

Is Conflict of Interest Becoming a Challenge for Institution-Based Institutional Review Boards?

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Abstract

Expansion of business relationships between academic institutions and their leaders and industry have become a reality, whereas media attention regarding conflict of interest (COI) at academic institutions has raised concerns about possible erosion of public trust. The Institutional Review Board (IRB) should collaborate with institutional COI committees to ensure that research with human subjects is in compliance with various applicable federal regulations. The IRB and COI committee should take additional independent action as necessary under their separate mandates to protect the welfare, safety, and rights of human subjects and to include limits on protocols affected by significant financial interests of the institution or its decision makers. If unable to review research due to an intrainstitutional conflict, the local IRB should consider transferring the study review and oversight to an external unaffiliated institutional or central IRB. A process for involvement of an executive institutional IRB is proposed. *Clin Cancer Res*; 19(15); 4034–9. ©2013 AACR.

Introduction

The purpose of the 1980 Bayh–Dole Act was to increase utilization and commercialization of intellectual property developed with federal funding at academic institutions. Six years earlier the U.S. Congress created and charged a national commission to identify basic ethical principles for conducting human research and formally established the Institutional Review Board (IRB) system with authority to approve human subject research. It was expected that Bayh–Dole would facilitate partnerships among academic institutions, scientists, and industry. Industry would then have access to another pipeline of potential commercial products from which the public could potentially benefit. Because federal agencies have been released from their reporting requirements, it will not be possible to determine how much intellectual property developed through the use of federal funding has been commercialized (1). Although industry has the largest research expenditure overall, for academic institutions, federal revenues account for 65% of biomedical research expenditures and further federal

increases are not expected (2). Because of this flat federal funding, institutions, particularly those involved in both health care and biomedical research, are increasingly turning to business relationships with the biomedical industry as additional revenue sources. However, expanding research and business relationships with the biomedical industry have also been accompanied by instances in which the interests of patients have not been appropriately balanced, leading to negative media reports and Congressional concern about conflict of interest (COI) at academic biomedical institutions. Broadly defined, a COI is "a situation in which an individual or a corporate interest has a tendency to interfere with the proper exercise of judgment on another's behalf" (3). Allegations of COI have involved investigators, institutions, and decision makers. These events contributed to guidance (3, 4) and revisions to the COI regulations (5) but are also offering new challenges to the institutional IRB, the cornerstone of the institutional human research protection program. Negative public sentiment generated from reports of biomedical institutions being in financial conflict with their mission to provide the highest-quality medical care and research could erode the public's trust in such institutions and may further erode the public enthusiasm for human subject research that is essential to the development of new drug treatments or devices used for prevention, early detection, or treatment.

Recent studies have shown that the public's trust is highest in academic institutions, followed by investigators, and finally the pharmaceutical industry (6), but trust could change as alliances with the pharmaceutical world become tighter. Based on several prospective studies Weinfurt and colleagues summarized the desires and perceptions of potential research subjects in regard to disclosure of an investigator's financial interests (6–8). The main message

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Table 1. Comparisons of federal agency regulations for financial conflict of interest in human subject research

PHS 42 CFR 50/45 CFR 94 HHS COI rules	21 CFR 54 and 56 FDA clinical research rules	45CFR46.10E The Common Rule
<ul style="list-style-type: none"> • Oversight and compliance of institution requesting or receiving federal funding, which then supervises individuals • Applies to researchers, subcontractors, institution, institutional committees, i.e., IRB and COIC • Goal: Maintain objectivity and integrity of research • Focus on investigators but not institutions or administrative decision makers' FCOI • Threshold \$5 k • Mandates include SFI disclosure, management, reduction or elimination of FCOI, and policy enforcement by "institutional officials" • Silent on IRB role or IRB-COIC cooperation; human subject protection and rights not addressed • Does not apply to nonfederally funded pharma-sponsored research • Requirement for training of investigators • Public site disclosure of FCOI (or release of information on request) related to specific HHS grants 	<ul style="list-style-type: none"> • Oversight and compliance of sponsors, investigators, and essential personnel involved in research on drugs and devices • Applies to sponsors, investigators, and essential personnel listed on 1572. 21CFR 56.107e same as 45CFR46.107e regarding IRB members' COI exclusion; ICH 3.2.1 addresses independence of members from sponsors • Goal: Maintain objectivity in assessment of efficacy and safety • Focus on sponsors (usually Pharma but could be institution or its senior personnel if holders of the IND or IDE) • Thresholds \$50 k and \$25 k • Mandates include disclosure of defined financial interests and relationships and steps taken to minimize bias in studies submitted for FDA review • No mandate for IRB review of 1572; regulation does not directly address human subject protection though future patients would be expected to benefit • Applies only to IND or IDE agents and products • No training mandate for investigators • No mandate for public reporting of FCOI even at review 	<ul style="list-style-type: none"> • Qualifies aspect of IRB review process • Applies to IRB members; precludes conflicted members from participating in initial or continuing review • Goals: silent • Focus on reviewers only • Silent • Only mandate precludes or restricts participation in IRB review if member has COI • Silent on policies or procedures to protect human subjects during primary or continuing review of research that is linked to an SFI • Silent • Silent

Abbreviations: CFR, Code of Federal Regulations; COIC, conflict-of-interest committee; FCOI, financial conflict of interest; FDA, U.S. Food and Drug Administration; HHS, Department of Health and Human Services; ICH, International Committee on Harmonization; IDE, Investigational Device Exemption application; IND, Investigational New Drug application; SFI, significant financial interest.

from these and other studies (9) is that trial subjects want to know about the financial interests of investigators and would be disappointed to discover them later, especially with higher risk studies. Disclosures of financial interests would not have dissuaded most individuals from being participants, but it is unclear how much information to disclose and how much is actually understood by potential subjects (8). Potential subjects understood that clinical trials require financial support and were less concerned about per capita payments to investigators, including salary,

than equity ownership on the part of researchers (6, 7). Many individuals felt that "disclosure would lead them to trust the researcher more" (8), although it is also possible that unqualified disclosure can distort informed decision making. Researchers and administrators have accepted that disclosures offer a *caveat emptor* caution to potential research participants and thus some protection from legal liability, although evidence for this is lacking (7). It is apparent that most of the quoted COI research relates to the investigator. The revised regulations (5) also focus on

the investigator's actions and responsibilities, although it is difficult in a modern academic institution with a complex hierarchical structure to separate the interests of institution and management from those of investigators. This is particularly the case for situations involving Bayh–Dole and novel intellectual property, because most academic institutions license their intellectual property to start-up companies in trade for an equity position in the new company.

Complexity of Existing and Revised Regulatory Structure for COI

Compliance with the revised and more stringent COI federal regulations is the responsibility of investigators, contractors, and designated institutional officials for federally funded research covered by revised Public Health Service (PHS) 42CFR50/45CFR94 (5), and the sponsor of a drug or device study under FDA 21 CFR 54 [see Table 1 for comparison of regulations that relate to significant financial interest (SFI) in research]. The purpose of both regulations is to protect integrity and objectivity in research and for the FDA the additional statutory mandate to assure the safety and efficacy of drugs and devices. Not directly addressed in either regulation are safety, welfare, and the rights of participating subjects, rules for financial COI (FCOI) involving institutions or decision makers, or information on how such disclosures should be made to participants (5). FCOI is defined as "a significant financial interest that could directly and significantly affect the design, conduct, or reporting of PHS-funded research." An SFI exists if the value of any remuneration received from the entity in the 12 months preceding the disclosure, when aggregated with the value of any equity interest in the entity as of the date of disclosure, exceeds \$5 k (see regulation for exclusions), whereas under 21 CFR 54 the FDA level for disclosure is \$50 k for equity interests and \$25 k for other financial arrangements unrelated to the trial. The revised FCOI regulations (5) stipulate requirements for institutions to enforce a FCOI policy that mainly includes investigators' disclosures of SFI; managing, reducing, or eliminating conflicts; promotion of public understanding of institutional COI policies and disclosures; and reporting of any FCOIs and any mitigation to the awarding components (i.e., NIH Institute or Center or other PHS-related agency). Note that the FDA mandates disclosure of financial interests but does not specifically define "SFI" or "FCOI." Designated institutional officials [assisted by a conflict-of-interest committee (COIC)] must review and act accordingly on investigators' financial disclosures. The federal regulations also encompass under "institutional responsibilities" individual researchers, who, while serving on institutional committees such as an IRB or COIC, would be subject to SFI disclosure. The federal regulations on human subjects research (45CFR 46 A–D, also called "the Common Rule") are actually silent on IRB responsibilities for reviewing investigator, institutional, or decision maker FCOIs. However, 45CFR46.107E and the FDA regulations [21 CFR 56.107(e)] preclude an IRB member's participation in the initial or continuing

review of a project in which the member has a conflicting interest except to provide information as requested by the IRB. A 2004 HHS guidance on financial relationships in research (10) also recommended that the IRB and COIC consider in an independent manner whether a particular financial relationship might adversely affect the rights and welfare of subjects and determine any necessary actions to protect human subjects. Regarding IRB review of investigational new drug (IND) or device studies under FDA jurisdiction, the FDA also recognizes International Committee on Harmonization (ICH) Guidelines 3.2.1 that "Only those IRB/IEC [Investigational Device Exemption] members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a treatment-related matter." The independence of the IRB could be affected when an institution is the study sponsor (i.e., when an IND or IDE is held by the local institution, when institutional funds like a faculty discretionary account are being used, or when the business interests of an institution or high-level institutional decision maker are involved), because all IRB members except the volunteer public voting members are likely to be institutional employees.

FDA 21 CFR 54 also requires SFI disclosure to the agency and assurances that effective steps are taken to minimize bias in the design and conduct of trials. SFI of investigators, sub-investigators, and other essential personnel must be disclosed by investigators listed in Form 1572 and included with other essential investigator documents (11). The IRB is not required to review the 1572 and financial disclosure documents but should be informed by the COIC of investigators' SFI to ensure due diligence in protecting human subjects' interests. The FDA warns (12) that failure to disclose or adequately manage financial interests that raise concern about a study's data integrity could result in reanalysis or audit of the sponsor's data, request for additional independent studies, or a refusal to accept the sponsor's data in a new drug application. Although it is commonly accepted that an FCOI can interfere with study integrity and objectivity, such relationships are generally difficult to prove, but clearly FCOI within a trial could jeopardize an approval under a New Drug Application or Biological License Application.

IRB Role in Review Process

Institutional COI has been of concern for many years (13), and despite some high-profile cases, including highly questioned adverse actions against investigators by two university administrations (14), investigator FCOI has continued to be the main target of PHS regulations, as well as COI policies at PHS-funded institutions. Institutions may also have vested interests in forming "strategic corporate alliances" with the biomedical industry that could yield lucrative funding arrangements, such as milestone payments for developing or testing a company's products. These arrangements and others, such as compensated activities of institutional decision makers on company boards with payments including equity or equity options, can be problematic and deserve a transparent and objective review

process. Although the IRB has no mandate to approve or disapprove financial interests of institutions or its decision makers, it can and should make determinations on any protocols linked to a potential FCOI. The IRB and COIC should collaborate to enforce PHS COI rules and to come up with management plans (typically orchestrated by a COIC) that protect the integrity and objectivity of research and the rights, welfare, and safety of human subjects. The IRB should be prepared to take additional enforcement measures as needed to protect human subjects.

Disclosures of SFI

No federal regulations mandate how COI should be disclosed to potential subjects. Disclosure could be oral or incorporated into a separate written statement or part of the informed consent document. Requirements stated in 21CFR50.20 and 45CFR116 are that "an investigator shall seek consent only under circumstances that provide the prospective subject . . . sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence." Disclosure of financial interests alone, however, does not protect the safety, welfare, or rights of subjects, as was seen in the well-publicized Gelsinger case (15). Unqualified disclosure of the SFI of an institution or decision maker to a potential subject could potentially contribute to a favorable "therapeutic misconception," particularly if the subject misinterprets the SFI disclosure or its approval by an institutional committee as an endorsement of the research being undertaken. The process of SFI disclosure deserves to be studied further, and investigators should also avoid terminology like "therapeutic research" during informed consent, because it could understate a study's experimental nature (16).

Place for an executive IRB in the review process

When an SFI involves an investigator or team members, the COIC and local IRB can take joint action to obtain resolution. Examples of management include an escalating sequence of options from appropriate disclosure, usually in the IRB-approved informed consent documents, to oversight, to replacement of a principal investigator, to requiring return of payments to a sponsor.

When the institution or its senior management has an FCOI and/or the institution is also the trial sponsor, a process needs to be in place to permit an IRB to carefully consider ramifications of the institutional FCOI and potential risk of harm to subjects. Some institutions' COI policies permit an institutional decision maker (i.e., president or chancellor) to grant a waiver that allows an investigator with FCOI to conduct an affected study. The IRB should consider using its authority to override the waiver if it has concerns about subjects' welfare or safety.

In instances when there is a FCOI involving the institution or its leadership, it would be appropriate for the review of the financial, scientific, and human subject aspects to be conducted through processes that are external to the institutional COIC or IRB (17). The protocol review process

could begin with an executive or coordinating IRB that includes officers (chairs and vice chairs) and unaffiliated members from the institution's other IRBs. A single IRB from a smaller institution could follow the same process. The executive IRB can invite nonvoting external consultants with expertise in human subject research and ethics under 45CFR46.107 to assist the IRB in making its determinations. An alternative model could assign the review of COI questions to an Institutional COI review committee that includes significant external membership. The process of external versus internal COI review of institutional COI may be different and depend upon whether the institution is private or state run because the governance is likely to be different. The IRB should follow the institutional COI policy and not reduce the stringency of the policy except in the very unlikely event that subjects could be at risk by precluding participation of a conflicted investigator with unique expertise to the study. IRB support staff should confer with COI staff to ensure that the convened IRB has accurate and sufficiently detailed financial information. The IRB might also request protocol contracts and should review decisions made by the institutional COIC because the IRB must retain its right to be more stringent than the COIC if the IRB feels a higher degree of constraint is necessary for the protection of human subjects or to guard the integrity of the research. IRB review of contracts between biomedical companies and institutions might lead to requests for removal of language that could support unethical conduct during a study, like contract language that imposes restrictions on disclosure of unanticipated toxicity that could influence a subject's continued participation in a trial (14), or less restrictive language on authorization to access protected health information by external non-covered entities, which is inconsistent with the obligatory principle of beneficence.

The executive IRB (or the institutional COIC) should consider four basic questions (also summarized in Fig. 1): (i) should the study be done at the local institution; (ii) if the research can be done at the local institution, should there be restrictions on the study; (iii) what should be disclosed to potential participants and how should disclosure be accomplished; and (iv) should the institutional IRB retain its authority or request transfer to an external IRB? With each potentially conflicted study there should be consideration of the "rebuttable presumption" that the study not be done at the local institution (17). A separate determination should be made for each study as for the value/risk assessments that an IRB does during its regular review of human subject research. A large multi-institutional trial, typically monitored by an external data and safety monitoring board and clinical research organization, might reasonably be conducted at the local site provided it is not "a lead site" and the "lead investigator" is from a different institution. The ICH terminology is "coordinating investigator," and this refers to someone usually appointed by the sponsor or a clinical research organization. The commonly used terms "lead site" and "lead investigator" have no federal regulatory definitions

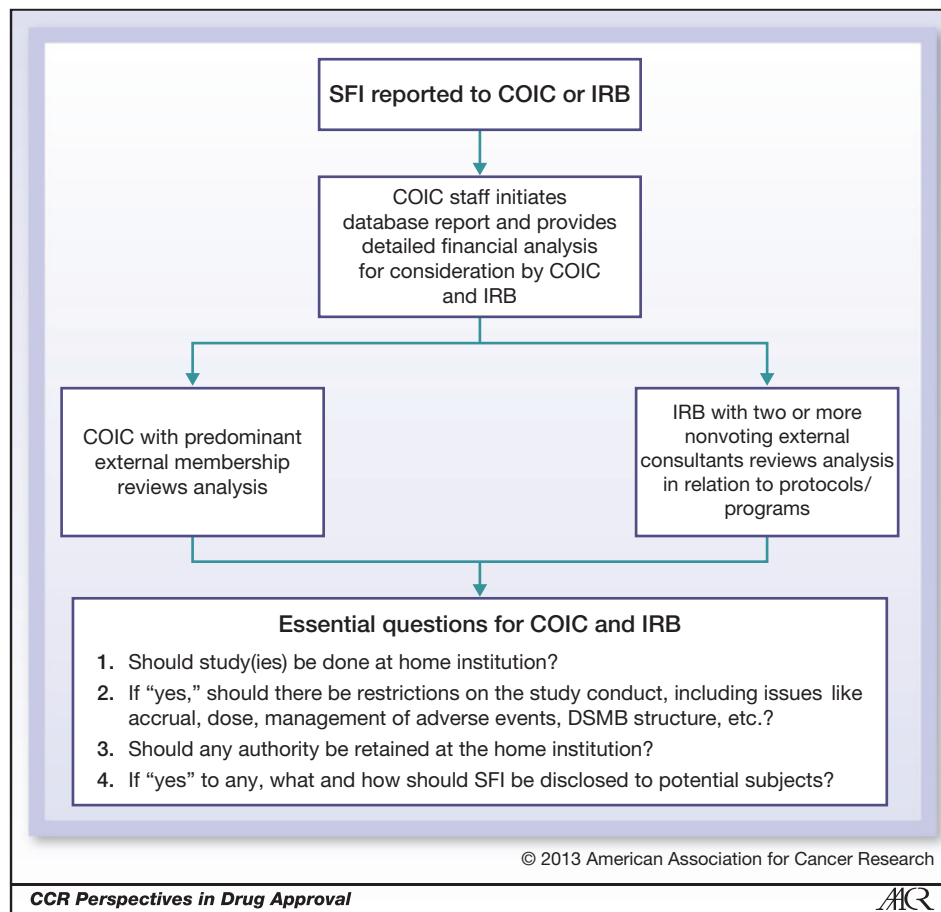


Figure 1. Algorithm showing the main steps for triaging protocols or programs potentially affected by an SFI of the institution or senior administrator. DSMB, Data and Safety Monitoring Board.

and should be defined for the institution. The IRB might also put limits on accrual at the local institution, and perhaps could limit dosage levels for participants, particularly in a first-in-human trial that has the potential for substantial risk of harms to subjects. The IRB should also determine whether the IRB of record should be from another institution or a central IRB (18). In addition, the IRB should consider certain nonfinancial conflicts, possibly involving "professional advancement or standing" of investigators (16). Clinical trial subjects can potentially be put at risk by poor professional decisions of investigators (e.g., recruitment of ineligible subjects or other safety violations) influenced by non-mission-related interests. The IRB should give particular attention to clinical trial design aspects like inclusion/exclusion criteria, assessments of efficacy endpoints, and adverse event reporting standards. Management plans should be formulated in consultation with the COIC to ensure effective firewalls between investigators and financially conflicted administrators who have responsibility for evaluating faculty for promotion and tenure. Rather than compromise the mission of their institutions some presidents and chancellors have voluntarily resigned from industry boards (3).

Even small studies involving a single institution can result in significant harm to participants, as in the case of

first-in-human trials (15). The IRB should determine if the study affected by a COI requires an external IRB, DSMB, or that the study be conducted at another institution that has suitable expertise. The local IRB, possibly the executive IRB, might retain by arrangement with the external IRB or contract research organization certain functions such as editing and translation of informed consent documents, internal auditing of the research process, and federal reporting of unanticipated problems. If the IRB (or the COIC) determines that conduct of this study at the local institution is in the subjects' best interests, perhaps because of issues like the unique expertise of local investigators or protocol requirement for drugs that must be produced locally, it should recommend an exception or waiver of the rebuttable presumption against doing the research at the conflicted site. The IRB could permit the study to be done at the local institution and delineate additional protections and monitoring. To assure independence of the executive IRB deliberations, a firewall should exist between the institution's administration and the IRB and anonymity of the minutes and voting should be assured.

Finally, education of researchers on COI is a requirement of the new PHS regulations. Education can be achieved through carefully written institutional policies, guidelines,

mandatory training reviews, and educational sessions at national meetings.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Writing, review, and/or revision of the manuscript: R.S. Freedman, R. McKinney

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