Conflicts of Interest in Human Subjects Research

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Introduction

Increasingly, researchers in academia are encouraged to partner with industry to conduct research, or discover and patent their own inventions, with the eventual goal of bringing unique innovations and therapies to market. The money received as a result of licensing and commercializing patents arising from such research is often shared with the organization that has funded and/or supported the research. This is just one example of how conflict of interest (COI) is nearly impossible to avoid in academia today. COIs can also be non-financial and therefore subtler (for example, in the case of a researcher's personal desire to secure grants and publish to improve the likelihood of achieving tenure).

COIs may arise in human subjects research when researchers and/or organizations have financial or personal relationships that may compromise or appear to compromise the integrity of the research, protection of human subjects, and/or reputation of the researchers or organizations. To mitigate this concern, processes must be in place so that COIs are properly disclosed, reviewed, and managed. COIs are unavoidable, and are not intrinsically bad, as long as a process that promotes transparency and management is in place.

This module provides an overview of COIs in human subjects research by identifying when an interest or relationship may result in a COI, differentiating types of COIs and when they should be reported, and discussing challenges and strategies to manage both individual and institutional COIs.

Learning Objectives

By the end of this module, you should be able to:

- Define interests and relationships that may result in a COI.

- Distinguish different types of COIs in research.
- Identify federal regulations that govern disclosure and management of individual COIs.
- Discuss challenges and strategies to manage individual and institutional COIs (ICOIs) in research.
- Recognize the ethical concerns associated with COIs in research.

Recent History of COI in Human Subjects Research

In 1995, the U.S. Public Health Service (PHS), a division of the Department of Health and Human Services (HHS) responsible for oversight of ten federal agencies including the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC), became the first division of the federal government to implement regulations requiring disclosure and management of individual research-related COIs (42 CFR 50, Subpart F). In 2011, that regulation was revised and reissued. The goal of the PHS regulation is to promote objectivity in research by ensuring that PHS-funded research is free from bias due to individual researchers' COIs. The regulation requires that organizations applying for or receiving PHS funding have comprehensive policies (including disclosure and management of individual COIs) and researchers submit financial interest disclosures no later than the time of the application for PHS funding.

While many organizations were grappling with implementing the PHS regulation to identify potential individual COIs, few had considered the issues that institutional COIs (ICOIs) can present. ICOIs became an issue of concern in the human subjects research community when a study subject, Jesse Gelsinger, died as a result of the experimental therapy he received in the study. In the investigation that followed, it was discovered that both the researcher responsible for the study's oversight and the university where the research was conducted had significant financial ties to the company sponsoring the research, as well as an intellectual property interest in the therapy being evaluated in the study (Wilson 2010, 295-325).

The investigation also discovered that Gelsinger did not actually meet the eligibility criteria for enrollment (but was enrolled anyway), and the sequence of events that caused his death was also experienced in pre-clinical trials (but never reported in the subsequent clinical research plan). The financial interests of the researcher and university called into question whether there was potential bias in the way the study was developed and conducted. As a result of the Gelsinger case, the Association of American Medical Colleges (AAMC 2002) issued a report recommending that academic organizations develop policies to identify and manage institutional conflicts related to human subjects research.

What is a COI?

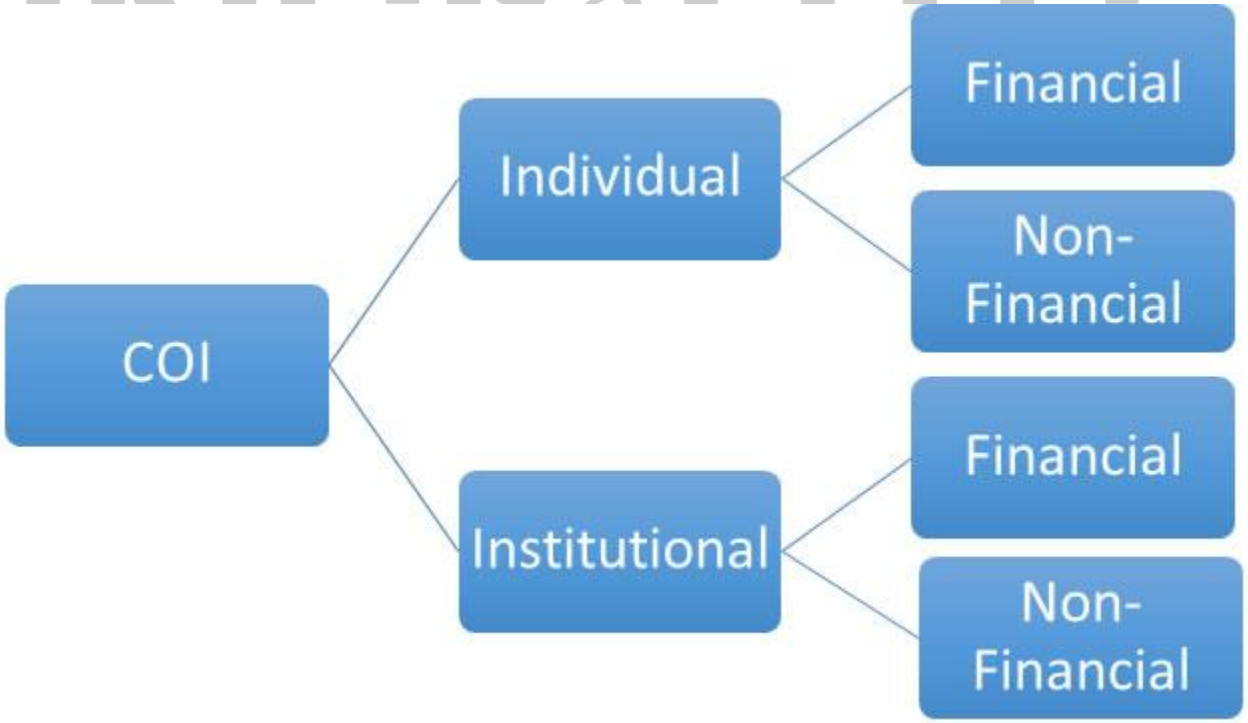
The term **conflict of interest (COI)** refers to situations in which financial or non-financial considerations may compromise, or have the appearance of compromising, a researcher's objectivity in meeting duties or responsibilities (including those associated with research activities). The potential bias that COIs may impart can affect multiple research activities including:

- Decisions about enrollment and inclusion/exclusion criteria
- Decisions choice of personnel to conduct the study
- Recruitment and consenting of research subjects
- Vendor selection in the purchase of equipment and other supplies
- Data collection, analysis, and interpretation
- Sharing of research results
- Choice of research design and statistical methods

Bias, or the appearance thereof, can be extremely detrimental to research integrity and erode the public trust in the research enterprise if not addressed in a transparent manner.

Types of COIs

The two major types of COIs are individual and institutional, which can be financial or non-financial in nature.



An **individual COI** may arise when an individual has a personal, financial, or other interest, which may affect or appear to affect the design, conduct, or reporting of the research (AAMC 2011).

An **institutional COI** may arise when the financial or other interests of an organization or institutional official, acting within his or her authority on the organization's behalf, may affect or appear to affect the objectivity of research conducted under the organization's auspices (AAMC 2011).

Financial versus Non-Financial COI

One example of a financial COI is a relationship that may have or appear to have the potential to result in financial gain. Examples of relationships that may create a financial COI include:

- Consulting
- Participation in industry speaker bureaus
- Ownership or equity interests in publicly or non-publicly traded companies
- Ownership of intellectual property that has been licensed or commercialized (for example, where royalties may result). Financial conflicts of interest tend to be tangible because they can be seen and measured. Review examples of financial COI.

A non-financial COI can arise in many ways. The desire for tenure or the need to produce data in support of an ongoing hypothesis are two examples of such COIs. Even personal relationships can result in a non-financial COI. Review an example of a non-financial COI.

Examples of COIs in Human Subjects Research

This section highlights some examples of COIs that may arise in the context of human subjects research.

Consulting and Advisory Board Membership

Researchers, as experts in their fields, are often sought after to consult, serve on advisory boards, or participate in speakers' bureaus for companies. These opportunities not only bring prestige to the individual researcher, but also to the organization by which they are employed. Nevertheless, these types of relationships often create significant COIs at organizations, and have the potential to bias the design, conduct, and/or reporting of the related research, and therefore must be disclosed and managed.

Intellectual Property Interests and Start-Up Companies

In the past few decades, advances in technology coupled with a change in federal law that allows universities to retain title to intellectual property developed using federal funds, have resulted in

significant improvements in commercialization of technologies developed in academia (Mowery and Ziedonis 2000, 187-220). A COI can arise when researchers conduct studies aimed at evaluating technology they developed and patented.

Many researchers who develop and patent technology while working at an academic organization go on to create companies designed to commercialize that technology (often called "spin-off" or "start-up" companies). After developing a start-up company, a researcher often serves as an officer or director in that company and may also want to conduct research sponsored by that company or involving the technology developed by and/or licensed to the company. Competing interests arise when an individual is both a researcher employed by the university and an owner of the company sponsoring the research. These potentially dueling roles may create COIs and conflicts of commitment, both of which can be difficult to manage.

Conflicts of Conscience

In the past few decades, another ethical challenge has come to light. It is referred to as a **conflict of conscience**, which comes about when a person has personal convictions that may jeopardize their objectivity in an area of science. For example, a Jehovah's Witness working in a hematology laboratory might not agree with research that takes place in that lab based on their beliefs. Conflicts of conscience may also arise in stem cell research. It can be difficult for some researchers to separate their moral beliefs from their passion for scientific advancement.

Institutional COI

An **institutional conflict of interest (ICOI)** may be present when the financial interests of an organization or institutional official (acting within his or her authority on the organization's behalf) may affect or appear to affect the research conducted under the organization's auspices (Policies of General Applicability 2011). An organization's financial interests can include receipt of gifts from donors, investments, and/or royalties from its researchers' commercialized inventions. As with individual researcher COIs, identification and management of ICOIs are integral to maintaining the public's trust in the organization, preserving research integrity, and protecting the rights, safety, and welfare of subjects.

To identify institutional officials' financial interests that may create ICOIs, many ICOI policies require such officials (typically, the president of the college/university, members of the board of

trustees, deans, chairs, and other administrators who have direct control over research being conducted at the organization) to disclose financial interests that may result from:

- Consulting
- Advisory board membership
- Intellectual property
- Equity in publicly and non-publicly traded companies
- Service as an officer, and/or director or board member of companies that may sponsor research or develop or manufacture products that will be evaluated in research conducted at the organization

To identify financial interests of the organization itself, periodic disclosure and review of its gifts, investments, and royalties is important to maintain transparency to avoid bias in the research conducted under the organization's auspices.

Note that to date, no federal regulations exist that govern disclosure or management of ICOIs. However, accrediting bodies (such as, the Association for the Accreditation of Human Research Protections Programs [AAHRPP]) require organizations seeking accreditation to have an ICOI policy governing human subjects research. Moreover, the AAMC and Association of American Universities (AAU) jointly issued guidance in 2008 recommending that universities develop and implement broad ICOI policies applicable to all types of research (not just human subjects research).

Federal Regulations and Policies Governing Disclosure of Individual COI

Federal regulations and policies governing disclosure of research-related individual COIs are broad, and in the case of the PHS regulation, somewhat complicated. The PHS, U.S. Food and Drug Administration (FDA), and National Science Foundation (NSF) regulations only address individual financial COIs.

There are some federal COI policies that are broader and may apply to personal relationships and ICOIs (for example, procurement-related issues that may create ICOIs). It is important for researchers to be aware of COI policies at their own organization, which often require disclosure beyond that required by any applicable federal regulations or policies.

PHS Regulation Regarding Objectivity in Research

Pursuant to the PHS regulation at 42 CFR 50 (Policies of General Applicability 2011), no later than at the time of proposal submission for PHS-funded research, each "investigator" named on a PHS proposal must disclose "significant financial interests" to a designated official at the applicant organization.

Investigator (researcher) is defined broadly as any person "responsible for the design, conduct or reporting of research funded by the PHS."

Significant financial interest (SFI) is defined as "a financial interest consisting of one or more of the following interests" that "reasonably appears to be related to the researcher's organizational responsibilities:"

- Remuneration received from a publicly traded entity in the 12 months preceding the disclosure and the value of any equity interest in the entity, which when aggregated, exceeds $5,000
- Remuneration received from a non-publicly traded entity in the 12 months preceding the disclosure, which when aggregated, exceeds $5,000 or any equity interest in a non-publicly traded entity
- Intellectual property rights and interests upon receipt of income related to such rights and interests (royalties that flow through the applicant organization are carved out and do not have to be disclosed)
- Reimbursed or sponsored travel (travel reimbursed or sponsored by a federal, state, or local government is carved out and does not have to be disclosed)

When an organization receives a PHS award, before expending any funds on the project, a committee or assigned individual must review the disclosures of all researchers on the project to determine whether any SFIs are related to the research. If there appears to be a related SFI, the organization must then conduct an analysis to determine whether the SFI in question rises to the level of being a "financial conflict of interest." PHS at 42 CFR 50, Subpart F (Policies of General Applicability 2011) defines a **financial conflict of interest (FCOI)** as an SFI that could "directly and significantly affect the design, conduct or reporting of PHS-funded research." If the SFI is determined to be a FCOI, then the organization must develop a management plan (if possible) and submit a FCOI report to the awarding agency; the FCOI report contains information about the researcher's FCOI as well as controls put into place to manage the conflict.

NSF COI Policy

The NSF also has a COI policy, found in its Proposal & Award Policies & Procedure Guide. Like the PHS regulation, the NSF policy requires researchers to disclose "significant financial interests" at the time a proposal is submitted to the NSF. The NSF's definition of "significant financial interest" differs somewhat from the PHS definition, but many of the same types of interests must be disclosed. Any related SFIs must be managed or eliminated prior to expenditure of funds.

FDA Regulation Governing Disclosure of COIs

The FDA's regulation governing disclosure of individual COIs became effective in 1999. It requires applicants submitting marketing applications for drugs, biologics, or devices to certify the absence of certain financial interests or to disclose financial interests of researchers who conducted clinical studies covered by the regulation at 21 CFR 54.4(a) (Financial Disclosure

2011). The regulation at 21 CFR 54.3(c) specifies that the FDA may refuse to file any marketing application that does not contain a disclosure of researchers' financial interests or a certification that the applicant acted with due diligence to obtain researchers' disclosures, but was unable to do so.

When FDA-regulated studies are conducted at academic organizations, researchers working on those studies are typically required to disclose COIs to the sponsor and to the Institutional Review Board (IRB) responsible for research oversight. If a researcher has a COI related to an FDA-regulated study, they may be required to have a COI management plan in place prior to engaging in the research, depending on the policies of their organization and the reviewing IRB.

It is important to note that the FDA's threshold for disclosure is much higher than that specified in either the PHS regulation or the NSF COI policy. In part for that reason, most academic organizations have COI policies that align with the PHS regulation and require disclosure at a lower threshold (some organizations have a zero dollar threshold). Therefore, researchers must be aware and comply with the COI policy at their own organization.

Management of COIs

Management of COIs is critical to ensuring research integrity, the public's trust in the organization, and the protection of human subjects' rights, safety, and welfare. Management of individual COIs is aimed at reducing the opportunity to bias the research.

COI Committees and Management Plans

Management controls used to reduce a researcher's opportunity to bias the research are either included in the study design or are additional controls put into place by a COI committee, which exists in some organizations.

A **COI committee** is a designated group at an organization that reviews relationships and interests that may create COI and develops and approves plans to manage those relationships and interests to minimize the risk that they will impart bias to the research.

A **management plan** is a document that explains the procedures or extras steps to be taken to minimize the risk of bias. The procedures or protections put into place to reduce the risk of bias are often called "controls." Management plans are typically tailored to the specific study and/or sponsor and the researcher's financial interests.

Examples of controls used in management plans may include one or more of the following:

- Adding an independent monitor to the study team to make sure that the research procedures are transparent
- Creating a safe environment for any research team member and/or student to report any perceived conflicts that may occur while the study is being conducted
- Disclosing the potential COI to the subjects in the informed consent form
- Reducing the researcher's role in the research if they have a COI (less interaction with subjects, less data analysis)
- Using an independent third-party review of data
- Ensuring a careful study design, which may include randomization and blinding
- Disclosure of the COI, including in publications or presentations of the study results
- Requiring an independent monitor to ensure that student progress is not affected by the conflicted mentor's activities (for example, doing work for the mentor's start-up company at the expense of doing work for a graduate or doctoral thesis)

Informed Consent as a Management Tool

One management control commonly utilized by COI committees to further reduce the risk of bias and protect human subjects is to preclude conflicted researchers from obtaining informed consent from subjects. This control is aimed at preventing such researchers from introducing bias into the research by exerting undue influence on subjects to agree to participate. Similarly, written disclosure of interested researchers' conflicts in the informed consent form is also used to minimize the risk of bias and protect the rights of subjects.

Example of Informed Consent Form Language with COI Disclosure
The researcher, Dr. Jane Smith, owns stock in the company that is paying for the research.

Additional Management Controls

COI committees utilize many tools in COI management plans to protect the integrity of research and human subjects. One tool is divestiture. If an individual researcher had a significant conflict

that was deemed unmanageable by other means, divesting (or selling) interests might be advised as a means of eliminating the source of the conflict.

When a researcher has a COI related to a study, a COI committee may require a third party (not associated with the research) to serve as an independent data reviewer, responsible for monitoring the research and reviewing the raw data at certain pre-determined intervals. An **independent data reviewer** is typically someone not involved with the research who does not have any related COIs (financial or otherwise) or report to the conflicted researcher. The independent data reviewer could be a faculty member within the university who monitors the raw data generated at that site.

The COI committee may also require researchers to disclose their financial interests in presentations and publications related to the research as another additional control.

Inherent controls (controls that are inherent in the study design) can often minimize the risk that a researcher with a COI may bias the research.

Table 1. Inherent Controls to Minimize COI	
Blinding Researcher to Treatment Arm	A researcher with a COI who is blinded to treatment arm would not likely be able to introduce bias into the research.
Independent Data Analysis	Use of an outside third party to conduct data analysis, so the researcher with the COI would not be able to introduce bias into the data analysis. In multi-site clinical trials, data analysis is often conducted by a contract research organization or the sponsor rather than by local researchers who may have financial COIs related to the study.
Limiting Subject Enrollment at Local Site	If a researcher at the organization disclosed a COI related to a multi-center clinical trial enrolling 1,500 subjects nationwide but only enrolling two subjects at the site locally, the fact that less than one percent of subjects will be enrolled at the local site minimizes the risk that the researcher could bias the research.
 **Consulting Related to an Industry-Sponsored Clinical Trial**	

Dr. Jones, a faculty member at your university, calls you to ask some questions about a contract her team is working on to conduct a clinical trial. Sun-X Pharmaceuticals will sponsor the study. Dr. Jones reports that she has done consulting for Sun-X in the past 12 months and has received $10,000 in remuneration from the company for her services. The study is a multi-center clinical trial; Dr. Jones will be the principal investigator (PI) of the local site at your university. The study will enroll 1,500 subjects worldwide; Dr. Jones expects to enroll ten subjects at your site. Sun-X has hired a contract research organization to conduct the data analysis.

- **Does Dr. Jones need to submit a COI disclosure to your university?**

  Because this is an industry-sponsored clinical trial, your organization's COI policy governs whether Dr. Jones needs to submit a COI disclosure. Many organizational COI policies contain thresholds that are consistent with those in the PHS regulation, requiring disclosure of remuneration received from publicly traded entities when, in aggregate, such remuneration exceeds $5,000 in the 12 months preceding the disclosure.

- **What types of controls might your university's COI committee utilize in Dr. Jones' COI management plan?**

  The COI committee may first consider whether there are any inherent controls that might reduce Dr. Jones' opportunity to bias the research. For multi-center clinical trials, local researchers are often only enrolling a very small percentage of the overall subjects, which limits their opportunity to introduce bias into the research. In fact, in this case, Dr. Jones only plans to enroll less than one percent of subjects, so this would be considered an inherent control that can be included in the management plan. Also, Dr. Jones will not be conducting data analysis at the local site. This is another inherent control that limits her opportunity to bias the research.

  Additional controls that a COI committee may put into place in Dr. Jones' COI management plan include:

- Precluding Dr. Jones from obtaining informed consent from subjects
- Requiring disclosure of Dr. Jones's COI in the informed consent form
- Requiring disclosure of Dr. Jones's COI in any publications or presentations that arise from the research

Management of ICOIs in Human Subjects Research

ICOIs may be managed utilizing some of the same controls discussed above for individual COIs (including inherent study design controls, reduced study roles or responsibilities, independent monitoring or data analysis, and required disclosure).

ICOIs can often be quite complicated. Therefore, management plans require the use of unique controls. If an ICOI has arisen because of an organization's financial interest, the first consideration may be whether the organization's interest can be divested to eliminate the COI altogether. Divestiture occurs when the organization eliminates its conflicting interest, usually by selling it (for example, selling its stocks in the medical device company that is sponsoring a clinical trial, so the organization would no longer be financially invested in the company and trial outcome). Divestiture is an example of a management control that can be utilized to reduce an organization's motive (whether actual or perceived) to bias the research.

However, if divestiture is not feasible, the ICOI may best be managed by involving external entities in the review and approval of the research. For example, many ICOI management plans require use of an external IRB when the organization has an equity interest in an entity related to human subjects research.

If an ICOI has arisen because an institutional official has financial interests related to the research, management of those interests may be achieved by removing that official from all lines of reporting tied to the research. For example, institutional officials are often responsible for approving research plans within the review process for IRB and grant submissions. When an institutional official has an interest in a research study they are tasked with reviewing, it may be prudent for them to recuse themselves from their normal role in the review process to avoid any perception of bias.

Just as individual COIs are disclosed in the informed consent form to subjects, so too are ICOIs. If the proposed research involves both an individual COI and an institutional COI, it is not uncommon for both interests to be disclosed in the informed consent document.

Intellectual Property and Faculty Start-up

Dr. Smith is a faculty member in your university's College of Medicine who has developed a new drug to treat glaucoma. The university has a patent on the drug and Dr. Smith has formed a start-up company, which has licensed the patent from the university. Dr. Smith is the chief operating officer of her start-up company and has a 70 percent equity interest. The university has a ten percent equity interest in the company. Dr. Smith wants to conduct a Phase I (first in humans) study to evaluate the safety of her new drug. She would like to conduct the study at your university and wants guidance on how the COI will be managed.

- **What COIs may need to be managed?**

Dr. Smith's proposed study has several related COIs, including both her individual interests and those of the university. Individually, Dr. Smith has an ownership interest in the drug that will be evaluated in the study because her company licensed the patent. Many organizations preclude researchers who hold equity in or are officers of their own start-up companies from serving as a PI of a human subjects research study investigating technology licensed to the company. Institutionally, the university's equity interest in Dr. Smith's start-up company creates a potential ICOI.

- **What types of management controls are typically used when a researcher has an individual COI related to human subjects research?**

When developing a management plan, a COI committee typically first considers whether there are any controls inherent in the study design. For example, if the interested researcher will not be conducting any data analysis, the opportunity to bias the data will be minimized. This is considered an inherent control.

COI committees also consider what types of additional controls will best minimize the interested researcher's opportunity to bias the research. In human subjects research, interested researchers are often precluded from obtaining informed consent from subjects; this control is aimed at preventing any perception of undue influence during the informed consent process.

Additionally, interested researchers are typically required to disclose their interest in the informed consent form. This control is designed to promote transparency and to give subjects the opportunity to make a more informed decision.

Another management control that is often employed in human subjects research is the use of an independent data reviewer. This is particularly common for small, researcher-initiated studies in which there is no external entity (for example, a sponsor or contract research organization) reviewing and analyzing the data. The independent data reviewer is often another faculty member who is not a member of the study team, does not have any related financial interests, and is not supervised by the interested researcher.

IRB Members and COIs

To ensure the integrity of the IRB process, IRBs typically have policies regarding IRB members reviewing research plans when they may have a perceived or actual COI. Many IRBs also require members to complete annual COI disclosures. IRB members should not participate in any IRB action (including the initial and continuing review of any project related to research in which they have a conflicting interest) except to provide information requested by the IRB. IRB members are expected to self-identify conflicting interests and should notify the IRB staff when assigned to review research in which they have a potential COI (which may require staff to re-assign the research plan for review to another IRB member).

An IRB member may have a COI when the IRB member or an immediate family member:

- Is involved in the design, conduct, or reporting of the research
- Has a financial interest related to the research or that may be affected by the outcome of the research
- Has a proprietary interest being evaluated in the research
- Has a leadership position in or consulting/advisory relationship with an entity related to the research
- Any other situation in which an IRB member believes that they may not be able to deliberate objectively on a research plan

Generally, IRB members should recuse themselves when the IRB reviews research in which they have may have a COI. The IRB will have a discussion once the conflicted member has recused him/herself. If the COI status of an IRB member changes during a study, the IRB member is required to disclose this to the appropriate official.

Summary

It is important to think about the transparency of any relationship or circumstance where a reasonable unaffected individual might conclude that an individual's decisions might bias the outcome of research. While there are situations where a COI is obvious, there may be many that are not obvious. If not dealt with transparently, bias in research or the appearance of any biases can be extremely detrimental to the integrity of research and erode the public trust in the research enterprise. When there are strong efforts to manage the perception of relationships within research collaborations, and the plan to manage them is followed, it leaves those evaluating and conducting the research to focus on the data and avoid the distraction of any potential improprieties.

When organizations have strong compliance programs to ensure disclosure and management of COI, the research conducted within those organizations and the resulting outcomes can be trusted and devoid of distraction from any real or potential improprieties. Transparency, through disclosure and management of COI, is critical to the integrity of research, advancement of science, and the protection of human subjects.

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