

Disclosure, Evaluation and Management of Financial Conflict of Interest in Research

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ABSTRACT

The most difficult aspect of financial conflict of interest (FCOI) and compliance with federal regulations involves the assessment and management of identified FCOIs. While some federal agencies provide examples of the structure and content of management plans, it is up to institutions to evaluate FCOI to determine whether and how research may be conducted when conflict is present. Unfortunately, there is minimal federal guidance on the evaluation and management aspect of FCOI and institutions must carefully consider and implement appropriate procedures to ensure compliance. Once a conflict has been disclosed and is known by the institution, the burden of responsibility falls squarely on the institution. Without clear direction from federal agencies, institutions may become paralyzed with indecision or refuse to allow any research to proceed where there is known conflict. Sources exist which provide some guidance on how to mitigate conflicts of interest. This paper provides information and steps to assist institutions with the evaluation and management of FCOI.

INTRODUCTION

Objectivity is essential in scientific research in order to maintain public trust and protect the health and safety of research participants, as well as those relying on the integrity of the research results. While it is

understood that university researchers may engage in the pursuit of outside economic interests, due consideration must be given to determining whether such interests could bias, or have the appearance of biasing, the design, conduct, or reporting of research. In addition, certain organizational interests

constitute a financial conflict of interest (FCOI) and must also be scrutinized. While federal agencies including the National Institutes of Health (NIH) and the National Science Foundation (NSF) have implemented specific policies regarding the disclosure of FCOI, what remains vague is how institutions should evaluate and manage FCOI.

Federal Regulations

Federal FCOI regulations are aimed at ensuring that the design, conduct, or reporting of research funded under the Public Health Service (PHS), NSF and other applicable agency-funded grants and cooperative agreements will not be biased by any conflicting financial interest of investigators responsible for the research. Current FCOI regulations include 42 CFR Part 50 Subpart F (grants and cooperative agreements), 45 CFR Part 94 (contracts) effective October 1, 1995, Final Rule on Financial Conflict of Interest Regulations (*Federal Register*, 2011), and National Science Foundation Award and Administration Guide, chapter IV. A. These FCOI regulations establish standards for the identification and mitigation of potential, actual, and apparent FCOI.

Disclosure

When a researcher has an outside economic interest that could affect the (apparent or real) conduct of a research project, FCOI may threaten the objectivity and integrity of research. In order to ensure

that FCOIs are identified and appropriately addressed, the National Institutes of Health (NIH) and NSF have specific policies for the disclosure, management, and reporting of FCOI. A summary of these policies is as follows:

NIH

An investigator is responsible for complying with their institution's FCOI policies and procedures, completing training on FCOI, and disclosing required significant financial interest (SFI) information to their institution whether the investigator is planning to participate in or is participating in PHS or other applicable agency-funded research.

Investigator

Investigator refers to “the project director or principal investigator and any other person, regardless of title or position who is responsible for the design, conduct, or reporting of research funded by the PHS (e.g., NIH), or proposed for such funding, which may include, for example, collaborators or consultants” (NIH, 2014).

A Financial Conflict of Interest (FCOI) exists when an institution “reasonably determines that an Investigator’s Significant Financial Interest is related to a NIH-funded research project and could directly and significantly affect the design, conduct or reporting of the NIH-funded research” (NIH, 2014). A Significant Financial Conflict of Interest “is defined by the regulation as anything of monetary value, including but

not limited to salary or other payments for services (e.g., consulting fees or honoraria); equity interests (e.g., stocks, stock options, or other ownership interests); and intellectual property rights (e.g., patents, copyrights, and royalties from such rights)” (NIH, n.d.). A reportable Significant Financial Interest (SFI) is one that an investigator has that could directly and significantly affect the design, conduct, or reporting of NIH-funded research. The determination regarding whether or not there is a Significant Financial Interest is made by the institution’s designated official(s).

The investigator must disclose SFIs, including those for their spouse and dependent children (1) at the time of application for research funding; (2) within thirty days of discovering or acquiring a new SFI; and (3) at least annually, in accordance with the specific time period prescribed by the institution, during the period of award.

Institutions are responsible for maintaining an up-to-date, written, enforced FCOI policy that complies with federal regulations and making the policy publicly accessible. If no publicly accessible website is available to display the Institution’s FCOI policy, access to the written policy must be provided upon request within five business days. Additional institutional responsibilities include, but are not limited to:

1. Soliciting and reviewing disclosures of investigators’ SFIs that are reasonably related to an investigator’s institutional responsibilities via a designated institutional official;
2. Determining whether an investigator’s SFI is related to the funded research and, if so related, whether the SFI is a FCOI (SFI that could directly and significantly affect the design, conduct, or reporting of the funded research);
3. Developing and implementing management plans, as needed, to manage FCOIs for awardee investigators and subrecipient investigators, if applicable;
4. Submitting initial and annual FCOI reports to the sponsor in accordance with the regulation;
5. Completing retrospective reviews when there is noncompliance with the institution’s policy or the FCOI regulation and updating any previously submitted FCOI report, if required after the retrospective review is complete;
6. Submitting mitigation reports when bias is found in funded research as a result of the finding from a retrospective review; and
7. Adequate record-keeping of disclosure, encompassing the institution’s response to and all actions taken regarding such disclosures. Records must be maintained for at least three years from

submission date or as specified in 45 C.F.R. 74.53(b) and 92.42 (b).

NSF

Investigators must disclose all SFIs (including those of the investigator's spouse and dependent children) (1) that would reasonably appear to be affected by the research or educational activities funded or proposed for funding by NSF; or (2) in entities whose financial interests would reasonably appear to be affected by such activities.

SFI means anything of monetary value, including, but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interest (e.g., stocks, stock options or other ownership interests); and intellectual property rights (e.g., patents, copyrights and royalties from such rights).

Institutions employing more than 50 persons must maintain an appropriate written and enforced policy on conflict of interest. NSF refers institutions to university associations and scientific societies for guidance in the development of FCOI policies. At a minimum, an institutional policy must ensure that investigators have provided all required financial disclosures at the time a proposal is submitted to NSF, and during the period of the NSF award, either on an annual basis or as new reportable SFIs are obtained. Additional NSF policy requirements include:

1. Designation of one or more persons to review SFI disclosures, determine whether a conflict of interest exists, and determine what conditions or restrictions, if any, should be imposed by the institution to manage, reduce, or eliminate such conflict of interest.
2. Adequate enforcement mechanisms, and provision for sanctions where appropriate.
3. Arrangements for keeping NSF's Office of the General Counsel appropriately informed if the institution finds that it is unable to satisfactorily manage a conflict of interest
4. Maintenance of records of all financial disclosures and of all actions taken to resolve conflicts of interest for at least three years beyond the termination or completion of the grant to which they relate, or until the resolution of any NSF action involving those records, whichever is longer.

EXCLUSIONS

The applicability of financial conflict of interest disclosures varies between PHS and NSF. NSF exempts organizations with fewer than 50 employees from the FCOI requirements. However, with PHS there are no exemptions from the requirements.

The term "significant financial conflict of interest" (SFI) excludes the following specific types of interests:

1. Salary, royalties, or remuneration from the employing institution

2. Income from seminars, lectures, or teaching engagements sponsored by public or nonprofit entities
3. Income from service on advisory committees or review panels for public or nonprofit entities
4. An equity interest that when aggregated for the investigator and the investigator's spouse and dependent children, meets both of the following tests: (1) does not exceed \$10,000 in value (NSF) or \$5,000 (PHS) as determined through reference to public prices or other reasonable measures of fair market value, and (2) does not represent more than a 5% ownership interest in any single entity
5. Salary, royalties, or other payments that, when aggregated for the investigator and the investigator's spouse and dependent children, are not expected to exceed \$10,000 (NSF) or \$5,000 (PHS) during the next 12-month period.

EVALUATION AND MANAGEMENT

As described above, both NIH and NSF have detailed, written policies regarding FCOI requirements, including a requirement for institutions to evaluate and manage FCOI. Institutions have implemented certain policies and procedures to comply with the regulations, but many institutional policies focus primarily on what constitutes FCOI, and whether and how to disclose FCOI. And

while institutional policies may include procedures for the evaluation of FCOI, what is unclear is how to evaluate and mitigate risk factors related to known conflicts of interest. This uncertainty can lead to institutional paralysis or a complete refusal by institutions to allow research to proceed under any circumstance when there is FCOI.

On the other hand, lack of proper institutional controls and disregard for identified conflicts can lead to research misconduct. Unmitigated conflict can also lead to injury or harm to research study participants and can damage the entire research enterprise by reducing public trust in research (Columbia University, n.d.).

The Bayh-Dole Act of 1980 was established to allow universities to retain ownership rights to intellectual property developed from federally funded research. It also allowed universities to share royalties with faculty inventors. This gave institutions and researchers a financial stake in the outcome of research, and created an inherent conflict particularly with respect to industry-sponsored clinical research (Beinkowski & Goldfarb, 2011).

A case at Duke University in 2010 involving Dr. Anil Potti provides a prime example of both individual and institutional conflict of interest, and the risks when successful research leads to potential commercialization and financial gain. In this case, Dr. Anil Potti was a research

scientist who claimed to have found the “holy grail of cancer” (CBS News, 2012). Dr. Potti claimed to have “discovered how to match a patient’s tumor to the best chemotherapy drug” (CBS News, 2012). Dr. Potti and his colleague, Dr. Joseph Nevins, showed tremendous advances with their research, including research that resulted in patent applications and a startup company to market their technology. A team of biostatisticians from MD Anderson Cancer Center, Drs. Keith Baggerly and Kevin Combes, attempted to reproduce the work in order to use the new technique. Serious flaws in the research were noted and although Dr. Potti and Dr. Nevins made attempts to publicly correct errors, many more were identified. Concerns were expressed to the administrators at Duke University. Research was temporarily halted for an external review, yet no problems were found in the review and the research was allowed to resume.

Upon Dr. Potti’s resignation from Duke in 2010, allegations from scientists elsewhere were being made, claiming that Dr. Potti had “stolen their data for inclusion in his paper in the *New England Journal*” (*The Economist*, 2011). Further investigation into the matter began and Duke made national headlines with this scientific misconduct investigation. The university found “lapses and errors including being slow to deal with potential financial conflicts of interests” (*The Economist*, 2011)

that were declared by the investigators. While the research misconduct became the focal point in this case, the layers of FCOI involved cannot be ignored.

An earlier case in 1999 involving a gene therapy trial at the University of Pennsylvania resulted in the death of 18-year-old Jesse Gelsinger (Wilson, 2010). The Gelsinger case brought to light not only the importance of the proper vetting of FCOI, but also the need for post-approval monitoring. In this case, the principal investigator, Dr. James Wilson, and Penn both had an interest in the biotech startup company funding the study, Genovo. In addition, Genovo agreed to give Penn \$21 million to fund research at Penn in exchange for a license to existing technology, and first right to license new technology resulting from such research (Wilson, 2010). While Penn had obtained outside counsel to develop and approve a management plan for the trial in light of the investigator and Penn’s conflicts of interest, what occurred during the conduct of the trial is what led to the death of Jesse. Namely, the protocol consent was modified by Wilson and co-investigators after approval by the IRB, and information about the death of animals and potential for toxicity and death were removed. In addition, Wilson continued to be directly involved in the conduct of the study despite Penn’s requirement that such participation be “avoided” (Wilson, 2010). Proper

oversight, independent monitoring and random study audits could have saved Jesse.

As demonstrated by the Potti and Gelsing case, proper controls are needed when FCOI is present, and most importantly when research involves human subjects. The Association of American Medical Colleges (AAMC) - Association of American Universities (AAU) Advisory Committee Report on Financial Conflicts of Interest in Human Subjects Research (2008) includes a template for analyzing conflicts

of interest in research involving human subjects. The steps for evaluation and management of conflicts included in the AAMC report can be applied to FCOI in non-human research, as well. Once a conflict of interest has been disclosed, the first step in assessment is a risk benefit analysis to determine if the conflict of interest can be managed, reduced or eliminated (AAMC, 2008). Figure 1 illustrates considerations for a risk-benefit analysis.

FCOI Risk-Benefit Analysis

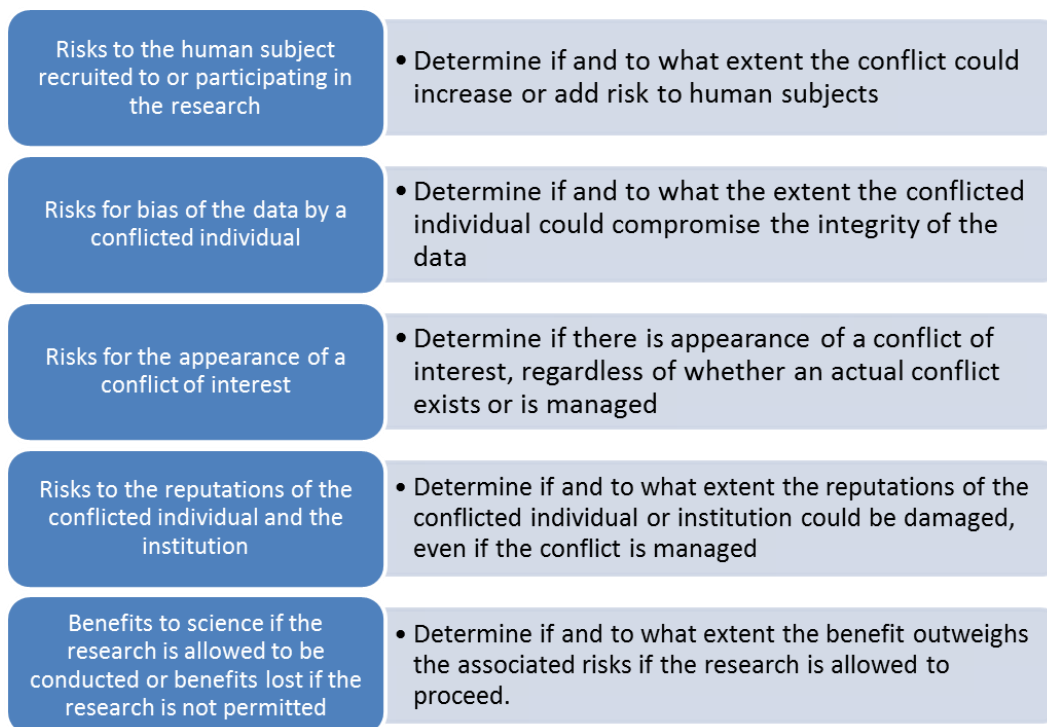


Figure 1. FCOI Risk-Benefit Analysis

Note: Adapted from AAMC report (2008), Appendix B

The next step in FCOI evaluation is determining whether the conflict can be managed, reduced or eliminated. If a conflict cannot be eliminated, and the benefits outweigh the risks, a management plan must be created. According to the NSF policy, examples of conditions or restrictions that might be imposed to manage, reduce, or eliminate conflicts of interest include, but are not limited to:

- a. public disclosure of significant financial interests;
- b. monitoring of research by independent reviewers;
- c. modification of the research plan;
- d. disqualification from participation in the portion of the NSF-funded research that would be affected by significant financial interests;
- e. divestiture of significant financial interests; or
- f. severance of relationships that create conflicts.

According to NIH, conditions or restrictions that might be imposed to manage a financial conflict of interest include, but are not limited to:

- a. Public disclosure of financial conflicts of interest (e.g., when presenting or publishing the research);
- b. For research projects involving human subjects research, disclosure of financial conflicts of interest directly to participants;

- c. Appointment of an independent monitor capable of taking measures to protect the design, conduct, and reporting of the research against bias resulting from the financial conflict of interest;
- d. Modification of the research plan;
- e. Change of personnel or personnel responsibilities, or disqualification of personnel from participation in all or a portion of the research;
- f. Reduction or elimination of the financial interest (e.g., sale of equity interest); or
- g. Severance of relationships that create financial conflicts.

The NSF and NIH guidance can be used by institutions in the creation of appropriate FCOI management plans.

As discussed in the book, *Rescuing science from politics* (Wagner & Steinzor, 2006), certain fundamental principles should be followed to protect research integrity, including *independence*, or the ability to conduct research without restriction, including sponsor influence and *transparency* via honest communication of data and research results to the research community and public. What is also discussed and perhaps most critical is the preservation of “disinterestedness” in the conduct of science. That is, science must be pursued objectively without external influence and for the pure benefit of scientific discovery. In the Duke situation, the FCOI created with the establishment of

a company and a clear opportunity for financial gain, disinterestedness is lost and risks are great. Similar conflict is created when private companies (e.g., pharmaceutical companies) sponsor research or enter into consultancy agreements with faculty for assistance with writing protocols, FDA submissions, journal articles, etc.

Figure 2 includes components necessary for proper evaluation and management of financial conflict of interest. In cases where human subject research is proposed and an individual conflict of interest has been identified, the AAMC report (2008)

indicated that there should be a presumption that the individual should not be allowed to conduct human subject research. This presumption is rebuttable, but there must be a thorough review and determination by institutional representatives, and such review must include compelling circumstances for participation by the conflicted individual. The Gelsinger case demonstrates the importance of further institutional vigilance in the form of independent monitoring and oversight, even after appropriate approvals are given.

Evaluation & Management of Financial Conflict of Interest (FCOI)

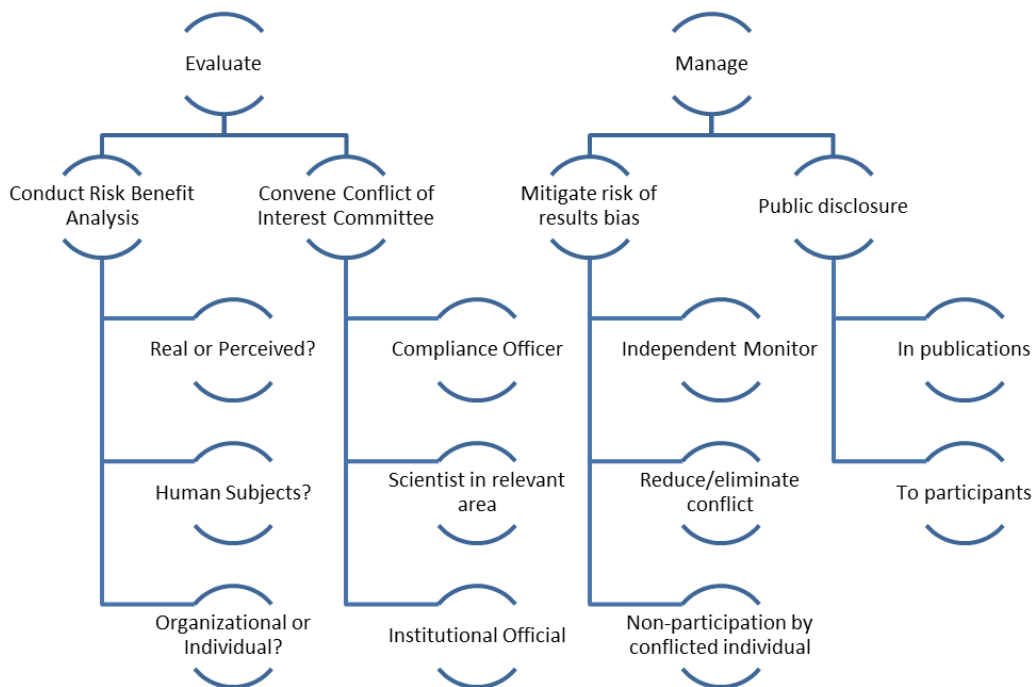


Figure 2. Components of Evaluation and Management of FCOI

COMPLIANCE

Federal regulations require that institutions establish adequate enforcement mechanisms, provide for employee sanctions, and take other administrative action, where appropriate. Institutions may determine the nature of the enforcement mechanisms and sanctions.

NIH

After determination has been made of an existing FCOI, the institution has 60 days to report the FCOI. If disclosure of a FCOI is not made in a timely manner by the investigator, the Institutional Official has 60 days to review the identified SFI and make a determination as to whether the FCOI exists and if it is related to the NIH-funded research. The institution must then implement a management plan and report these actions to NIH.

If an investigator fails to comply with an institution's FCOI policy or a FCOI management plan, the institution must complete a retrospective review within 120 days of determining noncompliance. This review will include evaluation of the investigator's activities and the NIH-funded research, documentation of the institution's methodology of reviewing the SFI, and determination of whether the design, conduct, or reporting of research was biased.

If bias is found, the institution must submit a mitigation report to the NIH, in

accordance with 42 CFR 50.605(b)(3).

Depending on the nature of the FCOI, an institution may determine that additional interim measures are necessary with regard to the investigator's participation in the research until such time that the institution completes the retrospective review in accordance with 42 CFR 50.605(a)(3) and 42 CFR 50.605(b)(3).

As part of the management plan, the institution is responsible for annually updating the agency with the status of the FCOI, along with any changes made to the management plan. Descriptions of the following elements must be provided in the management plan:

- (A) Role of investigator identified as having a FCOI and the duties in the research project;
- (B) Stipulations of the management plan;
- (C) Design of the management plan and the safeguards that will be in place for the research project;
- (D) Confirmation from the investigator indicating agreement with the management plan;
- (E) Steps the institution will take in order to monitor the management plan to ensure compliance by the investigator; and
- (F) Additional information as needed (Arango et al., 2014).

NIH will review FCOI information and take appropriate action, or require the institution to take further action. NIH may

advise the institution on how to promote and maintain appropriate objectivity in the NIH-funded research project. NIH may further require institutions employing such an investigator to enforce corrective actions prior to receipt of an NIH award involving the investigator.

Institutions are responsible for maintaining an up-to-date, written, enforced FCOI policy that complies with federal regulations and making the policy publicly accessible.

NSF

The NSF FCOI policy did not adopt the same changes as NIH that became effective August 24, 2012. Instead, NSF relies on the Office of the General Counsel (OGC) to follow up with the institution once an unmanageable conflict of interest is reported. Institutions are responsible for notifying the NSF OGC when an identified FCOI for an NSF-funded project cannot be managed. Notification of any conflict of interest that cannot be managed, reduced, or eliminated, and notifications when research will proceed without conditions or restrictions when a COI exists must be submitted to NSF via the Fastlane System (NSF AAG, 2014). Upon receipt of notification from an institution, the OGC will evaluate the case as follows:

1. Examine a copy of the institution's conflict of interest policy to determine if it includes procedures for addressing unmanageable conflicts.

2. Contact the authorized institutional representative to determine what actions the institution plans/has taken with respect to unmanageable conflict of interest.
3. Request confirmation from the institution when such actions have been completed.

CONCLUSION

While federal agencies including the NIH and NSF have implemented specific policies regarding the disclosure of FCOI, what remains vague is how institutions should evaluate and manage FCOI. Federal regulations related to FCOI have been established to manage the conflict created in situations such as the Potti and Gelsinger cases, and to ensure proper controls for the preservation of scientific integrity and, most importantly, protection of human subjects.

Institutional policies have been written and implemented to ensure compliance with federal regulations, but the burden of disclosure and management falls squarely on the scientist and the institution. Proper procedures, internal controls, an FCOI management committee including unbiased members, an empowered IRB, and a culture of transparency and compliance are critical to successful management of FCOI. When there is complete refusal by institutions to allow research to proceed in the presence of FCOI, or when questionable research sits idle on the desk of paralyzed institutional officials who are just not sure how to

proceed, everyone loses. Institutions must look directly into the face of conflict, utilize available tools, and take appropriate steps to evaluate and mitigate risks associated with individual and institutional FCOI. Institutions and investigators must ensure that the safety of human subjects is paramount, and that FCOI management

plans are detailed and enforced, including proper post-approval monitoring. Admittedly, in some cases, FCOI may not be manageable by an institution and other options must be explored. But we hope this paper will help mobilize officials into making informed decisions so that research may continue for the public good.

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