the stipends or research expenses of students or postdocs through sponsored research funding from commercial entities in which the faculty member has a financial interest. If a student is involved in research that is supported by a company-funded SRA, the SRA should state that the presentation of results will not be controlled by the company.
Types of Conflict of Interest

Conflict of Conscience: Conflicts of Conscience arise when scientists with deeply held personal views are asked to sit in judgment of projects whose very nature is unacceptable to the reviewer. This can occur when the convictions of an individual are allowed to override scientific merit in reaching a decision. (e.g. A scientist who opposes all research using laboratory animals may be unable to find merit in any study or report that is based upon such use.)
Types of Conflicts of Interest

- All of the preceding Conflicts of Interest are individual Conflicts of Interest
- There are also Institutional Conflicts of Interest
Institutional Conflicts of Interest

Institutional Conflicts of Interest can occur in a variety of ways. This includes when interests of the institution might affect or appear to affect institutional processes including the conduct, review, or oversight of human research. If an institution owns a financial interest in a company that holds a patent to a new drug or device, a conflict and/or a perception of a conflict can arise.

An IRB member can have a conflict of interest if he/she has a stake of any kind in a protocol being considered by the IRB. Other IRB conflicts can include: promoting research vs. protecting subjects, potential liability, concern for institution’s reputation, etc.
Above all, conflicts arise when career and personal advancement desires interfere, or appear to interfere, with research objectives.
Affects PHS governed agencies, such as the National Institutes of Health (NIH)

Regulations are found in: 42 CFR Part 50, Subpart F

Under the regulations, an investigator must disclose:

Any “significant financial interest” in entities whose financial interests might be affected by the research, and require the institution to designate an “institutional official(s)” to solicit and review the financial disclosure statements made by investigators
**PHS Definition**

PHS regulations define a significant financial interest as:

- Income (salary, royalties and other payments) which when aggregated for the investigator, an investigator’s spouse or dependent children exceeds $10,000 over twelve months OR

- An equity interest (including spouse and dependent children) in excess of $10,000 or 5% ownership in a single entity
Management of COIs

- The Institution, not PHS, selects the method for gathering information from investigators, determining if a COI exists, and if any COI that exists is properly managed.

- If an institution determines that an investigator has a conflict, it must report that conflict to the “PHS awarding component and explain whether the conflict has been managed, reduced or eliminated.”
NIH Grant Policy Statement

- Applies to any entity that gets funding from the NIH
- States that COIs might be handled by:
  - Public disclosure of significant financial interests
  - Monitoring of research by independent reviewers
  - Modification of the research plan
  - Disqualification from participation in all or part of the research
  - Divestiture of significant financial interests
  - Severance of relationships that create actual or potential conflicts
FDA COI Policy

- Regulations are found in 21 CFR Part 54
- Form FDA 3455 is the form used to make disclosures
- FDA form is only for the clinical investigators
- Form asks for:
  - Payments coupled to results
  - Compensation in the form of equipment, retainer for ongoing research or honoraria
  - Any proprietary interest in the product tested
  - Any significant equity interest held by the clinical investigator in the sponsor of the study.
FDA COI Policy

Under the regulation, an investigator must disclose:

- Any potentially conflicting financial interest of the investigator, the investigator’s spouse and dependent children when:
  - It is an equity interest in a publicly traded corporation in excess of $50,000 during the time the study is ongoing and for one year following the completion of the study
  - It is a proprietary interest in the test product (including patent, trademark, copyright, or licensing agreement)
  - It is a payment of other sorts (“spoos”) valued at more than $25,000, exclusive of costs of conducting the study, during the project and for one year after completion
**PHS and NIH Regulations**

- Both the PHS and FDA regulations demand reporting of financial interests only.
- They do not require any recusal by the researchers with a conflict of interest.
- There is no requirement for notification to research subjects.
**IRBs and Conflict of Interest**

- IRB conflict of interest issues are regulated under:
  - 45 CFR 46.107(e)
  - 21 CFR 56.107(e)

Under these regulations, “No IRB member may participate in initial or continuing research in which they have a conflicting interest except to provide information requested by the IRB.”

If a conflict is found, an IRB member must recuse him or herself.
Regulation Compliance

If an institution has an IRB, conducts research that is FDA regulated, and receives PHS funding, it must follow all three sets of regulations.
Other Recent Guidance

- Department of Health and Human Services (DHHS) – Draft Interim Guidance (January 10, 2001)
  - Replaced by a Draft Guidance on March 31, 2003

- General Accounting Office (GAO) Report 02-89 (November 2001)
  - Available at http://www.gao.gov
Other Recent Guidance

- American Association of Medical Colleges (AAMC): Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research (December 2001)
- American Association of Medical Colleges (AAMC): Principles and Recommendations for Oversight of an Institution’s Financial Interests in Human Subjects Research (October 2002)
- Both reports are available at: http://www.aamc.org/members/coitf/start.htm
Most Recent Guidance


Available at:
http://ohrp.osophs.dhhs.gov/references/fr03-7691.pdf
Draft Guidance (continued)

Points to Consider When Evaluating Financial Interests:

- How is the research supported or financed?
- Where and by whom was the study designed?
- Where and by whom will the resulting data be analyzed?
- Do individuals or institutions involved:
  - Have any proprietary interests in the product including patents, trademarks, copyrights, and licensing agreements?
  - Have an equity interest in the research sponsor and is it a publicly held or closely held company?
  - Receive significant payments of other sorts (grants, equipment, honoraria, retainers, etc.)
  - Receive payment per participant or incentive payments
- Given the financial relationships involved, is the institution an appropriate site for the research?
COI Committees

- Responsible for addressing institutional and investigator conflicts
- Establish criteria for the COI committee to use, including identifying leadership positions for which the individual’s conflict may need to be treated as an institutional conflict
- Establish clear channels of communication between the COI committee and the IRB
- Include investigators, institutional officials, IRB members and staff among individuals who report financial interests to the COI committee.
DHHS Guidance Recommendations

The Guidance asks: Would the rights and welfare of human subjects be better protected by any or a combination of the following:

- Reduction of the financial interest
- Disclosure of the financial interest to prospective subjects
- Separation of responsibilities for financial decisions and research decisions
- Additional oversight or monitoring of the research
- An independent data and safety monitoring committee or similar monitoring body
- Modification of role(s) of particular research staff or changes in location for certain research activities, e.g., a change of the person who seeks consent, or a change of investigator
- Elimination of the financial interest
How Should An Institution Respond to the Problem of COIs?

Objective:
The goal of an institution’s conflict of interest/conflict of commitment policy should be to:

• Protect the institution
• Protect those who volunteer to participate in the research though management of financial, relationships that create the potential for conflicts of interest
Management Techniques

1) Create a precise definition as to what constitutes a financial COI
   • Determine what standard will be used in evaluating what should be done with a conflict (i.e., “rebuttable presumption of not doing the research vs. “compelling circumstances”)
   • Articulate what is allowed in terms of investments, fees and honoraria, consulting fees, intellectual property rights, enrollment bonuses, payments coupled to results, and spouse/dependent finances
   • Establish enforcement mechanisms/sanctions
Management Techniques (continued)

2) Establish a standing COI committee. The committee should be responsible for:

• Reviewing any financial interests that may pose a conflict and determine whether disclosure, management, elimination, or another course of action is appropriate.

• Documenting the committee’s decisions

• Monitoring procedures and conditions surrounding research involving a financially interested individual.

• Communicating, on a regular basis with the IRB

• Developing a process by which COI committee or IRB decisions may be appealed by investigator
Management Techniques (continued)

3) Designate an institutional official(s) to solicit and review financial disclosure statements from investigators, and an outside official to review institutional disclosure statements.

4) Allocate space and personnel for maintaining records of investigator and institution disclosures and COI and IRB committee decisions.
Management Techniques  (continued)

5) Other important methods for dealing with COIs:
   • Ensure representation of public on COI committee
   • Design educational programs for all researchers, data managers, IRB members, institutional officials with research and finance decision-making responsibilities
   • Establish a firewall between offices responsible for financial decisions and those responsible for research decisions
Stokes and Penn Conflict of Interest Policies

All faculty and key employees of the University must annually complete and submit a Penn Conflict of Interest Disclosure Form. The forms must be submitted to the Vice President for Research Administration at Stokes and the Department Chair of the relevant Penn Dept.

All Stokes and CHOP employees must complete a CHOP Conflict of Interest Disclosure Form annually. The forms must be submitted to The Vice President of Research Administration.

All CHOP-based Penn faculty and Penn employees working full-time at Stokes, must complete either both the Penn and Stokes Conflict Forms or the Penn form, plus a CHOP “Cover Sheet”
Other Policy Requirements

Stokes policy also states that scientists and other persons within the scope of the policy may not, without the express permission of the Vice President of Research Administration or other member of Senior Management, accept gifts or favors of more than nominal value from a company with which the Hospital has or may have a sponsored-research, licensing or other relationship.
Other Policy Requirements

- All consulting arrangements must be in accordance with Stokes and CHOP policy. Areas of concern include: broad claims on intellectual property rights, confidentiality restrictions that unduly limit publication and other dissemination of information, and potential limitations on the research that the consultant may be permitted to conduct outside of the context of the consulting arrangement.

- Grant applications must disclose all relationships between the scientist or other person and a commercial entity that supports the research of the scientist or other person.
Other Disclosure Requirements

In accordance with federal government requirements and Stokes Policy, all Investigators must submit Protocol specific Conflict of Interest disclosure forms to the IRB for review.

Each “key” person involved in the research must also complete a disclosure form.
The Review Process

The Vice President for Research Administration will forward the annual disclosure forms to the Stokes Research Review Committee. That committee will review the forms and forward any actual conflicts of interest to the General Counsel and/or the President for final review.
Where is the Issue of Conflict of Interest Going From Here?

- Greater focus on the issue from Congress
- Increased regulation and guidance from PHS, FDA, OHRP, and other federal agencies
- Universities will need more precise policies and procedures which lay out not only a definition of conflict of interest, but also policies and procedures for identifying, disclosing, and handling conflicts of interest
The Penalty for Failure

Several recent civil lawsuits have linked failure to manage potential conflicts of interest to human subject harm.

Defendants have included: investigators, administrators, IRB members, sponsors, patient advocates.

Who is next???