

CONFLICTS OF INTEREST AND THREATS TO THE CONDUCT OF CLINICAL RESEARCH

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Abstract: *This article provides a brief primer on three levels of conflict of interest in clinical research: investigator, institutional review board (IRB), and institutional. The article focuses on investigator conflicts of interest. Ways to manage, reduce, or eliminate a conflict of interest are highlighted; these are: Public disclosure of significant financial interests, monitoring of research by independent reviewers, modification of the research plan, divestiture of significant financial interest, severance of relationships that create the actual or potential conflict, and disqualification of an investigator from participation in government-funded research. Areas of concern about current federal conflict of interest regulations are outlined.*

Recent headlines have called attention to conflicts of interest in clinical research, even at notable institutions such as the University of Pennsylvania, the Fred Hutchinson Cancer Center, the M.D. Anderson Hospital, and St. Elizabeth's Medical Center, Boston. In these situations where there was the appearance of conflicts of interest, there were research deaths.

Clinical researchers ascribe to three basic elements: scientific integrity, patient safety, and investigator objectivity. Conflict of interest can be defined as: "a situation in which financial or other personal considerations have the potential to compromise or bias professional judgment or objectivity." The importance of objectivity cannot be overstated.

Trust, the core ethical value, is essential in the scientific pursuit of truth. It is necessary with your colleagues, the government, study sponsors, and the public. Conflicts of interest involve the abuse—actual, apparent, or potential—of the trust that people have in professionals. An apparent conflict of interest is one in which a reasonable person would think that a professional's judgment is likely to be compromised. A potential conflict of interest involves a situation that may develop into an actual conflict of interest.

Conflicts of interest can lead to injury and harm to study participants and damage the entire research enterprise by reducing people's trust in research. Conflict of interest should not be confused with misconduct, which is fabrication, falsification, and plagiarism.

Conflict of Interest at the Investigator Level

Objectivity is crucial to scientific discovery, yet bias cannot be eliminated. Professional conflicts of interest can result from pressures to obtain: publications, funding, promotion, prestige, and even the Nobel Prize. Bias can influence judgment and objectivity through the desire to validate a pet theory, over-confidence about a particular concept, or over-reliance about a belief. These things can result in selective in-attendance, in which investigators overlook important data or observations. Bias can be too subtle to recognize. It can creep into: research questions; the research design; the selection of research participants; the collection, analysis, interpretation of data; and publication practices.

Dr. David Blumenthal has investigated the publication practices of researchers. He has documented that not only are negative results less likely to be published, but even positive findings are withheld if the authors believe this is advantageous (e.g., to give them time to apply for a patent or provide a lead over competitors). In one study, 20% of researchers reported delaying publication of results for their own advantage.

In assessing conflicts of interest, we often consider the likelihood of bias as well as the consequences of the conflict of interest. At times, the consequences can be lethal.

The Commercialism of Clinical Research

The research community has long recognized professional conflicts of interest. Tangible conflicts of interest—those caused by money, have captured the attention of the federal government, the scientific community, the public, and institutions. We are experiencing a paradigm shift in the research enterprise. Commercialism is driving the scientific establishment. As David Blumenthal said, “What we are watching is the industrialization of clinical research.”

This paradigm shift is beneficial, yet the intertwining of research and commercial interests can lead to financial conflicts of interest. Financial conflicts of interest seem easier to deal with than intangible conflicts of interest, but they may not be. Financial arrangements with sponsors are affecting many areas of scientific life. A growing and distributing literature, for example, is documenting how the new entrepreneurial environment is altering publication practices and prescribing patterns of investigators and clinicians. The specter of “infectious greed” is increasingly pervasive.

Before 1980, the federal government earned the rights to the research and discoveries of the investigators it funded. Concurrently, biotech companies were having difficulty obtaining licenses to manufacture and market their discoveries. It was obvious that the research enterprise was not thriving. Congress responded in 1980 by passing the Bayh-Dole Act, which permits recipients of federal funds to obtain the title of the inventions they develop under federally-funded projects, and to transfer the technology to the private sector. The Act also requires federally-funded researchers to obtain a patent for products developed, to seek commercial opportunities, and to report to the National Institutes of Health (NIH) on the use of their discoveries. Further, the act enables universities to benefit directly by sharing in the royalties, which provides incentives for the universities to encourage and even exhort the faculty to patent their discoveries. Financial conflicts of interest are an unintended consequence of the Bayh-Dole Act.

Federal Conflict of Interest Regulations

In 1995, the Public Health Service enacted “Responsibility of Applicants for Promoting Objectivity in Research” (<http://grants.nih.gov/grants/guide/notice-files/not95-179.html>). These federal regulations are designed to promote objectivity and decrease bias in the conduct of research. Institutions are required to have standards and procedures which ensure that the design, conduct, or reporting of research is not biased by the investigator’s conflicting financial interests. Key components are:

1. The institution, not the federal government or the sponsor, has the primary responsibility to develop internal policies and procedures. This seems easy, but compliance is not universal.

2. The investigators must disclose any significant financial interests to the institution. “Significant” has become very contentious.
3. The institution must report to federal funders if it believes an investigator’s significant financial interest could affect the research.
4. Federal funders can review all related information.

These regulations apply broadly to many types of institutions and funding arrangements. They call for investigators to provide a list of all known financial interests they, or their families, hold that could reasonably appear to be affected by the research and to update this list at least annually, or when anything significant happens. The regulations apply to investigators, defined as individuals responsible for the design, conduct, or reporting of research. The investigators’ spouses and dependent children are included.

Significant financial interest is defined as anything of monetary value, such as salary or other payments for services from an outside institution, equity interests, and intellectual property rights. It does not include salary, royalties, or other remuneration from the investigator’s home institution; income from seminars, lectures, or teaching sponsored by public or non-profit entities; or income from service on advisory committees or review panels for public or non-profit entities.

The definition of a significant financial interest has become a major point of contention. Federal government, in the US Public Health Service (PHS) regulations, has decided that any financial interest of \$10,000 or more is significant. Many investigators have \$10,000 in stock. The U.S. Food and Drug Administration (FDA) has decided that \$25,000 seems more reasonable.

The PHS regulations also state that equity interests cannot represent more than 5% ownership in any single entity. Five percent of Merck would be very significant, but 5% of a start-up company could be very trivial or, depending on the success of the start-up, could be spectacular. These numbers seem very arbitrary. We really do not know what the true numbers should be.

The federal regulations are designed to help institutions preserve and promote objectivity in research. Their goal is to identify, manage, reduce, or eliminate financial conflicts of interest. Institutions are required to designate an official to review disclosures of significant financial interests and manage conflicts of interest. Table 1 shows ways in which real or apparent conflicts of interest can be managed, reduced, or eliminated.

exclusively on financial conflicts, not on protecting research participants. There is no policy to deal with institutional or IRB conflicts of interest. The American Society of Gene Therapy issued a very strong policy on conflicts of interest, which states that its members can have no equity interests in any company that might be associated with their work (see <http://www.asgt.org/policy/index.html>).

Journals are more frequently asking authors to list companies that fund their research. The preoccupation with financial conflicts of interest, and the suggestion that if you have a financial conflict of interest or equity in a company supporting your work that ergo, you are a miscreant, is a concern. A new wave of McCarthyism is taking over. Web sites such as *Integrity in Science* (<http://integrityinscience.org>), which imply that if you have equity interests you are a “bad” scientist, are a cause for concern.

CONFLICTS OF INTEREST IN IRBs

Little is known about conflicts of interests in IRBs, which are mandated by the federal government to protect the rights and welfare of human participants in research. IRBs were created with the knowledge that there is an inherent conflict of interest between the dual roles of the clinical investigator as physician, whose primary responsibility and duty are to ensure the welfare of his/her individual patients, and as researcher, whose duty is to advance science for the sake of society.

We know of two egregious examples where conflicts of interest in research existed: the Tuskegee Study of Syphilis in the Negro Male (1932-1972) and the Willowbrook Hepatitis Studies (1963-1966). The clinical investigators were so caught up in their projects that they ignored the welfare and ultimately harmed the participants in these studies.

Many IRB members have equity interests, and may even have equity interests in companies sponsoring studies they are reviewing. We do not know whether IRB members are asked to recuse themselves when reviewing studies in which they have equity interests in the sponsoring pharmaceutical company.

TABLE 1
Ways to Manage, Reduce, or Eliminate Conflicts of Interest

- Public disclosure of significant financial interests
- Monitoring of research by independent reviewers
- Modification of the research plan
- Divestiture of significant financial interests
- Severance of relationships that create the actual or potential conflict
- Disqualification of an investigator from participation in government-funded research

NIH has been conducting not-for-cause visits to evaluate how institutions are carrying out the 1995 regulation. Table 2 outlines the findings. NIH found that policies it thought were clear were open to interpretation. Some institutions were very lax in their interpretation of the regulations and there was a great deal of variation. There were concerns about the invasion of privacy. Investigators did not always want to reveal their holdings. Disclosure was only made to institutional officials. There is no consensus as to what type of financial interest warrants attention.

Other areas of concern are that the level for significant financial interest may not be realistic. The regulations focus

TABLE 2

NIH Findings Regarding the Application of the Federal Conflict of Interest Regulations

Six areas of concern:

1. Details of policy and enforcement are left to the institutions—potential for lax compliance
2. Concerns with an invasion of privacy and breach of confidentiality
3. No consensus as to the nature or the magnitude of a financial interest that warrants attention
4. Current Public Health Service limits for “significant” financial interests may be unrealistic
5. Focus of the regulations is exclusively on financial conflicts
6. Absence of any policy to deal with institutional or IRB conflicts of interest

Some IRBs are developing strategies to deal with conflicts of interest that may interfere with their objectivity and deliberations. A recent Inspector General's report estimated that about 25% of IRBs in the NIH study were taking action.

Many IRBs are now charging fees to review protocols. This raises concern that IRBs might approve borderline protocols or that investigators will shop around for IRBs that will approve their protocols. Sometimes the institution may pressure the IRB to approve a protocol.

IRBs must approve protocols for serious, high-risk studies. These studies may generate a great deal of public attention and provide a strong incentive for the investigator to conduct the study. Ground-breaking research is essential, but it puts considerable pressure on IRBs to approve the protocols. Our investigators are working on a left ventricular assist device for patients who have chronic congestive heart failure. Despite some reservations of IRB members, there is a sense of obligation to approve the device.

IRB conflicts of interest are an area of interest and concern. IRB members should be sensitive to issues. For example, perhaps the informed consent form should have a sentence that says, "The investigator of your study is supported by the sponsor." Some potential research participants would think this statement meant that if the study is successful, the investigator will make money and the participant would get better – a "win-win" situation. Others might think the investigator was more interested in the money than in the participant. Most potential research participants probably do not even understand the complexity of the issue.

INSTITUTIONAL CONFLICTS OF INTEREST

We know even less about institutional conflicts of interest than we do about IRB conflicts of interest. Several recent gene therapy trials that went awry, and that had apparent institutional conflicts of interest, alarmed the public and the research community.

The death of 18-year-old Jesse Gelsinger at the University of Pennsylvania in a gene therapy trial is almost a metaphor now. It set off a firestorm that continues to smoke. The University's Institute of Human Gene Therapy, the trial sponsor, came under scrutiny because both the researchers involved with the trial and the University had financial conflicts of interest. Penn subsequently changed many of its policies, and discontinued all human gene transfer experimentation at the Institute of Human Gene Therapy. The principal investigator, James Watson, stepped down as President of the Institute.

We are increasingly aware of the strong ties that bind academia to industry. These ties grow stronger every day. With the cutbacks in federal spending, this is not necessarily a perilous relationship and is usually beneficial as funding is needed for technology to advance.

There are no federal guidelines on institutional conflicts of interest. For example, what happens if an institution holds a patent, then conducts research whose outcome could provide financial benefit to the institution? Should disclosure to the funding agency be required? Should the funding agency receive statements from the institution regarding how it manages such potential conflicts?

Concerns about institutional conflicts of interest have spurred a number of activities. In 2001, the Office for Human Research Protections (OHRP) drafted

guidelines for institutions entitled *Financial Relationships in Clinical Research: Issues for Institutions, Clinical Investigators, and IRBs to Consider when Dealing with Issues of Financial Interests and Human Subject Protection* (<http://ohrp.osophs.dhhs.gov/humansubjects/finreltn/finguid.htm>). NIH, OHRP, Harvard University, the Association of Academic Medical Centers, and the Association of American Universities (AAU) are all looking at institutional conflicts of interest. The AAU *Report on Individual and Institutional Conflict of Interest* defines these conflicts of interest and tries to promote some understanding of the issues. The NIH created a Web site with many and varied resources about conflicts of interest. <http://grants2.nih.gov/grants/policy/coi/resources.htm>>

Determining who will watch the institutions when they are involved in conflicts of interest is a conundrum. In some ways, it is like asking the fox to guard the henhouse. We do not know what will happen to the hens, chicks, and roosters.

CONCLUSION

It is clear that conflicts of interest will not go away. They will probably get worse. Intangible and tangible conflicts of interest will always exist. Financial conflicts of interest will become more complex and involved. Devising new means of disclosure and managing conflicts of interest will be ongoing challenges.

As David Blumenthal said, "Most conflicts of interest created by academic-industry relationships are real, consequential, but tolerable, so long as they are managed to contain their risks while preserving their benefits." Basically, a conflict of interest is not necessarily bad, only when it presents bias and a loss of objectivity. That is what we must be vigilant against.