



# Managing and Auditing Conflicts of Interest in Clinical Research

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In recent years, a number of well-publicized instances of death or serious injury to research subjects have highlighted concerns about the harm conflicts of interest (COIs) may cause if the COIs are not managed adequately by researchers and their sponsoring organizations. Plaintiffs have filed lawsuits against leading research organizations and affiliated physicians alleging that the organizations' and physicians' financial ties to companies funding research created COIs that support various causes of action, such as lack of informed consent, common law fraud, and misrepresentation. In addition, the government has imposed sanctions on both researchers and research organizations, including onerous institutional integrity agreements, to address COIs and other concerns.

**Researchers and organizations not identifying or managing harmful Conflicts of Interest operate at a compliance and risk-management disadvantage.**

In today's enforcement and litigation climate, researchers and organizations that do not identify and manage potentially harmful COIs operate at a compliance and risk-management disadvantage. Therefore, organizations must pay attention to COIs as part of their overall research compliance program. This article describes

the available legal authority and guidance on COIs in clinical research and provides a compliance framework for managing them.

### Background

The term "conflict of interest" commonly describes situations in which an organization or individual has conflicting loyalties or interests. Organizational COIs in the research setting are often referred to as "institutional COIs," and COIs on the part of researchers or other individuals are often referred to as "individual COIs." Many COIs are financial in nature, but non-financial COIs, such as the desire for faculty advancement or public recognition, also exist.

COIs arise in clinical research when personal or institutional interests are potentially at odds with other important interests related to the human subject research. For example, a COI exists if a clinical researcher or research institution has an ownership interest in the product being tested by the research and stands to profit financially if the product is ultimately brought to market. The COI concern is that the proprietary interest might compromise the researcher's or institution's objectivity in conducting the research, thus jeopardizing the welfare of individual research subjects or the integrity of the research data.

COIs are inherent to some degree or another in all clinical research and so the objective should not be to eliminate all COIs. Rather, organizations should develop a process to identify, review, and effectively manage COIs. While the potential for harm caused by a particular COI varies, the overriding imperative is for the organization to identify the COI and subject it to a reasonable management process.

### Authority

There is a patchwork of authority, both binding and nonbinding, addressing COIs in clinical research. Organizations should review and understand this authority as a basis for its COI management strategy.

### Institutional Review Boards (IRBs)

The federal Department of Health and Human Services (HHS) and the federal Food and Drug Administration (FDA) regulations require that organizations performing research regulated by HHS and FDA ensure the research is reviewed and approved by an institutional review board (IRB) (45 CFR part 46; 21 CFR parts 50 and 56). IRBs are responsible for, among other things, determining that risks to subjects are minimized and reasonable in relation to anticipated benefits to subjects; selection of subjects is equitable; informed consent will be sought from each prospective participant; and the possibility of coercion or undue influence is minimized. Since COIs can affect any one of these areas, review of COIs arguably falls within the IRB's responsibility, even if the regulations do not expressly reference COIs.

HHS and FDA regulations also require IRBs to ensure that IRB members who review research have no conflicting interest. IRB members are prohibited from participating in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

### HHS and FDA Guidance on Financial Relationships and Interests

The HHS document, "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection," published on

May 12, 2004, applies to human subjects research conducted or supported by HHS or regulated by FDA (the Guidance). Although not binding, the Guidance includes general approaches and points for consideration by organizations, IRBs, and investigators in determining whether specific financial interests in research could affect the rights and welfare of human subjects, and if so, what protective measures could be considered.

#### **Public Health Service (PHS)-Funded Research**

The PHS regulations (42 CFR. §§ 50.600 through 50.607) contain binding requirements concerning COIs that apply to all organizations that receive PHS grants or cooperative agreements for research and to investigators participating in the research. The regulations require each organization to maintain a written policy on COI, but give the organization discretion in reviewing and managing conflicts.

The PHS regulations require investigators who participate in PHS-funded research to disclose to a designated organizational official, annually and as new reportable interests arise, a list of the investigator's "significant financial interests" and those of his or her spouse and dependent children. A "significant financial interest" means anything of monetary value, including salary, consulting fees, honoraria, equity interests such as stock and stock options, and intellectual property rights such as patents, copyrights, and royalties. The threshold for disclosure of COIs is \$10,000 in annual income or equity in a relevant company, or five percent ownership of such a company. All disclosures must be updated either on an annual basis or as new reportable interests arise.

#### **FDA Marketing Approvals**

FDA regulations at 21 C.F.R. part 54 require research sponsors seeking marketing approval for products to disclose to the FDA certain financial interests held by investigators, or to certify that such interests do not exist. These regulations require research sponsors to report: (1) financial arrangements between the sponsor and the investigator where the value of the investigator's compensation could be influenced by the outcome of the trial; (2) any proprietary interest in the product studied held by the investigator; (3) significant payments of other sorts

over \$25,000 beyond costs of the study; or (4) any significant equity interest in the sponsor of a covered entity.

#### **Non-Governmental Organizations and Accreditation Organizations**

A number of non-governmental organizations have published guidelines for the management of COIs, including the American Association of Universities ([www.aau.edu](http://www.aau.edu)), the American Association of Medical Colleges ([www.aamc.org](http://www.aamc.org)), the Ethics Committee of the American Medical Association ([www.ama-assn.org](http://www.ama-assn.org)), and the American Society of Gene Therapy ([www.asgt.org](http://www.asgt.org)). In addition, at least two accreditation organizations—the Association for the Accreditation of Human Research Protection Programs ([www.aahrpp.org](http://www.aahrpp.org)) and the National Committee on Quality Assurance ([www.ncqa.org](http://www.ncqa.org))—have standards for COIs.

#### **State Law Requirements**

State-specific requirements, if any, should be taken into account when developing COI policies and management strategies.

### **Framework for COI Management**

#### **Policies and Procedures**

An organization that seeks to minimize the risk of potentially harmful COIs in clinical research must have a written policy and procedures in place

**Written COI policy provides of protection against undesirable effects of unmitigated organizational and individual COIs.**

to identify COIs, determine which COIs need to be managed, and decide upon and implement appropriate methods for managing those COIs. Whether or not PHS-funded research is conducted at an organization, a written COI policy that governs the organization's clinical research activities is that organization's first line of protection against the undesirable effects of unmitigated organizational and individual COIs.

Organizational officials can rely on a written COI policy to guide them in potential conflict situations that are especially complicated or sensitive. In addition, a written COI policy puts researchers on notice that certain interests must be disclosed or are prohibited by the organization. If an undisclosed or prohibited conflict is identified after the research has begun or ended, the organization can impose sanctions against the researcher based on the COI policy violation.

Most healthcare organizations have general COI policies in place, in accordance with their corporate compliance programs. If an organization already has a general COI policy, the organization should determine whether the policy is comprehensive enough to adequately address the types of interests that arise in the clinical research context. These general COI policies may not provide a sufficient level of detail to help researchers and organizations scrutinize in a meaningful way the wide variety of potential conflicts that can arise due to relationships between and among clinical researchers, institutions, and research sponsors. For example, a general COI policy that requires the disclosure of a researcher's interests, but fails to define what constitutes an "interest" in the research setting, leaves much up to the interpretation of the researcher, and could lead to the existence of any number of unreported interests related to active studies.

If the organization's current COI policy does not inadequately cover the particulars of clinical research, the organization could either adopt an additional COI policy for clinical research or amend its current policy to include provisions addressing clinical research. The policy should describe to whom the policy applies (the "covered persons"); the types of interests that must be disclosed; the types of interests that are prohibited, if any; the mechanism for disclosure to or within the organization; the decision-making body responsible for determining how COIs will be managed; the options for managing COIs; and penalties for failure to comply with COI policies and procedures.

#### **Covered Persons**

The policy should apply to all principal and co-investigators. In addition, the interests of immediate family members

should be covered by the policy. The policy should define “family members” in sufficient detail so it is clear which family members are covered. The policy should apply to employees, contractors, medical staff members, interns, residents, graduate students, and others involved in clinical research studies. In addition, the policy should cover the institution itself, so that the policy also addresses the management of institutional COIs.

#### *Disclosable and Prohibited Interests*

The COI policy should indicate the categories of interests that must be disclosed. These interests could include salaries, consulting fees, honoraria, stock, stock options, intellectual property rights, loans or gifts, or decision-making positions such as director or officer positions with the sponsor of the research. The organization may wish to specify a certain threshold that triggers disclosure. For example, the organization may decide that the COI policy will require disclosure of an interest only if the interest meets the PHS threshold of \$10,000 in annual income or five percent ownership interest. However, the federal threshold may be an inadequate measure of disclosable interests and stricter disclosure thresholds may be warranted.

In addition to requiring disclosure for certain types of interests, the COI policy could prohibit researchers from holding specific types of interests. Outright prohibition of certain interests currently is a less common approach, perhaps because it is more challenging to implement from a political perspective. If an organization does implement prohibitions on holding specific types of interests, it should be extremely cautious in making exceptions for certain persons or types of interest, such as newly recruited faculty or family gifts or inheritances. In most cases, it is difficult to justify these exceptions in light of the objective of protecting research subjects from risks associated with COIs.

#### *The Decision-Making Body*

The COI policy should indicate to whom a disclosure must be made, usually an organizational official or committee. The policy could require disclosure to the IRB, the funding agency or sponsor, research subjects, or the professional community (in publications or presentations). The policy should specify the protocol for the review of the disclosed interest by the designated official or committee.

The designated organizational official or committee that reviews the disclosed interest should be independent from the research itself. Some organizations have created a COI committee that is separate from the IRB and has a specific focus on reviewing disclosed interests, mitigating COIs, and assigning penalties where appropriate. Such a committee could also address COIs that are identified after the research has begun or ended. If it is not feasible for the organization to establish a COI committee, the organization could assign primary responsibility in this area to the IRB. However, IRBs typically are already overextended and may be unable to devote sufficient time and attention to ensure thorough review and management of COIs.

### **COI policy should describe options for managing COIs.**

#### *Options for Managing COIs*

An organization’s COI policy should describe the various options available to the reviewing official or committee for managing COIs. The PHS regulations offer the following management strategies: divestment of the interest, withdrawal of the investigator from the project, additional disclosures, modifications of the research plan, monitoring of the project, or public disclosure. Some organizations may require that, at a minimum, the researcher disclose the interest to the research subject through the informed consent process. Note, however, that although this strategy may help mitigate certain legal claims, such as lack of informed consent, it may not address all legal or ethical concerns, especially where the COI is so significant that further action is warranted (such as divestment or withdrawal from the study).

The policy should describe the mandatory nature, if any, of the various options for managing COIs. Many COI policies give the organizational official or committee broad discretion in selecting and applying strategies on a case-by-case basis. Although such discretion may initially seem appealing, it also may generate allegations of disparate treatment among researchers. Alternatively, the

organization could consider identifying recurring types of COIs and developing a routine protocol for managing them. This approach not only would promote equitable treatment of researchers, but also would help ensure consistency from a compliance and risk management perspective, and even ease the work of the reviewing official or committee. The organization may also wish to offer a process by which researchers could appeal an unfavorable COI determination to a higher authority within the organization.

#### *Penalties for Non-Compliance*

The COI policy should describe the types of penalties that could be imposed for violating the policy. These penalties could include removal of the individual from the specific project, reprimand, suspension, or termination of the individual’s affiliation with the organization.

#### *Education and Training*

As with any compliance program, education and training is a critical component of the program. Training should address, at a minimum, the organization’s COI policies and procedures; any related forms that must be completed before, during or after the research; examples of common COIs and particularly suspect COIs; and penalties for non-compliance.

### **Ensure training addresses organization’s COI policies and procedures, as well as forms related to research and non-compliance penalties.**

With regard to institutional COIs in particular, the organization should be sure to train senior administrative and clinical staff to recognize relationships that might create organizational COIs and should educate them on the procedures for vetting and resolving them. Be sure to include in the training a discussion of real-life problems COIs have created for both organizations and individuals. It is important to ensure individuals

understand that failing to manage COIs effectively may affect them negatively on a personal level; this will help align the individuals' personal interests with the organization's broader compliance objectives.

The challenge of education and training in this area lies not only in developing the substantive content to be communicated through the training, but also in identifying—and actually reaching—the appropriate audiences. Regardless of the research setting, training should be provided upon the individual's affiliation with the organization, and on some periodic basis thereafter, if the individual's responsibilities will or may involve clinical research.

The COI training could be part of a broader research compliance initiative or addressed separately to ensure sufficient time and attention is paid to the topic. In addition, the organization should set up a system of checks and balances to ensure everyone who should be trained is trained. For example the IRB application could include a question asking if all researchers have received COI training (or broader research compliance training, if applicable), or the IRB could require "sign off" by the COI official or committee that training has occurred. If training has not occurred, the IRB could refuse to review the study, defer the study until training has been completed, or disallow participation in the study by those who have not completed training until such time as they complete training.

#### **Auditing Compliance with COI Policies**

As with any compliance initiative, regular auditing activities are key to determining compliance with an organization's COI policies and procedures. However, there are some inherent limitations for the auditor or compliance officer in auditing COI compliance, since the COI process relies primarily on investigators and other individuals to identify and report COIs. If these individuals do not report a particular COI, the auditor or compliance officer is unlikely to know that the COI exists, unless a lawsuit is filed or a whistleblower reports the COI within the organization or to a state or federal agency. In addition, even when COI policies are in place and adhered to, the policies themselves may be deficient, such that the underlying framework within which

COIs are managed by the organization is in need of remedy.

Notwithstanding these limitations, following are examples of some of the items auditors should consider when reviewing compliance with an organization's COI policies and procedures (and the federal and state requirements, if applicable):

- Review disclosure forms for identified conflicts. Ensure there are signed forms on file for all employees, contractors, medical staff members, IRB members and others for whom a COI disclosure form is required.
- Review files and other documentation kept by the IRB, COI committee, or the institutional COI official (as applicable) to ensure that each is following applicable procedures and satisfying their respective obligations for managing identified COIs.
- Review study files for documentation concerning financial payments from sponsors and for any evidence of unreported financial interests.
- Interview researchers regarding interests and relationships related to the research.
- If the IRB application requires disclosure of COIs or confirmation of COI training, review applications and compare to COI forms, information in study files, and centralized documentation of COI training (i) to determine if any inconsistencies exist and (ii) to ensure the IRB has taken appropriate action based on the responses in the application.
- Review informed consent forms to ensure COIs are disclosed as per policy or as mandated by the IRB, COI committee, or institutional COI official, as applicable.
- Review IRB documentation to ensure IRB members have submitted annual COI forms. Review IRB minutes to ensure members appropriately recused themselves where COIs existed.
- Review COI management decisions of the COI committee, the institutional COI official, the IRB, or other COI decision-maker and track to ensure the decision was implemented (e.g., informed consent disclosure, divestment of interest).

## **Conclusion**

Addressing and managing COIs in a proactive way through policies and procedures, education and training, and auditing activities is critical to minimizing risks to the health and welfare of subjects, preserving the reputation of the organization, and minimizing regulatory and liability exposure due to unchecked institutional and individual COIs. ■

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