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Identifying and Managing Nonfinancial Conflicts of Interest for Systematic Reviews

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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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 in 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.govepc@ahrq.hhs.gov.

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Management of Nonfinancial Conflicts of Interest for Systematic Reviews

Introduction

Evidence based systematic reviews are expected to help policy-makers and clinicians to deliver "recommended care to the right patient at the right time, resulting in improvement in that patient's health."[1, p. 404] Systematic reviews (SRs) serve a critical role in ensuring that health care decisions are increasingly evidence based. 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, 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, but are not sufficient to, ensure the credibility. 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. When a clear financial link exists between the sponsor of the research or the investigators themselves, and the desired outcomes, the judgment of reviewers is at risk of bias. Research has shown that such financial conflicts of interest (COI) can threaten the internal and external validity of primary studies and SRs.[2, 3] Conflicts may go well beyond the financial: strongly held beliefs (personal or professional) and the desire for academic recognition or advancement could also bias the conduct or reporting of SRs.[2] These issues fall under the umbrella of nonfinancial conflict of interest (NFCOI) and are the focus of this document, specifically for SR team members. The guidance 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 expert panel members may be selected specifically because they have professional or personal perspectives that could be considered COI. We view the issues with the SR team to be quite separate.

Prominent organizations involved in the production of SRs take different approaches in addressing the issue COI (Appendix 1). Many organizations tend to focus on financial COI; such conflicts are considered to be more objective, quantifiable, and easy to assess and mitigate.[4-6] 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 and assess the severity of NFCOI.[7-10]

The purpose of this document is to (1) define NFCOI, (2) create practical suggestions for SR teams about how to identify, characterize and manage NFCOI through examples, and (3) improve transparency of judgment regarding NFCOI for users of reviews. This is a field with minimal other guidance, and we believe it would be premature to arrive at an arbitrary list of NFCOI rules for all circumstances. Our intent, therefore, is not to create absolute standards; rather, we intend to offer users an approach to recognizing potential NFCOIs and ways to address them. It also aims to engage the community in further discourse on this vital issue. This work is exploratory; implementation will require some assessment of its impact on reducing risk of bias, feasibility, and burden on investigators.

Our overall approach is to discuss ways in which NFCOI can be reported and managed, and we do not take the view 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 potential conflicts does not inevitably lead to punitive action, nor should it be viewed as such.

Anticipated users of this guidance include the Agency for Healthcare and Quality (AHRQ)-funded Evidence-based Practice Centers (EPCs), AHRQ, organizations with similar interests (e.g., Institute of Medicine [IOM], Cochrane, the Patient-Centered Outcomes Research Institute [PCORI]), other systematic review teams, and users of systematic reviews.

Methods

We used a workgroup consensus process to define NFCOI, suggest ways to elicit information on NFCOI, and recommend methods to mitigate the bias from NFCOI. This document will be revised in response to peer review and public comment.

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,[5, 7] the Cochrane Collaboration,[8] the U.S. Department of Health and Human Services (DHHS),[4] the International Committee of Medical Journal Editors (ICMJE),[11] the National Institute for Health and Clinical Excellence (NICE),[10] and the PCORI.[9] 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 unambiguously suggest guidance about managing NFCOI across all topics and contexts. Our approach is to highlight circumstances in which NFCOI may be present; use examples, based on our experience, to demonstrate how they may be considered conflicts; and provide guidance on assessing whether the potential conflicts pose a risk of bias.

Definition of Conflict of Interest

We considered other definitions and build on the work of other organizations, particularly that of the IOM.[4-11] In coming to a consensus about the definition of conflict of interest, we considered whether or not to incorporate three dichotomies (1) financial vs. nonfinancial COI, (2) institutional vs. individual COI, and (3) perceived vs. real COI. In evaluating these concerns, we favored 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 specifying that the quality and integrity of the SR will always be the *primary interest*.

Financial and non-financial 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 non-financial in nature, but may be driven in part by concerns about his or her ability to compete for future funding or receive financial raises. Rather than drawing sharp distinctions between financial and nonfinancial COI, we recognize that these interests are interrelated.

In considering whether or not to make a distinction 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 directly lead to NFCOI for individual investigators with no relationship to the patent because of the risk that the employer might have indirect bearing on the faculty member's judgment and action in the systematic review process. In considering these two issues, we do not call out distinctions between 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*.

We also considered the issue of "real" vs. "perceived" COI, particularly in light of recent recommendations in the Institute of Medicine (IOM) *Standards for Systematic Review* (2011).[5, 7] Standard 2.2 lays out the IOM's expectations for SR teams: each team member should disclose potential COI and professional or intellectual bias, exclude individuals with a clear financial conflict, and exclude individuals whose professional and intellectual bias would diminish the credibility of the review in the eyes of the intended user. This guidance frames intellectual and professional bias in terms of 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. The SR team or the sponsor may be left to speculate about the possible perceptions of the many "intended users" regarding non-financial conflict of interest. If the standard is interpreted strictly, it could result SR teams being composed of participants with no expertise in the field and limited means to interpret the evidence appropriately. In contrast, a different IOM report—*Conflicts of Interest in Medical Research, Education, and Practice* rejects distinguishing between actual and perceived conflict of interest on two grounds.[5] First, the distinction suggests that perceived conflict of interests are not actual conflicts until the decision maker "favors secondary interests over primary interests." Second, the distinction leads to "overly broad and excessively subjective rules."[5] In other words, the distinction between "real" and "perceived" conflicts should be irrelevant to the management of conflicts. The goal of the research team should to identify and manage the *risk of undue influence*, not necessarily to eliminate all "perceived" conflicts.

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

A set of circumstances that creates a risk that the primary interest, 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 on *Conflicts of Interest in Medical Research, Education, and Practice*.[5] It departs from definitions in the *Standards for Systematic Review* and the Cochrane Collaboration manual in that it does not maintain a distinction between real and perceived conflicts.[5, 8]

Types of COI

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, friends, colleagues), and interests held by 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 with one another.

Identifying, Measuring, and Managing NFCOI

Based on workgroup discussions, we identified four key steps, described in greater detail below: (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 systematic review, (5) monitor and report NFCOI regularly..

Context-specific Issues

Context-specific concerns that raise the potential for NFCOI include topics with intense advocates, active policy debate, large inter-specialty variations, and few clinical experts. This exercise will help to identify the potential range of remedies: topics with high context-specific stakes may require greater attention to composition of the SR team to include a more diverse set of participants or even exclude all participants with NFCOI. 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 is not relevant; rather, it presents a wider range of options for managing NFCOI.

Advocacy/Policy Positions

People involved in setting or influencing policy with stated positions can be biased because findings from an evidence report may impact their policy agenda. In other cases, organizations that people work for, are members of, or are affiliated with can have stated positions on key questions being posed in a comparative effectiveness review. A person involved in these organizations might be, or might appear to be, conflicted when asked to be involved as SR team member or expert panelist.

If the person is conflicted between the loyalty to the stated position and with 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 be done to cause or lean the report towards his/her preconceived notion (Exhibit 1).

Exhibit 1. Examples of Advocacy/policy positions

Example 1, Personal Position:
The Veterans Affairs system is advocating the implementation of the primary care medical home model, dubbed the Patient-Aligned Care Team (PACT). AHRQ commissions an SR about the effectiveness of this model. The SR team seeks a senior VA administrator who has a background in health services research and who has been charged with regional implementation of the PACT 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 a 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. 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.

Inter-Specialty Variations in Practice

Patient Centered Outcomes Research (PCOR) examines not only head-to-head trials of drugs and devices, but also has a substantial emphasis on the effects of systems of care on health care outcomes. The US 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, there may be a number of

diagnostic approaches and treatment alternatives, and each may be favored by a particular type of providers or specialties. Patients, insurers and policymakers want to know the most effective type (or types) of treatments to seek for a given clinical problem. If a review author is trained and experienced in a certain specialty, this perspective may lead to an unconscious bias because they are familiar with and trust a particular approach more than other approaches (Exhibit 2). Bias may arise because providers may have professional pride in delivering the "best" care; secondary financial issues include revenue derived from clinical volume.

Exhibit 2. Example of Inter-specialty 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 associated 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 sub-acute back pain when treatment is initiated with one of the above providers. The review includes neurosurgeons only and comes to very different conclusions from a previous review that included multiple provider types as well as spine surgeons.

Few Clinical Experts

Small fields such as in 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. It is not unusual for there to be essentially one source of research funding, often a pharmaceutical company, and one treatment. In this scenario, the ability to compete for any small pool of funding is both 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 a high premium is placed 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 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 that is un-conflicted yet knowledgeable about the subject matter.

Exhibit 3. Example of limited clinical expertise in the field

A systematic review of a condition that affects fewer than 4000 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 RCTs. 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, etc. 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 the very least 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 each other. They are all aware that as researchers of a rare disease their access to government funding is challenging to say the least, 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 nurse who runs a clinic caring for patients with the condition. She is the only team member with direct clinical experience, but because all clinics are enrolling patients in the drug trials, she is actively enrolling patients. Her

name appears on publications by the drug company that appear at the same time as the systematic review, triggering letters to the editor casting doubt on the objectivity of the systematic review.

Table 1 suggests three possible questions for funders and lead 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 PIs of systematic reviews

During the initial stages of the systematic review (topic development and topic refinement), the 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 question 9-10 for individual team members.

2. Does the topic have inter-specialty variations in diagnostic or treatment approaches?

   ☐☐Yes ☐☐No

   If yes, consider question 12-13 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 COI to ensure adequate expertise on the team.

Disclosure of Potential NFCOI

The identification and disclosure of NFCOI requires a choice of measures. One potential approach is to ask individuals whether they consider themselves to be at risk of NFCOI. Evidence suggests, however, that individuals are not sensitive to recognizing bias in themselves.[12] An alternative is to search for proxies of bias other than individual self-perception. Although previously stated opinions, clinical specialty, or organizational affiliations could serve as proxies for the risk of NFCOI, these measures offer no absolute proof of NFCOI. Likewise, the absence of such circumstances does not preclude strongly held beliefs from influencing the investigator's judgment. Nonetheless, previously published opinions could serve as one proxy of the risk of NFCOI. Nonfinancial interests of individuals might potentially be assessed using information in the individual's prior publications. This information might be in the form of results or conclusions presented in primary research that the individual authored, or may be expressed as opinions in correspondence, blogs, interviews, expert testimony, editorials, or narrative reviews. Other publications such as systematic reviews, policy papers, or clinical practice guidelines may also provide insights into an individual's competing interests.

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

Mrs. Alomar is a Nurse Practitioner who is asked to work on a project evaluating the comparative benefits and harms of Physician Assistant care in patients with hypertension versus that of a Nurse Practitioner. She went to school 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. Mrs. Alomar believes that the caring and nurturing provided by nurses cannot be substituted by Physician Assistants, that the level of training given to Physician Assistants 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 to the team that the proposed literature search excludes a number of journals that are relevant and frequently have physician assistant authors but she does explicitly recommend searching a nursing specific database. The report finds that there is not enough information to evaluate the quality of care provided by physician assistants.

Personal Relationships

Personal relationships (including those that are adversarial)[13] can be a source of conflict that makes it difficult for reviewers to objectively evaluate 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 between family, friends, 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

Joe Schneider is working on a comparative effectiveness review 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 their commercial business is brisk. Neither Joe nor anyone in his family has financial investments in the company. 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, as a senior investigator, persuades the other SR team members to ignore myocardial infarction as a harm because he feels that the findings were the result of chance.

Institutional Relationships

Due to the influence of their institutional role, an investigator may face a competing interest that makes it difficult to objectively evaluate studies. The pressure to conform the findings of a systematic review to the outcome most beneficial for their institution may preclude an unbiased evaluation of the evidence (Exhibit 6).

Exhibit 6. Example of institutional conflicts

University A holds a patent for a medical device included in a CER being conducted by the university-affiliated EPC. Members of the review staff are aware of the university-held patent. The lead investigator on the CER knows that the early literature (prior to the year 2000) on the device highlighted some potential adverse effects. The device developers made some modifications and later studies did not report adverse effects. The lead investigator concluded that the absence of adverse effects in recent studies were due to the device modification completed in the year 2000. During protocol development the lead investigator decides to include studies published after the year 2000, thereby avoiding the inclusion of these potential adverse effects that were observed in early studies but were not present in the post-2000 literature.

Career Advancement

Carrying out academic research has several rewards that include the satisfaction of making contributions to scientific knowledge, affecting people's well-being, peer recognition, and career advancement. The perception of one's peers and superiors is a significant consideration in academic promotion. We note that striving for career advancement is not by itself a competing interest. However, a potential 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 is likely to be a post hoc conflict, i.e., the conflict arises when the evidence is summarized and may not be known a priori (Exhibit 7).

Exhibit 7: Example of career advancement

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 US populations. The participants' dietary intake of saturated fat in the various studies is 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. A number 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 (which were not prespecified in the systematic review 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.

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. 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 negative 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 ☐Don't Know

6. If yes to #5, are you involved in formulating/voting for positions?

☐Yes ☐No

If yes to #6, 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 #6, please explain

Inter-specialty variations in practice: There are no correct answers to these questions. Responses to these questions are intended to ensure adequate disclosure

7. What is your primary clinical specialty or subspecialty?

8. Do you prescribe or otherwise recommend the test or treatment to be examined in this review?

Judging the Risk of Bias from NFCOI

Arriving at a judgment of risk of bias from NFCOI requires caution, particularly when evaluating proxy measures of NFCOI.[5] No empirical data that we are aware of support the assertion that viewpoints inferred from prior publications correlate with an inability of the author to incorporate new or revised viewpoints when presented with new data in the context of a

systematic review. However, 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 of discretion of the reviewer over important decisions during the research process can .influence the extent to which secondary interests might exert undue influence on the primary interest, the systematic review.[5]

Managing the Risk of Bias from NFCOI

One helpful approach, developed by Public Responsibility in Medicine and Research (PRIM&R), classifies COI into three categories according to how they would be managed: (1) activities or relationships that are routinely allowable; (2) activities or relationships that may be permissible following disclosure and review; (3) activities or relationships that are impermissible.[14] 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 those activities that may be permissible to explicitly include: activities permissible after public disclosure of NFCOI, and activities permissible upon expansion of the team to ensure that it includes diverse perspectives. We would also distinguish between activities that are impermissible to include: activities that would result in exclusion from certain SR activities, and activities that would result in exclusion from the project.

One or more management strategies could have been used to mitigate the risk of bias in the case examples described above, if NFCOI had been disclosed. The option requiring the least change to the proposed team relies on disclosure alone. However, the discretion that conflicted team members have over important decisions in the systematic review process and publication may be so large that transparency alone may not 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, the proposed team could exclude the conflicted team member entirely from participation in the review. This approach may be appropriate when 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 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. In the example case of limited clinical expertise, the nurse expert could be replaced by a pediatric geneticist who does not work in the clinic specific to the condition.

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 also including methodologists with disinterested perspectives. In the example of inter-specialty variations, the team could be balanced by including a spine surgeon, a general internist, and a methodologist who serves as the lead investigator.

Another option is to circumscribe the activities of conflicted team members. Potentially conflicted investigators should never be in a position to 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 team members. 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 the 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. Team members should disclose NFCOI before the start of the review. Once the SR team is assembled, updates of NFCOI should occur on an ongoing basis, that is, as events warrant, but no less frequently than once a year.

Next Steps

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

A second set of questions relate to the utility of the proposed NFCOI guidance in this document. Do peer reviewers, funders, lead investigators, team members, and users of reports find additional NFCOI guidance of use in identifying NFCOI and mitigating the risk of bias from NFCOI?

A third area of investigation relates to implementation. Any attempted implementation of the questions proposed in the document requires evaluation of respondent burden and variation in interpretation of the questions relating to identifying NFCOI. A better understanding of the barriers to implementation can help to fashion appropriate dissemination strategies of future guidance.

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 guidance document is a consensus effort attempting to achieve the right balance between supplying needed expertise and minimizing NFCOI by proposing preliminary recommendations in identifying and evaluating NFCOI. However, its utility and barriers to implementation need to be investigated.

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