

Identifying and Managing Nonfinancial Conflicts of Interest for Systematic Reviews



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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodologic issues in systematic reviews. These methods research projects are intended to contribute to the research base and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although they may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers and the health care system as a whole by providing important information to help improve health care quality. The reports undergo peer review prior to their release as a final report.

We welcome comments on this Methods Research Project. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Identifying and Managing Nonfinancial Conflicts of Interest for Systematic Reviews

Structured Abstract

Objectives. Systematic reviews of comparative effectiveness topics are increasing in number, and groups including the Institute of Medicine emphasize the importance of attention to financial conflicts of interest. Little guidance exists, however, on how to manage the risk of bias for systematic reviews (SRs) from nonfinancial conflicts of interest (NFCOI) such as strongly held beliefs, personal relationships, and desire for career advancement. Our objective was to provide practical guidance on ensuring adequate clinical or content expertise while maintaining independence of judgment on SR teams by (1) defining NFCOI as it applies to SR teams, (2) developing guidance and an instrument, supported by examples, on to identify, characterize, and manage NFCOI, and (3) improve transparency of judgment regarding NFCOI for users of reviews.

Study design and setting. Fourteen workgroup members reviewed existing guidance from international and domestic institutions on managing conflicts. We built on these approaches to define NFCOI. We then developed practical guidance in the form of an instrument and examples for each potential source of conflict. Authors revised the draft document following peer review and public comment.

Results. We modified the Institute of Medicine’s definition of conflict of interest to arrive at a definition specific to NFCOI in the context of systematic review. We define NFCOI as “a set of circumstances that creates a risk that the primary interest—the quality and integrity of the systematic review—will be unduly influenced by a secondary or competing interest that is not mainly financial.” We believe that context influences the risk of NFCOI. We propose questions for funders and SR principal investigators to evaluate whether the SR topic is subject to intense advocacy, active policy debate, large interspecialty variations, and limited availability of clinical or content expertise. Responses to these contextual questions can serve as a guide to creating an SR team that appropriately balances critical clinical and content expertise with independence of judgment. Once the team is assembled, we suggest additional questions on personal beliefs, previously published opinions, institutional relationships, and career advancement. Once the risk of NFCOI has been identified, the range of options for managing conflicts include: disclosure followed by no change in the SR team or activities, inclusion on the team along with other members with differing viewpoints to ensure diverse perspectives, exclusion from certain SR activities, and exclusion from the project entirely. The selection of one or more approach will depend upon the risk of NFCOI based on the context of the topic.

Conclusion. NFCOI, when ignored, can call into question the impartiality of a review. Equally, the results of a review can be invalid when management of NFCOI results in the exclusion of necessary topical expertise. This document is a consensus effort attempting to achieve the appropriate balance between supplying needed expertise and minimizing NFCOI by proposing approaches to identify and evaluate NFCOI. However, the utility of these approaches and barriers to implementation must be investigated.

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Introduction

Clinicians and patients regularly face important health care decisions without adequate information.¹ Systematic reviews (SRs) serve a critical role in ensuring that health care decisions are evidence based. In doing so, they ensure that the recommended care is given “to the right patient at the right time, resulting in improvement in that patient’s health.”² SRs summarize and synthesize large and sometimes contradictory research results, clarify their implications for diverse stakeholders, account for variations in the risk of bias of individual studies when interpreting results, compensate for lack of power in individual studies through pooling, and identify findings relevant to populations, and subgroups of interest. To meet all these goals, SRs must be credible.

Rigorous methods and consistent application of standards lay the foundation for ensuring the credibility of SRs, but are not sufficient. An unavoidable component of SRs is the role that judgment plays in the framing of research questions, the selection and application of methods, the conduct of the specific research steps, and the interpretation of the results. Research has shown that financial conflicts of interest (COI) can threaten the internal and external validity of primary studies as well as SRs.³⁻⁵ Conflicts may go well beyond the financial: strongly held beliefs (personal or professional) and the desire for academic recognition or advancement can also bias the conduct or reporting of SRs.³ These issues, which fall under the umbrella of nonfinancial conflict of interest (NFCOI), are the focus of this document, specifically as they apply to SR team members. The guidance in this document does not address NFCOI for other participants in the review process, such as Technical Expert Panel members, stakeholder groups, and peer reviewers. Some stakeholders or Technical Expert Panel members may be selected specifically for particular professional or personal perspectives that could be considered COI, and efforts must be made to identify and balance these perspectives. We view potential NFCOI issues within the SR team to be quite separate, and because such issues are not often considered, we believe it is all the more important that guidance be provided on their management.

Prominent organizations involved in the production of SRs take different approaches in addressing COI (Appendix A). Many organizations tend to focus on financial COI (FCOI); such conflicts are considered to be easier to assess in objective terms because they are quantifiable and easier to mitigate.⁶⁻⁸ Other organizations describe NFCOI in vague terms such as “personal association,” “professional or intellectual bias,” or “other” conflicts, but provide little guidance on how to identify, assess the severity of, and manage the NFCOI.⁹⁻¹²

The purpose of this document is to (1) define NFCOI as it applies to SR teams, (2) create practical suggestions for SR teams, through examples, about how to identify, characterize, and manage NFCOI, and (3) improve transparency of judgment regarding NFCOI for users of reviews. Given the lack of evidence in this area, we believe that any list of NFCOI rules for all circumstances would be arbitrary. Our intent, therefore, is not to create absolute standards; rather, we intend to offer users an approach for recognizing NFCOIs and addressing them. This document also aims to engage the community in further discourse on this vital issue. This work is exploratory: As the approach is implemented, its feasibility, burden on investigators, and impact on reducing risk of bias should be concurrently assessed.

We do not believe that the presence of NFCOI implies professional misconduct on the part of the individuals who disclose these circumstances. Our work builds on the premise that NFCOI needs to be evaluated in the context of each review. A given faculty or staff member who may have NFCOI for one topic may have no NFCOI for other review topics. The disclosure of

conflicts does not inevitably lead to punitive action, nor should it be viewed as requiring such action.

Anticipated users of this guidance include the Agency for Healthcare Research and Quality (AHRQ), the Evidence-based Practice Centers (EPCs) funded by AHRQ, organizations with similar interests (e.g., Institute of Medicine [IOM], the Cochrane Collaboration, the Patient-Centered Outcomes Research Institute [PCORI]), other SR teams, and SR users. This guidance may be of particular interest to organizations sponsoring SRs that have audiences with competing interests. Taxpayer-funded reviews, in particular, have an obligation to meet the needs of a broad audience and must be particularly sensitive to the risk of bias. We believe that when funders establish and maintain clear and consistent standards for disclosure and management of NFCOI, public confidence in the products is improved.

This document focuses on the management of competing concerns, that is, ensuring adequate clinical or content expertise on SR teams while maintaining independence of judgment. Clinical and content expertise, in our view, can arise from a broad range of clinical, practice, and research experience and is not a term reserved solely for experts whose primary research will be included in the SR. By clinical expertise we refer to expertise gained from patient care for a specific clinical area. For nonclinical topics, content expertise may arise from research or practice in the substantive concerns of the field. Our view is that such clinical and content expertise is vital to interpreting the evidence appropriately and framing the discussion in terms of decisional dilemmas. Our approach contrasts with that of Gøtzsche and Ioannidis, who advocate that SRs exclude “content area experts” by default:¹³ we anticipate that a balance between scientific rigor and utility will require the involvement of methodologists as well as content and clinical experts.¹⁴ On the other hand, our perspective is distinct from that suggested by Krimsky, who proposes that intellectual interests cannot be separated from the scientific enterprise, are generally a matter of public record, and “a scientist’s propensity toward one theory or another can be discussed and addressed in open communication with the scientific community.”¹⁵ In our view, SRs, unlike primary research, require the interpretation and synthesis of studies for an entire body of evidence that may be based on a variety of theories. Because SR teams and expert panels consist of a limited number of individuals, a small number of investigators or experts sharing a common interest could guide the review in a biased direction and open communication with the scientific community may not suffice to correct this bias. Our approach seeks to mitigate the risk of bias while ensuring clinical utility and relevance for decisionmaking.

Methods

We used a workgroup consensus process to define NFCOI, suggest ways to elicit information on NFCOI, and propose methods to mitigate the bias from NFCOI. The workgroup for this chapter included 16 individuals from 10 EPCs and AHRQ. All members of the workgroup had specifically expressed interest in working on the guidance, and many had prior experience assessing and handling COI of staff, consultants, and expert panelists. The workgroup lead (MV) set the scope and timeline, scheduled and led conference calls, developed and distributed meeting summaries, assigned and coordinated tasks of group members, drafted sections of the guidance chapter, and edited materials. All members participated in monthly conference calls, made suggestions regarding the scope of the chapter, and submitted written contributions to the chapter.

The workgroup identified several examples of NFCOI, and in discussions, expanded or collapsed categories as relevant. For instance, an early draft separately discussed NFCOI in cases of intense advocacy and policy debate, but feedback from reviewers and workgroup members suggested that these two sources of NFCOI should be combined because the central issues were similar. We developed questions to elicit responses for each source of bias separately, and then combined and revised questions to flow in a logical sequence. This document, including specific examples and NFCOI questions, was revised in response to peer review. We also posted the document for public comment but received no feedback. We reviewed published COI policies and recommendations from several prominent organizations that sponsor, conduct, publish, or are otherwise involved in the production of SRs. These organizations include the IOM,^{7,9} the Cochrane Collaboration,¹⁰ the U.S. Department of Health and Human Services,⁶ the International Committee of Medical Journal Editors,¹⁶ the National Institute for Health and Clinical Excellence,¹² and PCORI.¹¹ From these policies, we developed our working definition for NFCOI specifically for SR teams. We also searched for empirical evidence and well-established theoretical frameworks on NFCOI but found none. Therefore, we cannot unequivocally suggest guidance about managing NFCOI across all topics and contexts.

Our approach is to highlight circumstances in which NFCOI may be present; use real-world examples whenever possible, based primarily on our experience with some details altered for reasons of confidentiality. Our purpose was to demonstrate how they may be considered conflicts; and provide guidance on assessing whether the conflicts pose a risk of bias.

Definition of Conflict of Interest

In crafting a definition of COI, we considered and built on definitions other organizations use, particularly the IOM.^{6-12,16} We considered whether or not to incorporate three dichotomies: (1) financial versus nonfinancial COI, (2) institutional versus individual COI, and (3) perceived versus real COI. In rejecting these sharp distinctions, we offer a general definition of NFCOI that can be applied across clinical areas and topics to address the wide spectrum of EPC work and EPC contributors, while emphasizing that the *primary interest* is always the quality and integrity of the SR.

Financial Versus Nonfinancial COI

Financial and nonfinancial COI are not necessarily mutually exclusive. Financial concerns may indirectly drive NFCOI. For example, an individual's concerns about his or her professional reputation may be nonfinancial, but may be driven in part by concerns about his or her ability to

compete for future funding or receive increased compensation. In contrast to some other literature in this area, rather than drawing sharp distinctions between financial and nonfinancial COI, we recognize that these interests may be interrelated.

Individual Versus Institutional COI

In considering whether or not to distinguish between individual and institutional COI, we noted that institutional COI may lead to NFCOI for individuals, although the literature generally defines institutional conflicts in financial terms. For instance, when faculty members review the evidence for a medication in which their university holds the patent, institutional COI may lead to NFCOI for individual investigators with no involvement in the patent because of the risk that the employer might have indirect bearing on the faculty member's judgment and action in the SR. In addition to these conceptual overlaps, practical considerations also support the disclosure of these interests under NFCOI. Existing FCOI policies fails to elicit these conflicts because they frame disclosure in relation to the individual rather than the institution. Such conflicts are more likely to emerge in evaluating NFCOI. In considering financial versus nonfinancial COIs and individual versus institutional COIs, we do not distinguish among financial, institutional, and individual interests. Instead, we support the use of definitions that collectively call out all such interests as *secondary or competing interests that are not mainly financial*.

Real Versus Perceived COI

We also considered the issue of real versus perceived COI, particularly in light of recent recommendations in the IOM's report, *Standards for Systematic Review* (2011).^{7,9} Standard 2.2 lays out the IOM's expectations for SR teams: each team member should disclose potential COI and professional or intellectual bias, and the project lead should exclude individuals with a clear financial conflict and individuals whose professional and intellectual bias diminish the SR's credibility in the eyes of the intended user. This guidance frames intellectual and professional bias as perceived conflict—*in the eyes of the intended user*—and thereby dramatically expands the potential range of intellectual perspectives and professional affiliations that might be considered grounds for exclusion. This guidance requires the SR team or the sponsor to speculate about the possible perceptions of the many intended users regarding NFCOI. If the standard is interpreted strictly, SR teams could result that include no participants with expertise in the field and, thus, limited ability to interpret the evidence appropriately. In contrast, another IOM report, "Conflict of Interest in Medical Research, Education, and Practice," rejects the distinction between actual and perceived COI on two grounds.⁷ First, such a distinction suggests that perceived COIs are not actual conflicts until the decisionmaker "favors secondary interests over primary interests." Second, the distinction leads to "overly broad and excessively subjective rules."⁷ In other words, the distinction between real and perceived conflicts should be irrelevant to the management of conflicts. According to this view, the goal of the research team should then be to identify and manage the *risk of undue influence*, not necessarily to eliminate all perceived conflicts, since the research team cannot control the perceptions of all possible readers of the review.

Based on these considerations, the EPC workgroup has chosen to define NFCOI broadly as follows:

A set of circumstances that creates a risk that the primary interest—the quality and integrity of the systematic review—will be unduly influenced by a secondary or competing interest that is not mainly financial.

This definition is largely based on the definition of COI in the IOM report, “Conflict of Interest in Medical Research, Education, and Practice.”⁷ It departs from definitions in the IOM report, “Standards for Systematic Review,” and the Cochrane Collaboration manual in that it does not maintain a distinction between real and perceived conflicts.^{7,10}

Types of NFCOI

No taxonomy exists for NFCOIs. Interests relating to the individual (intellectual, professional, career advancement), persons with whom the individual has a close personal relationship (e.g., family members, partners, friends, colleagues), and the employer or organization with which the index person is affiliated (e.g., employer, academic institution, specialty organizations, other professional organizations, and community interests) all tend to overlap somewhat. Nonetheless, this hierarchy offers an approach to identifying and categorizing NFCOI, described below, related to interests of (1) the individual through personal beliefs, (2) others through personal relationships, and (3) the institution through institutional relationships. Interests related to career advancement, a fourth type of NFCOI, draw upon the interests of the individual, others with a personal relationship with the individual (such as mentors), and the institution.

Identifying, Measuring, and Managing NFCOI

Based on workgroup discussions, we identified five key steps, described in greater detail below, for identifying, measuring, and managing NFCOI: (1) identify context-specific issues, (2) identify and disclose NFCOI, (3) assess the degree to which the potential for undue influence from NFCOI exists, (4) manage NFCOI that has the potential to unduly influence the SRs, and (5) monitor and report NFCOI regularly.

Identify Context-Specific Issues

Context-specific concerns that raise the potential for NFCOI include topics with intense advocacy, active policy debate, large interspecialty variations, and limited availability of clinical or content expertise (as in the case of small fields such as the study of rare diseases). These situations do not automatically give rise to NFCOI, but they raise the risk of NFCOI. The process of identifying the context helps to narrow the potential range of remedies: topics with high context-specific stakes may require greater attention to the composition of the SR team to include a more diverse set of participants or even exclude all participants with NFCOI. These circumstances are particularly pertinent for comparative effectiveness research, where multiple active treatments may be compared in a heated policy environment. We note, however, that the absence of context-specific issues (e.g., no strong advocacy position, no active policy debate) does not imply that NFCOI cannot occur; rather, it presents a wider range of options for managing NFCOI that does occur.

Advocacy/Policy Positions

Although SRs are typically commissioned in response to uncertainty about clinical or policy questions, areas in which such uncertainty has spawned intense advocacy or policy debate have a higher risk of NFCOI. People involved in setting or influencing policy with stated positions can be biased because findings from an evidence report may impact their policy agenda. Likewise, organizations for which people work, of which they are members, or with which they are affiliated can have stated positions on Key Questions being posed in a comparative effectiveness review (CER). A person involved in such an organization might be, or might appear to be, conflicted when asked to be involved as a SR team member or expert panelist.

If the person is conflicted between loyalty to the stated position and providing unbiased work on the project, then the Key Questions generated, literature search strategy, inclusion and exclusion criteria, study selection, definition of outcomes, analysis strategies, or interpretation of results may contribute to the report being biased towards his/her preconceived notion (Exhibit 1).

Exhibit 1. Examples of advocacy/policy positions

Example 1, Personal Position:

A national health system is advocating the implementation of the primary care medical home model. AHRQ commissions an SR about the effectiveness of this model. The SR team seeks a senior administrator from the health system who has a background in health services research and who has been charged with regional implementation of the medical home program to serve as a team member. As a team member, she urges a broad definition of primary care practice organization and management, and inclusion of studies aimed at specific components of practice change, with the net effect of including a large number of favorable studies of marginal applicability. Hence, the resulting report seems to be more supportive of these sorts of interventions, albeit with a lower strength of evidence than might have been found using a narrower view of the intervention.

Example 2, Affiliated Organization Position:

A State neurology society has a position statement saying that medications for restless leg syndrome are ineffective and have no place in therapy. Dr. Archibald is the president-elect for the society but not an author of their position paper. He is asked to be an SR team member on a project looking into the comparative effectiveness of medications for restless leg syndrome versus supportive care alone. Dr. Archibald does not hold a strong personal opinion about the benefits and risks of medications for restless leg syndrome, but he is conflicted. Becoming president is the culmination of several years of hard work. He would feel uncomfortable if the results of the report were contrary to the organization's position paper. Given his knowledge of the literature, he knows that studies looking at one symptom scoring scale show medications to be effective while studies using another scale do not show evidence of effectiveness, but both scales are valid and commonly used, but have different strengths and weaknesses. He persuades the SR team (given his neurology experience and stature in the neurology community) to use one scale exclusively. The report subsequently finds no benefits are derived from the use of medications for restless leg syndrome.

Interspecialty Variations in Practice

Patient-centered outcomes research not only examines head-to-head trials of drugs and devices, but also considers the effects of systems of care on health care outcomes. The U.S. health care system is complex: the cost, quantity, and quality of care vary by geographic region and type of provider. For the same clinical problem, multiple diagnostic approaches and treatment alternatives may exist, and particular type of provider or specialty may favor each. Patients, insurers, and policymakers want to know the most effective type (or types) of treatments to use for a given clinical problem. Quite apart from financial conflicts with the practice of a particular approach under review, if a review author is trained and experienced in a certain specialty, this training can result in a perspective that may lead to an unconscious bias because the author is familiar with and trusts a particular approach more than other approaches (Exhibit 2). NFCOI may arise simply because providers have professional pride in delivering the “best” care.

Exhibit 2. Example of interspecialty variations

Patients with low back pain may seek care from a variety of providers, including allopathic specialists (orthopedic surgeons, physical medicine and rehabilitation, neurologic surgeons, rheumatologists), osteopathic physicians, doctors of chiropractic, and physical therapists. Descriptive research has shown that the types of treatments and their costs vary substantially across these specialties. Multiple studies, including large cohort studies, secondary data analyses, and some trials, have examined both cost and functional status outcomes. The review question is to compare the clinical outcomes in acute and subacute back pain when treatment is initiated with one of the above providers. The review team includes neurosurgeons only and comes to very different conclusions from a concurrent review that included multiple provider types as well as spine surgeons.

Limited Availability of Clinical or Content Expertise

Small fields such as the study of very rare diseases are often characterized by a small pool of experts and limited funding sources. Particularly in complex areas such as rare metabolic conditions or very rare cancers, patients are treated by one of a small number of specialists,

typically at academic medical centers. With such rare conditions, one source of research funding, often a pharmaceutical company, is not unusual; and only one treatment is often available. In this scenario, the ability to obtain even a small amount of funding is intensely competitive and requires substantial collaboration among investigators to conduct studies of adequate size. Thus, researchers and funders tend to work in a highly integrated way, investigator perspectives are well known and investigators place a high premium on the ability to collaborate across groups of patients.

In a small field where “everyone knows everyone,” dependence for nontangible support such as letters for promotion, positive reviews of manuscripts, opportunities to present and future employment, or opportunities to “play” in the field can be substantial (Exhibit 3). Influential investigators may be banking on future success of novel compounds and, thus, may be invested in having their studies reviewed positively. If they have the ability to influence opportunities for individuals participating in the review, conflict can arise. These conditions combine to make it difficult to compose an SR team without COI yet knowledgeable about the subject matter.

Exhibit 3. Example of limited availability of clinical expertise in the field

An SR of a condition that affects fewer than 4,000 individuals in the country is conducted. The condition is debilitating if not treated, and a new drug has been approved, based on two fairly small randomized controlled trials. Other drugs are in the pipeline and early research is available on some compounds. The pharmaceutical company that produced the drug funds almost all research in the field and their scientists are major players at scientific meetings. All patients are treated at a limited number of specialist clinics, mostly at academic centers. All clinics are engaged at some level of research, at minimum by enrolling patients in the drug trials. The community of scientists engaged in this work and seeing patients is very small and they all know one another. They are all aware that, as researchers of a rare disease, their access to government funding is challenging, and they feel a strong solidarity based on their perceived lack of attention in the larger clinical research arena. They also serve as strong advocates for their patients, and the family advocacy groups are very connected to the researchers. The SR team includes a clinical staff person who runs a clinic caring for patients with the condition. This individual is the only team member available with direct clinical experience, and has important expertise in a complicated clinical condition, but because all clinics are enrolling patients in the drug trials, the staff member’s name may appear in drug company publications about the drug being reviewed. This individual is salaried and his/her career does not depend on research productivity, but it is possible that the inclusion of the name on the report and on publications related to clinical trials funded by the pharmaceutical company could trigger letters to the editor casting doubt on the SR’s objectivity.

Table 1 provides suggestions for three possible questions for funders and principal investigators to consider in judging context-specific bias.

Table 1. Questions to assess the context for nonfinancial conflicts of interest for systematic reviews

Questions for funders and principal investigators of systematic reviews (SRs)
During the initial stages of the SR (topic development and topic refinement), the principal investigator (PI) should enlist key stakeholders and clinical/content experts to answer the following context-specific questions. PIs should always consider these questions prior to requesting information from individual team members.

1. Is the topic the subject of advocacy or policy change?

Yes No

If yes, consider questions 5–6 from Table 2 for individual team members.

2. Does the topic have interspecialty variations in diagnostic or treatment approaches?

Yes No

If yes, consider questions 7–8 from Table 2 for individual team members.

3. Is there a limited pool of experts with knowledge in this field?

Yes No

If yes, consider management strategies other than exclusion of team members with conflict of interest to ensure adequate expertise on the team.

Identify and Disclose NFCOI

The identification and disclosure of NFCOI requires the selection of appropriate indicators of NFCOI. A potential minimal approach is to ask individuals whether they consider themselves to be at risk of NFCOI. Evidence suggests, however, that individuals do not recognize bias in themselves. Thus, such an approach is insufficient by itself. Disclosure alone is likely to be inadequate, even for FCOI,¹⁷ and may even exacerbate bias¹⁸ because the individual disclosing the conflict may exaggerate recommendations in anticipation of discounting on the part of the audience, or be explicitly biased because the audience has been warned.¹⁹ An additional strategy is to document proxies of bias other than individual self-perception such as previously stated opinions, clinical specialty, or organizational affiliations. We note that these indicators offer no absolute proof of NFCOI. Likewise, the absence of such circumstances does not preclude strongly held beliefs from influencing the investigator's judgment. Funders and PIs could also search for evidence of NFCOI by reviewing the individual's publication and internet record. This information might be in the form of opinions in correspondence, blogs, interviews, expert testimony, editorials, or narrative reviews. Other publications such as SRs, policy papers, or clinical practice guidelines may also provide insights into an individual's competing interests. We note, however, that an exhaustive search through publication and Internet records is likely to be resource-intensive and possibly counter-productive to team relations, and is not likely to produce definitive evidence of the presence or absence of conflicts.

Personal Beliefs

Individuals may have strong and unwavering personal beliefs that can introduce bias when evaluating the comparative effectiveness of a treatment. Through decisions on the formulation of Key Questions, literature search strategy, inclusion and exclusion criteria, selection of studies, definition of outcomes, analysis strategies, or interpretation of results, a team member may slant the SR in favor of findings supporting his or her beliefs (Exhibit 4).

Exhibit 4. Example of personal beliefs exerting an undue influence

Ms. Alomar is a nurse practitioner who is asked to work on a project evaluating the comparative benefits and harms of physician assistant care versus nurse practitioner care in patients with hypertension. She attended college for 4 years to become a registered nurse, worked in practice for 5 years, and then went back to school for 2 years to become a nurse practitioner. Upon graduation, she struggled for acceptance in her medical center but has now established a successful primary care practice that sees patients with hypertension. Ms. Alomar believes that physician assistants cannot substitute for the care and nurturing nurses provide, that physician assistants' training is substandard to provide quality care, and that findings showing that physician assistants provide quality care will harm her and the profession she loves. She is included in the team and does not reveal that the proposed literature search excludes some relevant journals that frequently publish articles by physician assistants; however, she explicitly recommends searching a nursing-specific database. The report finds insufficient information to evaluate the quality of care provided by physician assistants.

Personal Relationships

Personal relationships (including those that are adversarial)²⁰ can be a barrier to objective evaluation of the quality and outcomes of research. In addition to direct relationships between investigators and the authors of studies eligible for the review, networks of relationships among family, friends, partners, colleagues, and the authors of the eligible studies may also lead to conflicts. Investigators may face implicit or explicit conflicts between an unbiased evaluation of the evidence and maintaining or promoting these personal relationships, which may not be evident to an external observer. These conflicts can affect their selection of Key Questions, outcomes, and interpretation of results (Exhibit 5).

Exhibit 5. Example of personal relationships as conflicts of interest

Joe Schneider is working on a CER on treatments for breast cancer. Joe is friends with Stuart, an old college roommate who owns a startup company that manufactures Wonderdrug, a new medication to treat breast cancer. Wonderdrug has received substantial media coverage and its commercial business is brisk. Neither Joe nor anyone in his family has financial investments in the company, but Joe is very familiar with the details of Wonderdrug because of conversations with Stuart over the years. Studies of Wonderdrug report favorable remission rates, but one study reports myocardial infarction among women taking Wonderdrug. Studies of other drugs and comparator groups found no similar events. Joe feels that the findings were the result of chance and sees no plausible biological link between the drug and the risk of myocardial infarction. As a senior investigator, his viewpoint influences the other SR team members to ignore myocardial infarction as a harm.

Institutional Relationships

An investigator's institutional role can create a competing interest that makes objective evaluation of studies difficult. The pressure to conform the findings of an SR to the outcome most beneficial for the investigator's institution may preclude an unbiased evaluation of the evidence (Exhibit 6).

Exhibit 6. Example of institutional conflicts

University A holds a patent for a genetic test included in a CER conducted by the university-affiliated EPC. Members of the review staff are aware of the university-held patent. The CER finds evidence of no difference between the genetic test and comparators on health outcomes. The lead investigator rewrites the conclusions to suggest the need for more research, rather than focusing on the lack of benefit from the test.

Career Advancement

The rewards of pursuing academic research include the satisfaction of making contributions to scientific knowledge, affecting people's well-being, peer recognition, and career advancement. COI and NFCOI could converge when the perception of one's peers and superiors is a significant consideration in academic promotion and future funding. We note that striving for career advancement is not by itself a competing interest. However, a competing interest may arise if research findings contradict the prevailing opinion in the field and if the conclusions of an SR could be negatively perceived by peers whose opinions and evaluations play a role in one's academic advancement. Thus, a researcher may review the evidence in a biased manner if his or her career may be impacted by peers' perceptions of the SR's conclusions. A further difficulty is that this conflict is likely to be post hoc, i.e., the conflict arises when the evidence is summarized and may not be known a priori (Exhibit 7).

Exhibit 7. Example of desire for career advancement as a potential source of COI

A widely held belief is that saturated fat is bad for cardiovascular health. Dr. Smith has been asked to conduct a CER comparing Drug X with Drug Y to prevent primary myocardial infarctions in U.S. populations. The participants' dietary intake of saturated fat in the various studies was also analyzed. The findings showed that Drug X is more effective than Drug Y in preventing myocardial infarctions. The CER also found that high dietary intake of saturated fat is associated with a decreased risk of myocardial infarctions independent of Drug X or Drug Y. Dr. Smith, an assistant professor, is being considered for promotion to associate professor. Some of his mentors and peers built their academic careers reporting the harms of saturated fat. Worried that even hinting saturated fat may not be so bad could jeopardize his career advancement (or Dr. Smith fundamentally disbelieves the conclusions because of his faith in his mentors' prior research findings), Dr. Smith decided to take on additional analyses (that were not prespecified in the SR protocol). Based on one of the additional analyses, he concluded that the association was spurious after all. Dr. Smith further buttressed that position by explaining why this particular analysis was sound, but not others.

Table 2 suggests four questions for SR team members based on the examples above. Investigators may be asked to answer additional context-specific questions. Some questions require implicit or explicit judgment about the likely direction of the review. Questions that require judgment about institutional or organizational conflict rather than individual conflict specify that respondents answer to the best of their knowledge. These questions will not identify all risks of NFCOI, given the limits of self-disclosure. In addition, PIs and funders should be prepared to review curriculum vitae of investigators on the team and consider whether to conduct searches of publication records.

Table 2. Questions to disclose nonfinancial conflicts of interest for systematic reviews

Please answer the following questions to the best of your existing knowledge. The questions are not intended to require additional research or time-intensive inquiry beyond your current awareness.

Personal beliefs

1. Do you have strongly held beliefs related to the topic area that would make it difficult for you to consider alternative conclusions on this comparative effectiveness review in an unbiased manner?
Yes No

If yes, please explain.

Previously published opinions

2. Have you ever authored, coauthored, or publicly provided an opinion related to the topic area of this comparative effectiveness review?
Yes No

If yes, what were those views and where were they made?

Institutional relationships

3. To the best of your knowledge, could your institution benefit or be harmed based on whether this review finds benefit, harm, or no difference in outcomes?
Yes No Don't Know

If yes, please explain.

Career advancement

4. How would you characterize the support you would receive from your primary mentor, institution, or other entities, if your work generated a strong reaction from peers outside your institution?

Answer the following questions, if applicable:

Advocacy/policy positions

5. To the best of your knowledge, do you work for, or are you a member of an organization with a stated position (e.g., position statement, blog, editorial, legislature or legal testimony, or related document) related to the topic area of this comparative effectiveness review?
Yes No

6. If yes to #5, are you involved in formulating/voting for positions?
Yes No

If yes to #5, could positive or negative findings of this evidence report conflict with policies you have promoted or are obliged to follow?
Yes No Don't Know /Not Applicable

If yes to #5 or #6, please explain

Table 2. Questions to disclose nonfinancial conflicts of interest for systematic reviews (continued)

Interspecialty variations in practice:
7. What is your primary clinical specialty or subspecialty?
<input type="text"/>
8. Do you prescribe or otherwise recommend the test or treatment to be examined in this review?
<input type="text"/>

Assessing the Risk of Bias From NFCOI

Arriving at a judgment of risk of bias from NFCOI requires caution, particularly when evaluating proxy indicators of NFCOI.⁷ Reviewers run the risk of biased judgment when new data conflict with viewpoints expressed in prior publications. Previously expressed viewpoints, particularly those reiterated multiple times in the literature, could represent an individual's strongly held view on a particular issue. Factors to consider in judging the risk of bias from NFCOI include the value of the secondary interest, the scope of the relationship, and the extent to which secondary interests might exert undue influence on the primary interest, the SRs.⁷

Managing the Risk of Bias From NFCOI

One helpful approach, developed by Public Responsibility in Medicine and Research, classified COI into three categories according to how they would be managed: (1) routinely allowable activities or relationships; (2) permissible activities or relationships following disclosure and review; (3) impermissible activities or relationships.²¹ Although this action-focused grouping is not intended to help individuals critically consider and identify their own possible conflicts, the categorization is helpful for considering possible management options. We suggest expanding the list for permissible activities to explicitly include: permissible activities after public disclosure of NFCOI, permissible activities upon expansion of the team to ensure that it includes diverse perspectives. We note that impermissible activities or relationships do not always require excluding the individual from the project: they may, in some cases, be managed by excluding the individual from certain SR activities.

We note that these actions can help mitigate risks of NFCOI at the start of the project when the team is being constituted or, if a new conflict emerges during the course of the project, as soon as the risk of conflict becomes apparent. Ad hoc actions taken during the project may not be able to mitigate the risk of bias from NFCOI.

The IOM notes that management of COI requires proportionality; that is, the policy should be effective, efficient, and directed at the most important and most common conflicts. After evaluating the likelihood of undue influence and seriousness of possible harm, and the benefits of having the conflict outweigh the harms, the conflict may be allowed to stand.⁷ This reasoned approach to NFCOI management means that each type of NFCOI cannot always be managed the same way. If NFCOI had been disclosed, one or more management strategies could have been used to mitigate the risk of bias in the case examples described above. The option requiring the

least change to the proposed team relies on disclosure alone. However, the discretion that conflicted team members have in important decisions in the SR process and publication may be so large that transparency alone may not sufficiently mitigate the risk of bias. Thus, we suggest using this strategy only when the level of discretion exercised by conflicted team members is unlikely to result in bias or when the input from the conflicted team member is irreplaceable.

On the opposite end of the spectrum, one management approach is to routinely exclude content area experts from review teams based on the assumption of a high level of inherent conflict. As noted earlier, we believe that such an approach risks invalidating the review because of inadequate interpretation of the findings. Nonetheless, exclusion from the review team is the appropriate management approach when conflicts of interest are likely to raise the risk of bias of the review and investigators with similar clinical or content expertise but without conflicts of interest can substitute for the conflicted team member. The greatest challenge to this approach occurs in clinical topics with a limited pool of clinical or content experts. One potential solution is to find individuals whose work is tangential or partially overlapping with the clinical area, but whose careers are unlikely to be affected by the outcome of the review.

Two other options require less drastic changes in the team but rely on more active management of conflicts during the review process. One option is to balance the conflicted team member's perspective with an opposing view. This approach runs the risk of deadlock: opposing perspectives may fail to find common ground in the evidence. If teams elect to balance conflicted perspectives, they can avoid stalemates in decisionmaking by including methodologists with disinterested perspectives as tiebreakers, or requiring the PI or the primary author(s) to be completely free of conflict. In the example of interspecialty variations, the team could be balanced by including a spine surgeon, a general internist, and a methodologist who serves as the principal investigator.

Another option is to circumscribe the activities of conflicted team members. Conflicted investigators should never review their own research nor should they be singly responsible for analysis. In the examples of strong advocacy or active policy debate, conflicted team members could serve as technical experts rather than authors of the review. Alternatively, their input in search strategies, protocol development, analysis, and interpretation should be limited to components of the review for which they have no conflict.

Monitoring and Reporting NFCOI: Accountability and Timing

In internally funded or self-funded projects, the PI is responsible for making team-specific decisions, and is held accountable during the peer-review process. For externally funded projects, although funders typically have the authority for final decisions, funders and lead investigators should work together to ensure that the review includes appropriate topic-related expertise and that the management of NFCOI addresses concerns of proportionality and fairness while also addressing the risk of bias. Funders may want to consider an unbiased outsider to serve as ombudsman for disputes about the management of NFCOI. As noted earlier, funders have the additional responsibility to provide guidance for NFCOI team members.

Team members should disclose NFCOI before the start of the review. Once the SR team is assembled, updates of NFCOI should be ongoing, that is, as events warrant, but no less frequently than once a year.

Next Steps

Many questions remain unanswered in this underevaluated area of research conduct. The first and most basic questions relate to the incidence and impact of NFCOI: When NFCOIs have been identified in the past, in what category do they typically occur? To what degree has NFCOI affected the conduct of reviews in the past? Such research needs to involve both literature review as well as surveys of researchers and EPC administrators.

A second set of questions relates to the utility of the proposed NFCOI guidance in this document. Do peer reviewers, funders, principal investigators, team members, and users of reports find additional NFCOI guidance of use in identifying NFCOI and mitigating the risk of bias from NFCOI? How does the influence of NFCOI compare with that of FCOI?

A third area of investigation relates to implementation. Any attempted implementation of the questions proposed in the document requires evaluation of respondent burden, variation in interpretation of the questions relating to identifying NFCOI, and the extent of differences of judgment on appropriate management strategies within review groups and between review groups and funders. A better understanding of the barriers to implementation can help to fashion appropriate dissemination strategies of future guidance. Another concern is how to jointly manage FCOI and NFCOI: we recognize that overlap exists between FCOI and NFCOI policies, as discussed above. Ongoing communication between groups addressing FCOI and NFCOI policies will help.

Conclusions

NFCOI, when ignored, can call into question the impartiality of a review. Equally, the results of a review can be invalid when management of NFCOI results in the exclusion of necessary topical expertise. This document is a consensus effort attempting to achieve the appropriate balance between supplying needed expertise and minimizing NFCOI by proposing approaches to identify and evaluate NFCOI. However, the utility of these approaches and barriers to implementation must be investigated.

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Appendix A. Institutional Standards and Definitions for Managing Conflicts of Interest

Table A-1. IOM Standards for Systematic Reviews (2011)

Overall Standards/Policies	
2.2	Manage bias and conflict of interest (COI) of the team conducting the systematic review (SR)
2.2.1	Require each team member to disclose potential COI and professional or intellectual bias
2.2.2	Exclude individuals with a clear financial conflict
2.2.3	Exclude individuals whose professional or intellectual bias would diminish the credibility of the review in the eyes of the intended users.
2.3	Ensure user and stakeholder input as the review is designed and conducted
2.3.1	Protect the independence of the review team to make the final decisions about the design, analysis, and reporting for the review
2.4	Manage bias and COI for individuals providing input into the SR
2.4.1	Require individuals to disclose potential COI and professional or intellectual bias
2.4.2	Exclude input from individuals whose COI or bias would diminish the credibility of the review in the eyes of the intended user
Definitions and Examples	
Conflict of interest	A set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest
Secondary interest	The pursuit of professional advancement, future funding opportunities, and recognition, and the desire to do favors for friends, family, and colleagues
Other Recommendations	
<ul style="list-style-type: none"> Mere disclosure of a conflict does not eliminate it. Review teams should also evaluate and act on the disclosed information. Eliminating the relationship, further disclosure, or restricting the participation of the researcher with COI may be necessary. Bias and COI may be minimized by creating review teams that are balanced across relevant expertise and perspectives as well as competing interests. 	
<ul style="list-style-type: none"> Because SRs may take a year or more to produce, the SR team members should update their financial COI and personal biases at regular intervals 	
<ul style="list-style-type: none"> If a SR is a prerequisite to developing a clinical practice guideline (CPG), it is important that the SR team be responsive to the questions of the CPG panel. There are various models of interaction between the CPG and SR teams in current practice, ranging from no overlap between the two groups to the SR and CPG teams interacting extensively during the evidence review and guideline writing stages. Although the models have not been formally evaluated, the committee believes that a moderate level of interaction is optimal because it establishes a mechanism for communication between the CPG panel and the SR team, while also protecting against inappropriate influence on SR methods. 	
<ul style="list-style-type: none"> To protect the scientific integrity of the SR process from sponsor interference, the types of interactions permitted between the sponsor and SR team should be negotiated and refined before the finalization of the protocol and the undertaking of the review. The sponsor should require adherence to SR standards, but should not impose requirements that may bias the review. An independent peer review process allows a neutral party to determine whether an SR follows appropriate scientific standards and is responsive to the needs of the sponsor. Sponsors should not be allowed to delay or prevent publication of an SR in a peer-reviewed journal and should not interfere with the journal's peer review process. 	

Source: Institute of Medicine. Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: The National Academies Press; 2011.

Table A-2. The Cochrane Collaboration (2011)

Overall Standards/Policies	
2.2.1	<p>General principle</p> <p>The essential activity of the Cochrane Collaboration is coordinating the preparation and maintenance of systematic reviews of the effects of healthcare interventions performed by individual reviewers according to procedures specified by the Collaboration. The performance of the review must be free of any real or perceived bias introduced by the receipt of any benefit in cash or kind, any hospitality, or any subsidy derived from any source that may have or be perceived to have an interest in the outcome of the review. It is a matter of Cochrane Collaboration policy that direct funding from a single source with a vested interest in the results of the review is not acceptable. Sponsorship of a Cochrane review by any commercial source or sources is prohibited. There should be no direct funding of Cochrane Centres (or Branches of Centres) by commercial sources. This includes the funding of core and non-core functions of Cochrane Centres. Non-direct funding of non-core activities (such as translation) is permitted after 2010 from a central fund.</p>
2.2.2	<p>Recommendations</p> <ol style="list-style-type: none"> 1 Receipt of benefits from any source of sponsored research must be acknowledged and conflicts of interest must be disclosed 2 If a proposal raises a question of serious conflict of interest, this should be forwarded to the local Cochrane Centre for review (and the Steering Group notified accordingly). If the issue involves a Cochrane Centre, the issue should be referred to the Steering Group. 3 It is not mandatory to send funding proposals to the local Cochrane Centre or Steering Group prior to accepting them. However, such reviews would be desirable in cases of restricted donations, or any donation that appears to conflict with the General Principle 4 The Steering Group should receive (and review at least annually) information about all external funds accepted by Cochrane entities. The Steering Group will use this information to prepare and distribute an annual report on the potential conflicts of interests attendant on the Collaboration's solicitation and use of external funds 5 The Steering Group should constitute a subcommittee to view potential conflicts of interests, to offer recommendations for their resolution, and to consider appropriate sanctions to redress violations of the General Principle
2.2.3	<p>Conflict of interest statements in reviews</p> <p>Under the heading 'Conflict of Interest' reviewers should report any conflict of interest capable of influencing their judgments, including personal, political, academic, and other possible conflicts, as well as financial conflicts. It is impossible to abolish conflict of interest, since the only person who does not have some vested interest in a subject is somebody who knows nothing about it.^a Financial conflicts of interest cause the most concern, can and should be avoided, but must be reported if there are any. Any secondary interest (such as personal conflicts) that might unduly influence judgments made in a review.</p>
Definitions and Examples	
Conflict of interest	Any real or perceived bias introduced by the receipt of any benefit in cash or kind, any hospitality, or any subsidy derived from any source that may have or be perceived to have an interest in the outcome of the review
Financial interests	Research funding, paid consultancies, honoraria, patents, share-holdings, equity, loans, employment, or management positions in an organization related to the subject of the systematic review
Nonfinancial interests	Any other competing interests that could pose a potential conflict of interest that might reasonably appear to be related to the review (e.g., clinical practice, involvement in primary research in the subject area of the review)
Commercial sponsorship	Any for-profit manufacturer or provider of health care, or any other for-profit source with a real or potential vested interest in the findings of a specific review. Whilst government departments, not-for-profit medical insurance companies and health management organizations may find the conclusions of Cochrane reviews carry financial consequences for them, these are not included in this definition. Also not included are for-profit companies that do not have real or potential vested interests in Cochrane reviews (e.g., banks).

Table A-2. The Cochrane Collaboration (2011) (continued)

Other Recommendations

- People with a direct financial interest in a particular intervention should not be involved in a review of that intervention, either as authors, editors, or peer reviewers.
-
- Sponsorship of a Cochrane review, Methods Groups, or peer reviewers by any commercial source or sources (as defined above) is prohibited. Other sponsorship is allowed, but a sponsor should not be allowed to delay or prevent publication of a Cochrane review, and a sponsor should not be able to interfere with the independence of the authors of reviews in regard to the conduct of their reviews
-
- Authors of reviews should declare financial support for the review, private clinical practice (if relevant), stocks, legal advice, consultancies, involvement in primary research in the subject area of their review, and any other 'competing interests' that they judge relevant. If an author has been actively involved in a study or studies that was/were eligible for their review, they should have, as a co-author, someone who was not involved in the study/studies. The co-author could act as a 'guarantor.'
-

Source: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]; The Cochrane Collaboration; 2011.

^aSmith R. Conflict of interest and the BMJ. BMJ. 1994 Jan 1;308(6920):4-5. PMID: 8298354.

Table A-3. International Committee of Medical Journal Editors (2010)

Overall Standards/Policies	
Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest	
The following should be disclosed:	
Financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what authors write in the submitted work.	
Interactions with any entity that could be considered broadly relevant to the work should be disclosed.	
All sources of revenue paid (or promised to be paid) directly to the author or institution on the author's behalf over the 36 months prior to submission of the work should be reported. This includes all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research.	
Interactions with the work's sponsor that are outside the submitted work should also be listed.	
Grants from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome, should be disclosed.	
Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed.	
Relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, the submitted work.	
Definitions and Examples	
Conflict of interest	When an author (or the author's institution), reviewer, or editor has financial or personal relationships that inappropriately influence (bias) his or her actions (such relationships are also known as dual commitments, competing interests, or competing loyalties).
Financial interests	Grants, consultant fees, honorarium, payment for lectures, support for travel, accommodations, meeting expenses; fees for participation in review activities; payment for writing or reviewing the manuscript; provision of writing assistance, medicine, equipment, or administrative support; board memberships; employment; stock ownership; patents, etc.
Non-financial interests	Personal relationships, academic competition, intellectual passion; relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, the submitted work.
Other Recommendations	
<ul style="list-style-type: none">• Authors are responsible for disclosing all financial and personal relationships that might bias their work. To prevent ambiguity, authors must state explicitly whether potential conflicts do or do not exist.• Authors should identify individuals who provide writing or other assistance and disclose the funding source for this assistance. Additionally, authors should describe the role of the study sponsor, if any, in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication. If the supporting source had no such involvement, the authors should so state.• Investigators must disclose potential conflicts to study participants and should state in the manuscript whether they have done so• Editors who make final decisions about manuscripts must have no personal, professional, or financial involvement in any of the issues they might judge. Editors should publish regular disclosure statements about potential conflicts of interest related to the commitments of journal staff.• Reviewers must disclose any conflicts of interest that could bias their opinions of the manuscript, and they should recuse themselves from reviewing specific manuscripts if the potential for bias exists.	

Source: International Committee of Medical Journal Editors. ICMJE Form for Disclosure of Potential Conflicts of Interest. 2009. http://www.icmje.org/coi_disclosure.pdf. Accessed 5-7-12.

Table A-4. Patient-Centered Outcomes Research Institute (Establishing legislation, 2010)

Overall Standards/Policies	
A conflict of interest shall be disclosed:	
i.	By the Institute in appointing members to an expert advisory panel, in selecting individuals to contribute to any peer-review process, and for employment as executive staff by the institute.
ii.	By the Comptroller General in appointing members of the methodology committee
iii.	By the institute in the annual report, except that, in the case of individuals contributing to any such peer review process, such description shall be in a manner such that those individuals cannot be identified with a particular research project
Definitions and Examples	
Conflict of interest	An association, including a financial or personal association, that have the potential to bias or have the appearance of biasing an individual's decisions in matters related to the Institute or the conduct of activities under this section
Real conflict of interest	Any instance where a member of the Board, the methodology committee, or an advisory panel, or a close relative of such member, has received or could receive any of the following:
a.	A direct financial benefit of any amount deriving from the result or findings of a study conducted under this section
b.	A financial benefit from individuals or companies that own or manufacture medical treatments, services, or items to be studied under this section that in the aggregate exceeds \$10,000 per year. For purposes of the preceding sentence, a financial benefit includes honoraria, fees, stock or other financial benefit and the current value of the member or close relative's already existing stock holdings, in addition to any direct financial benefit deriving from the results or findings of a study conducted under this section.
Other Recommendations	
<ul style="list-style-type: none">Conflicts of interest should be disclosed as soon as practicable on the Internet website of the Institute and of the Government Accountability Office. The information disclosed under the preceding sentence shall include the type, nature, and magnitude of the interest of the individual involved, except to the extent that the individual recuses himself or herself from participating in the consideration of or any other activity with respect to the study as to which the potential conflict exists.	

Source: Subtitle D-Patient-Centered Outcomes Research. Subtitle D-Patient-Centered Outcomes Research. Public Law Number: 111-148, Statute Number: 124 STAT. 727, Section: 6301; Mar. 23, 2010.

Table A-5. Department of Health and Human Services (2011)

Overall Standards/Policies	
Responsibilities of investigators	
Investigators must disclose all significant financial interests to the institution	
Each Investigator who is participating in PHS-funded research must submit an updated disclosure of significant financial interests at the time of application for PHS-funded research, at least annually, and within 30 days of discovering or acquiring a new significant financial interest	
Responsibilities of institutions regarding investigator COI	
a	Maintain an up-to-date, written, enforced policy on FCOI that complies with DHHS regulations and make such policy available via a publicly accessible Web site.
b	Inform each Investigator of the Institution's policy on FCOI, the investigator's responsibilities regarding disclosure of significant financial interests, of the DHHS regulations, and require each investigator to complete training regarding the regulations prior to engaging in research related to any PHS-funded grant, every 4 years, and immediately when joining an institution, when the institution revises its FCOI policies, or when an Institution finds that an Investigator is not in compliance with the policies.
c	If institution carries out PHS-funded research through a sub recipient, the awardee Institution must ensure that the sub recipient complies with these policies
d	Designate an institutional official to solicit and review disclosures of significant financial interests from each Investigator who is planning to participate in, or is participating in, PHS-funded research
e	Require that each Investigator who is planning to participate in PHS-funded research disclose to the Institution's designated official the Investigator's significant financial interests (and those of the Investigator's spouse and dependent children)
f	Provide guidelines consistent with DHHS policies for the designated institutional official to determine whether an Investigator's significant financial interest is related to PHS-funded research, and if so related, whether the significant financial interest is a financial conflict of interest
g	Take such actions as necessary to manage conflicts of interest including any financial conflicts of a sub recipient
h	Provide initial and ongoing FCOI reports to the PHS
i	Maintain records relating to all investigator disclosures of financial interests and the Institution's review of such disclosures for at least 3 years from the date the final expenditures report is submitted to the PHS
j	Establish adequate enforcement mechanisms and provide for employee sanctions
k	Certify in each application for funding that the institution will fully comply with these policies
While we acknowledge that non-financial conflicts of interest can influence the scientific process, we chose to retain the focus of these regulations on FCOIs because we believe this is a discrete area in which there is a heightened need to strengthen management and oversight.	
Definitions and Examples	
Financial conflict of interest	A significant financial interest that could directly and significantly affect the design, conduct, or reporting of Public Health Services (PHS)-funded research
Financial interest	Anything of monetary value, whether or not the value is readily ascertainable
Significant financial interest	A financial interest consisting of one or more of the following interests of the investigator (and those of the investigator's spouse and dependent children) that reasonably appears to be related to the Investigator's institutional responsibilities:
i	With regard to any publicly traded entity, a significant financial interest exists if the value of any remuneration received from the entity in the twelve months preceding the disclosure and the value of any equity interest in the entity as of the date of disclosure, when aggregated, exceeds \$5,000. For purposes of this definition, remuneration includes salary and any payment for services not otherwise identified as salary (e.g., consulting fees, honoraria, paid authorship); equity interest includes any stock, stock option, or other ownership interest, as determined through reference to public prices or other reasonable measures of fair market value.
ii	With regard to any non-publicly traded entity, a significant financial interest exists if the value of any remuneration received from the entity in the twelve months preceding the disclosure, when aggregated exceeds \$5,000, or when the Investigator (or the Investigator's spouse or dependent children) holds any equity interest (e.g., stock, stock option, or other ownership interest)

Table A-5. Department of Health and Human Services (2011) (continued)

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- iii Intellectual property rights and interests (e.g., patents, copyrights), upon receipt of income related to such rights and interests.
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Investigators must also disclose the occurrence of any reimbursed or sponsored travel. The term *significant financial interest* does not include the following types of financial interests: salary, royalties, or other remuneration paid by the Institution to the Investigator if the Investigator is currently employed or otherwise appointed by the Institution

Other Recommendations

Management and reporting of FCOI

- i. Public disclosure of financial conflicts of interest
 - ii. Disclosure of financial conflicts of interest directly to participants for research projects involving human subject research
 - iii. Appointment of an independent monitor capable of taking measures to protect the design, conduct, and reporting of the research against bias resulting from the FCOI
 - iv. Modification of the research plan
 - v. Change of personnel or personnel responsibilities, or disqualification of personnel from participation in all or a portion of the research
 - vi. Reduction or elimination of the financial interest
 - vii. Severance of relationships that create financial conflicts.
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Source: U.S. Government Printing Office. Proposed Rules. Fed Regist. 2011 August 24;76(164):52918-929.

Table A-6. IOM—Conflict of Interest in Medical Research, Education, and Practice (2009)

Overall Standards/Policies	
3.1	Institutions that carry out medical research, medical education, clinical care, or practice guideline development should adopt, implement, and make public conflict of interest policies for individuals that are consistent with the other recommendations in this report. To manage identified conflicts of interest and to monitor the implementation of management recommendations, institutions should create a conflict of interest committee. That committee should use a full range of management tools, as appropriate, including elimination of the conflict financial interest, prohibition or restriction of involvement of the individual with a conflict of interest in the activity related to the conflict, and providing additional disclosures of the conflict of interest.
3.2	As a part of their conflict of interest policies, institutions should require individuals covered by their policies, including senior institutional officials, to disclose financial relationships with pharmaceutical, medical device, and biotechnology companies to the institution on an annual basis and when an individual's situation changes significantly. These policies should request disclosures that are sufficiently specific and comprehensive (with no minimum dollar threshold) to allow others to assess the severity of the conflicts; avoid unnecessary administrative burdens on individuals making disclosures; and require further disclosure, as appropriate, for example to the conflict of interest committee, the institutional review board, and the contracts and grants office.
3.3	National organizations that represent academic medical centers, other health care providers, and physicians and researchers should convene a broad-based consensus development process to establish a standard content, a standard format, and standard procedures for the disclosure of financial relationships with industry.
3.4	The U.S. Congress should create a national program that requires pharmaceutical, medical device, and biotechnology companies and their foundations to publicly report payments to physicians and other prescribers, biomedical researchers, health care institutions, professional societies, patient advocacy and disease-specific group, providers of continuing medical education, and foundations created by any of these entities. Until the Congress acts, companies should voluntarily adopt such reporting.

Definitions and Examples

Conflict of interest	A set of circumstances that create a risk that professional judgments or actions regarding a primary interest will be unduly influenced by a secondary interest
Primary interest	Primary interests vary according to the purpose of professional activity; they include promoting and protecting the integrity of research, the welfare of patients, and the quality of medical education. These primary interests are sometimes stated as ends or goals, as obligations, or as rights. The committee uses the term primary "interests" to encompass all of these values, however they are stated.
Secondary interest	Secondary interests may include not only financial gain but also the desire for professional advancement, recognition for personal achievement, and favors to friends and family or to students and colleagues.
Financial conflicts	Research grants and contracts; consulting agreements; participation in speakers bureaus; honoraria; intellectual property, including patents, royalties, licensing fees; stock, options, warrants, and other ownership (excepting general mutual funds); position with a company; company governing boards; technical advisory committees, scientific advisory boards, and marketing panels; company employee or officer, full or part time; authorship of publications prepared by others; expert witness for a plaintiff or a defendant; other payments or financial relationships.
Non-financial conflicts	Desire for professional advancement, recognition for personal achievement, and favors to friends and family or to students and colleagues.

**Table A-6. IOM—Conflict of Interest in Medical Research, Education, and Practice (2009)
(continued)**

Other Themes and Recommendations	
•	The goal of conflict of interest policies in medicine is to protect the integrity of professional judgment and to preserve public trust rather than try to remediate problems with bias or mistrust after they occur
•	Disclosure of individual and institutional financial relationships is a critical but limited first step in the process of identifying and responding to conflicts of interest. Disclosures should provide sufficient information about the nature, scope, duration, and monetary value of relationships to allow institutions to assess the risk that secondary interests might unduly influence judgments about research, clinical care, education, or other primary interests
•	Conflict of interest guidelines and policies can be strengthened by engaging physicians, researchers, and medical institutions in developing policies and consensus standards
•	A range of organizations—public and private—can promote the adoption and implementation of conflict of interest policies and help create a culture of accountability that sustains professional norms and promotes public confidence in professional judgments
•	Research on conflicts of interest and conflict of interest policies can provide a stronger evidence base for policy design and implementation
•	If medical institutions do not act voluntarily to strengthen their conflict of interest policies and procedures, the pressure for external regulation is likely to increase
•	Some COI policies state that professionals should avoid “even the appearance of a conflict of interest” That requirement may lead to confusion. All COI involve perceptions or appearances because they are specified from the perspective of people who do not have sufficient information with which to assess the actual motives of a decision maker and the effects of those motives. Policies that contrast actual & perceived conflicts give rise to 2 problems:
1.	The contrast suggests that there is no conflict (only an appearance of a conflict) unless the decision maker actually favors secondary interests over primary interests.
2.	If perceived conflicts are treated as different from the other (so-called actual) conflicts that the policy regulates, conduct that is proper can be unfairly called into question
•	Conflicts are not binary; they can be more or less severe. The severity of a conflict depends on:
1.	The likelihood that professional decisions made under the relevant circumstances would be unduly influenced by a secondary interest <ul style="list-style-type: none"> • <i>What is the value of the secondary interest?</i> The greater the value, the more probable its influence. Although absolute value is important, secondary interest should be measured in relation to the typical income for the relevant class of professionals, or in relation to the value of a research project, institutional budget, or medical practice. The economic value of nominal gifts or relationships (pens, meals, etc.) is low, but small gifts may help to create & sustain relationships. • <i>What is the scope of the relationship?</i> Duration and depth • <i>What is the extent of professional discretion?</i> How much latitude a professional enjoys in making important decisions.
2.	The seriousness of the harm or wrong that could result from such influence: <ul style="list-style-type: none"> • <i>What is the value of the primary interest?</i> • <i>What is the scope of the consequences?</i> The greater the scope of the consequences, the more serious the potential for harm • <i>What is the extent of accountability?</i>

Source: Institute of Medicine. Conflict of Interest in Medical Research, Education, and Practice. Washington, DC: The National Academies Press; 2009.

Table A-7. Drug Effectiveness Review Project (2001)

Overall Standards/Policies

An investigator or staff member working on a project must state that he/she has no financial interests in any pharmaceutical company. The assurance of an absence of conflicts of interest related to financial interests in pharmaceutical companies is declared annually for any investigator or staff member continuing to work with DERP.

Definitions and Examples

Financial interests	Current direct ownership of stock of a pharmaceutical company (does not include ownership of mutual funds that may partly include pharmaceutical company stock); current research funding received from a pharmaceutical company; current membership on a speaker's bureau of a pharmaceutical company; consulting fees or honoraria accepted from a pharmaceutical company during the project period.
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Source: Oregon Evidence-based Practice Center. Policy on Conflicts of Interest re: Work on the Drug Effectiveness Review Project. Oregon Evidence-based Practice Center; 2001.

Table A-8. National Institute for Health and Clinical Excellence (based in the UK; 2009)

Overall Standards/Policies	
3	What interests are involved?
3.3	Personal pecuniary interest (see definition below)
3.4	Non-personal pecuniary interest (see definition below)
3.5	Personal non-pecuniary interest (see definition below)
3.6	Personal family interest (see definition below)
3.7	It is inappropriate for the chair or non-executive directors of the institute, the chairs of its advisory bodies, or the employees of the institute's clinical guidelines national collaborating centres, to have any current personal interests as defined in paragraph 3.3. Nor should they accept expenses or hospitality from the healthcare industries, other than to seek reimbursement for the reasonable and proportionate costs involved in travel, accommodation, and associated subsistence, for attending conferences at which they have been asked to speak of or otherwise play a formal role.
4	When should interests be declared and what action is required?
4.1	The chair the other non-executive board members, and employees of the Institute must declare all categories of interests on appointment, and then annually. Only the name of the company and the nature of the interest are required; the amount of any salary, fees, shareholding, grant, etc. need not be disclosed. Non-personal interests involving less than £1000 from all sources in the previous year need not be declared.
4.2	The chair of the Institute, the other non-executive directors, the chairs of the advisory bodies, the employees of NICE and the employees of the clinical guidelines national collaborating centres should divest themselves of their personal pecuniary interests (as defined in 3.3) on appointment, or as soon as practical thereafter.
4.3	The declaration of personal family interests by a member or employee will not be a bar to his or her employment or appointment to the Board or advisory body.
4.4	Any uncertainty about potential conflicts of members of advisory boards on appointment should be resolved at the discretion of the relevant chair and recorded in the letter of appointment. Members with conflicts that could be regarded as prejudicing their contribution to the discussion should be excluded from the group or committee. It is recognized that individuals may have some interaction with the healthcare industry and, while this should be declared, it does not necessarily preclude membership of an advisory body.
4.5	Advisory body members and other individuals who are attending to take part in the meeting should declare relevant interests at each advisory board meeting and appeal panels and state into which category they believe the interest falls. <ul style="list-style-type: none">• A person declaring a personal or family specific pecuniary interest shall take no part in the proceedings as they relate to the intervention or matter and will normally leave the meeting until the matter has been concluded.• A person declaring a personal non-specific pecuniary interest may take part in the proceedings unless the chair rules otherwise.• A person declaring a non-specific pecuniary interest or personal family non-specific interest may take part in the proceedings unless he or she has personal knowledge of the intervention or matter either through his or her own work or through direct supervision of other people's work. In either of these cases, he or she should declare this interest and not take part in the proceedings except to answer questions.• A person declaring a non-personal non-specific pecuniary interest may take part in the proceedings unless the chair rules otherwise.• When someone declares a personal, non-pecuniary interest the chair of the advisory board shall determine, on a case-by-case basis, whether he or she should take part in the proceedings.
4.6	Where an individual is responsible for authoring, in whole or part, a document that is prepared specifically to inform one of the institute's advisory bodies, they must declare any interests in accordance with this code.

Table A-8. National Institute for Health and Clinical Excellence (based in the UK; 2009) (continued)
Definitions and Examples

Personal pecuniary interest	Involves a current personal payment, which may either relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as 'specific' or to the industry or sector from which the product or service comes, in which case it is regarded as 'non-specific.' The main examples include the following: any consultancy, directorship, position in or work for a healthcare industry; any fee-paid work; any shareholdings or other beneficial interests; expenses and hospitality in or provided for by a healthcare industry company beyond that reasonably required for accommodation, meals, and travel to attend meetings and conferences; or other funds or investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.
Non-personal pecuniary interest	Involves payment or other benefit that benefits a department or organization for which an individual has managerial responsibility, but which is not received personally. This may either be considered 'specific' or 'nonspecific.' The main examples include the following: the holding of a fellowship endowed by the healthcare industry; any payment or other support by the health industry, or by NICE, that does not convey any pecuniary or material benefit to an individual personally but that might benefit him or her (e.g., grants, contracts, fellowships, or other payment; commissioning of research, other work by, or advice from staff in a certain unit.
Personal non-pecuniary interest	Might include, but is not limited to: a clear opinion, reached at the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review; a public statement in which an individual has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence; holding office in a professional organization or advocacy group with a direct interest in the matter under consideration; other reputational risks in relation to an intervention under review.
Personal family interest	Relates to the personal pecuniary interests of a family member and involves a current payment to the family member of the employee or member. The interest may be 'specific' or 'non-specific'.

Source: National Institute for Health and Clinical Excellence. A Code of Practice for Declaring and Dealing With Conflicts of Interest: National Institute for Health and Clinical Excellence.