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ETHICS (CR MACKENZIE AND I DE MELO-MARTÍN, SECTION EDITORS)

Conflicts of interest in research: looking out for number one means keeping the primary interest front and center

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Abstract Conflicts of interest represent circumstances in which professional judgments or actions regarding a primary interest, such as the responsibilities of a medical researcher, may be at risk of being unduly influenced by a secondary interest, such as financial gain or career advancement. The secondary interest may be financial or non-financial, and the resultant bias may be conscious or unconscious. The presence of conflicts of interest poses a problem for professional, patient, and public trust in research and the research enterprise. Effective means of identifying and managing conflicts are an important element in successfully achieving the goals of research. These strategies typically focus on the investigator and rely upon disclosure, which has substantial limitations. Additional management strategies include process-oriented steps and outcomes-oriented strategies. More attention to identifying and managing non-financial conflicts is needed. Future empirical research will be important for defining which conflicts need to be better addressed and how to achieve this goal.

Keywords Conflict of interest · Research · Disclosure · Financial interests · Non-financial interests · Intrinsic interests

Introduction

Medical research requires people, time, and money. The fruits of research, including both knowledge and valuable tangible products, have advanced medical care and provided great public benefit, while at the same time helped to fuel growth in both the academic institutions that produce this knowledge and in the pharmaceutical, biotechnology, and device industry. Not surprisingly, commercial interests have wisely partnered with and invested heavily in the academic research enterprise, in both people and institutions upon whom they rely to provide a substantial piece of the knowledge needed to create medications, devices, and other products, which have helped them to earn enormous sums of money for investors. In turn, investigators have increasingly relied over recent decades upon that industry support [1].

The growth of the medical-industrial complex during the 20th and early 21st century has been paralleled by a deepening interest in the ethical conduct of research on human subjects. This interest in medical ethics has been driven, in part, by interacting social and historical forces, including political and economic interests and advances in science and technology, together with the growth of concerns for broader protection of human rights [2]. The tensions related to the interactions between these various forces have been among the factors leading to an increased interest in medical ethics and in issues of conflicts of interest in medical research, given the frequently divergent, even though sometimes overlapping, goals and values that inform patient care, research in the laboratory and on animal and human subjects, investigators and research subjects, clinicians and patients, hospitals, medical schools, research institutions, governments, commercial interests, and others.

Recognition of the multiple and sometimes divergent interests of the stakeholders involved in medical research and the risk that some interests may undermine others, including the integrity of medical research, has resulted in efforts to reduce or eliminate the potential for divergent and conflicting interests to adversely impact the research process and trust in that process. As the impact of conflicts of interest has been increasingly recognized and examined [3], the importance of developing effective strategies to identify and manage such

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conflicts has been a matter of particular interest in education, medicine, and science [4, 5].

This review will briefly address the nature of conflicts of interest in research, including the importance of both financial and non-financial conflicts, and the potential effectiveness and limits of various strategies for managing such conflicts.

What are conflicts of interest?

Conflicts of interest may be defined as "circumstances that create a risk that professional judgments or actions regarding a primary interest will be unduly influenced by a secondary interest" [5, 6]. Broadly stated, the primary duty of the investigator in medical research is to obtain scientifically valid results, while promoting and protecting the integrity of research. The goals of science are in sharp contrast with the goals of medical care of individual patients; in the former, there is the need to use the best experimental design and analysis to produce generalizable knowledge, while in the latter, it is achieving the medical goals and preferences of the individual patient [7]. The conduct of research in an ethical manner that protects the rights of research subjects and trust in the research enterprise helps to achieve the goals of medical research [8]. The secondary interest of principal concern is usually financial gain, with the worry that such financial interests (e.g., payments from a manufacturer of a drug or device for services other than the research) will influence the professional judgment or actions of the investigator to obtain and present results that inappropriately favor the source of such financial gain. Such bias affecting professional judgment may then influence the manner in which an investigator conducts or presents the research; it has the potential to unduly influence the development of research hypotheses; the selection of experimental and analytic methods, including the statistical analysis; and the presentation and interpretation of the results, including decisions regarding what to publish and where to publish it [9].

This problem is not just theoretical. Multiple reports indicate that industry sponsorship of trials of drugs or devices is strongly associated with more favorable trial results [3], and even well-constructed studies of the efficacy of drugs or devices, without evidence of heightened risk of bias upon analysis of research design, may obtain results demonstrating greater efficacy and fewer harms if they are industry-sponsored rather than non-industry sponsored [10•]. Some recent examples from the orthopedics literature, an area of interest to the readers of this journal, can serve as illustrations of this issue: a study of abstracts of podium presentations from the annual meeting of the American Academy of Orthopaedic Surgeons found that presentations by authors with conflicts of interest related to royalties, stock options, consulting, or employment were significantly more likely to have positive findings; self-reported conflicts were most common in the areas of adult reconstruction of the knee or of the hip and spine surgery [11]. A systematic review of all publications on spinal research in leading journals in a single year found that industry funding was associated with a lower level of evidence and more favorable outcomes compared with publicly and foundation-funded studies [12•]. A systematic review of randomized trials of hyaluronic acid injections for knee osteoarthritis showed that the presence of self-reported conflicts was associated with study results showing greater efficacy compared with studies in which conflicts were not reported [13]. Other specialties each have their own examples, and clinicians view these issues as matters of importance. Rheumatologists, for example, report that conflicts of interest, both in the clinical and research setting, as well as issues of bias, are among their most prominent ethical concerns [14].

Secondary financial interests are the focus of most conflict of interest policies [4–6, 15]. The attention to financial gain has been justified by the recognition that financial interests are "more objective, fungible, and quantifiable" than other secondary interests [5] and are thus easier to regulate fairly and effectively than less tangible incentives [6]. However, despite the usual attention to financial interests, non-financial interests and other secondary interests intrinsic to the research process are also understood to have the potential to influence professional judgment [6, 16, 17, 18••]. Secondary interests without direct or even any financial element, such as the desire to obtain and publish research findings that lead to recognition and career advancement, vindication of one's intellectual biases, support for friends and colleagues, or advocacy for strongly held social or political points of view, represent potent secondary interests that may have meaningful or even greater impact on professional judgment than financial factors. Indirect benefits with a financial element include support for the time and salaries of the investigator(s) and their staff. While not providing financial gain beyond the institutional paycheck and the operating budget of the research endeavor such support defines the nature of the potential investigator's professional position, identity, and activities, and thus, may have potent impact on professional judgments and actions.

It is important to recognize that conflicts of interest are usually quite legitimate activities, which on their own are neither unethical nor illegal. An expert in a particular field may have a great deal to offer as an inventor, consultant, or speaker; and royalties, fees for services, or honoraria may be well deserved. Career choices, professional advancement, and time with family are each independently valued. The question that is critical with respect to conflicts of interest is whether these other professional or personal actions or responsibilities may compromise judgment with respect to a primary interest or responsibility, which in this case is to the research. A key issue in understanding the nature of conflicts of interest in medicine and research (and in other fields as well, including business

and law) is that the value or weight of the competing interests is asymmetric. In typical ethical conflicts in the medical setting, different values are being weighed and a decision depends upon choices between competing values, so that decisions of what is right to do, all things considered, depend upon the stakeholders, the particularities of the situation, the most important principles and values, and the particular context. Conflicts of interest are strikingly different from such ethical conundrums. There is a primary interest, and protecting that interest is what must have priority. Despite the clarity of the conflict, minimizing or eliminating its effects is not necessarily easy.

Unfortunately, assertions of honesty and good will, personal integrity, and a capacity for personal discretion in professional judgments are insufficient to guarantee that one is not affected by a significant conflict. Another problematic issue is that bias is often unconscious; moreover, unconscious bias may affect judgment upon receipt of even small incentives, despite one's own belief otherwise [19–21]. Furthermore, even if a research investigator is not unduly influenced by money, career advancement, or other factors, and the research is conducted impeccably, how can an observer know with confidence that is truly the case? Because trust in the conduct of research is critical to the advancement of science and the public good, it is vital that the risks of potential conflicts of interest are reduced to the minimum possible level and that how conflicts are managed engenders trust. Thus, in some respects, there is no meaningful difference between real, perceived, and potential conflicts of interest, as the failure to effectively manage such conflicts results in greater risk of personal and public mistrust and in reduced confidence in research results, and risks leading to diminished public support for medical research.

Managing conflicts of interest

It can readily be seen that the extent and variety of conflicts poses a substantial management challenge, and reliance upon good intent and good character is inadequate to address these issues [20]. Indeed, focus only upon individual financial interests is also insufficient, and strategies for managing financial and non-financial interests and intrinsic conflicts can be seen as falling into three interrelated, sometimes overlapping domains. These include the following:

- Regulation of the individual
- Design and regulation of the research process
- Critical assessment of the research product

Regulation of the individual

The strategies that have received the most attention typically focus on the individual researcher, such as disclosure of financial interests or prohibition from research on a product in which one has an equity interest. This is the approach often taken by institutions and regulatory bodies and recommended by expert panels [4, 5, 15]. Approaches focused on the individual and on financial conflicts have noted that the degree of control exercised over the individual with the conflict should be proportional to the strength and severity of the conflict [6]. Thus, regulations often define specific financial thresholds as acceptable or not, depending upon the type of activity being regulated.

Disclosure, usually only of financial interests, is widely used and attractive for its simplicity. Disclosure of financial conflicts to one's institution, to peer reviewers, and in publications is widely seen as a minimal requirement, and included in major guidelines, while needs to limit financial interests are also advocated [5]. Yet, disclosure has its limits, including how it may be interpreted by other physicians, scientists, patients, or the public, and how it may affect the individual making the disclosure. Compelling arguments can be made that disclosure does not effectively prevent, help identify, or avoid the appearance of investigator bias [9]. Potential research subjects report a strong interest in disclosure of investigator conflicts [22, 23]. As a way of achieving transparency disclosure might be expected to increase trust. However, evidence indicates that physicians and research subjects both have diminished confidence in the quality of trial design when the trial is industry-funded (or described as such in test scenarios), and confidence in the results as well as willingness to prescribe a trial drug based upon the evidence in such a scenario is also significantly reduced [22, 24, 25••]. Some patients indicate that conflict disclosures could influence their decisions regarding whether to participate in research studies [22].

Another problem with disclosure is that self-reported conflict disclosure is often inadequate as a method for ascertaining whether conflicts of interest are present. At a large orthopedic meeting, the rate of self disclosure of payments from manufacturers of hip and knee prosthesis during the prior year was only 79 % for presenters who received payments directly related to the topic of presentation and just 50 % for payments that were indirectly related to the subject of the presentation; the greater the payment, the more likely it was to be disclosed [26]. Another striking example involved a study of authors identified in whistle-blower complaints of manufacturers involved in off-label marketing activities; these authors disclosed their financial relationships with the defendant manufacturers in only 15 % of published articles related to the off-label use in the subsequent 3 years, and 43 % of the articles had no disclosure [27••].

Disclosure to potential research subjects has been strongly advocated as a way of promoting better informed consent, respecting the subjects rights, maintaining trust, minimizing legal risk, deterring troubling financial relationships, and protecting the welfare of research subjects [28]. Nonetheless, disclosure to potential research subjects, however desirable, may also be insufficient due to the intrinsic limitations of disclosure and the informed consent process [7, 29]. Research subjects indicated in one study that only equity interests were likely to strongly influence their likelihood of trial participation [30], but the basis for that conclusion is uncertain and the "right" threshold is unknown and might vary between individual investigators. There is risk that the patient's trust may be misplaced or at least disproportionate to the risk of bias, and other interests may result in significant bias. A study of patients receiving total joint arthroplasty found that patients had a poor overall understanding of financial conflicts of interest, although higher educational level and previous discussions of financial conflict of interest predicted better understanding [31]. Other research has shown that disclosure can lead the individual making the disclosure to more readily offer biased advice [32•]. This occurs by several mechanisms, including a sense of moral licensing based on a feeling that the recipient of the information has been adequately warned. Although described in the context of physician-patient clinical interactions, this phenomenon may apply to disclosures in research presentation or publication as well.

Other strategies aimed at the individual, such as abstention or prohibition from certain activities, may be required. An example would be individuals with particularly strong financial interests in the outcome of a research study (e.g., holding significant equity interests that may be affected by the outcomes of a research study). Specific financial thresholds for compensation or equity are often used, with the assumption that greater financial interests pose more risk, but this approach fails to account for the findings that even small gifts and relationships may influence individuals. Moreover, the relative value of comparable financial interests to different individuals may not be possible to discern or meaningfully assess. The use of blind trusts and requirements for complete divestiture are not frequently employed in regulating scientific investigators. It is unclear how these would be managed and regulated in the academic medical research setting or the consequences of such approaches.

Design and regulation of the research process

The second type of strategy tends to focus on the process, i.e., the methods of investigation and analysis, and the presentation of the research, and strives to optimize these processes to get the best possible research product. As examples, these include education of investigators regarding elements of research design that can help limit or prevent the influence of bias, informed and non-conflicted IRB review of research proposals, rigorous overview by research supervisors, and public registration of trials. These all can help build a system or context in which the research takes place that increases the capacity to obtain scientifically valid research outcomes that are not unduly influenced by secondary interests of individual investigators.

In this regard, elements of research design, such as adequate blinding and allocation techniques, appropriate comparisons, and proper data analytic techniques, can diminish some of the effects of secondary interest and bias. However, excessive levels of scrutiny of researchers and their methods beyond the level of the laboratory or clinical research group could become intrusive to a degree that investigators and their immediate supervisors find onerous, so a balance must be struck. Additionally, hospitals and other research institutions and their research groups have their own collective conflicts, desiring "good results" that promote the institution and bring in greater funding for the component departments and research groups. Institutions and the institutional leadership often have relationships with industry, and these represent conflicts that may impact how the work of individual investigators is viewed. It is thus important that attention be given to the conflicts of decision-makers in their management roles, including the institutional, department, and research group leadership. Avoiding conflicts among the leadership and of the members of committees that regulate research should also be understood as an area where particular conflicts may pose special risk, but also where prevention, attention, and management of conflicts may provide institutional solutions.

Another logical locus for regulation and intervention is the institutional review board (IRB), also referred to as the human subjects research committee, but such committees and their members are not immune to conflicts, which often remain poorly addressed, and IRB's respond to financial and non-financial conflicts with great variability [33]. The IRB is often poorly equipped to manage their own conflicts, especially those which are indirect and non-financial, and greater attention to effective review and guidelines for the management of conflicts of interest of members of the IRB should receive greater attention as part of a comprehensive conflict of interest management program [33].

Critical outcomes assessment

The third strategy, in addition to the individual and the research process, is a focus on close, skilled, and non-conflicted review of the outcome or product produced by the investigator and the research itself. This final piece is exemplified by the journal editorial process, particularly peer review. This approach has been advocated as a solution for addressing the myriad of non-financial conflicts that may pose an enormous challenge to identify, catalogue, assess, and

address. As one expert has suggested in commenting on the editorial review process of a highly respected medical research journal, "The antidote to fame, power, politics, and greed seized upon by journals in the twentieth century was vigorous peer review….Transparency and disclosure are the weapons they have aggressively deployed. Peer review is the other great protection against conflicts of interest" [34].

Strategies with mixed focus and non-financial conflict management

These three aspects of conflict management are not mutually exclusive domains. As an example, the level and scope of peer review and analysis of evidence for the development of clinical practice guidelines require the creation of teams that can compensate for individual weaknesses, whether scientific or due to risk of conflict from secondary interests. By the creation of a group of individuals with the requisite complementary qualifications as well as different conflicts, the body as a whole can potentially function in an effective fashion in which undue secondary influences on particular individuals are much less likely to adversely affect the group process. This requires attention to the individual, a system/team-based management process, and acts to mitigate the risks that conflicts have undue adverse impact on the quality of the peer review process.

An example of this approach, which could be applicable, with some modification, to addressing conflicts of interest in research, has been proposed as a way to help systematic review teams retain needed expertise while still minimizing biases stemming from non-financial conflicts of interest [35••]. These authors propose a limited number of questions to identify non-financial conflicts relating to four categories, including interest of: the individual, through personal beliefs; others, through personal relationships; the institution, through institutional relationships; and career advancement, which relates to all three of the other categories. They then describe a five-step process for identifying, measuring, and managing non-financial conflicts of interest. This process requires transparency in documentation, accounts for context, and relies on judgment in evaluating risk of particular conflicts. It is most applicable to teams, such as systematic review teams and practice guideline development committees, but their strategy for identifying and assessing non-financial conflicts may be applicable in other settings, even when all of the proposed management strategies may not.

It has been argued that non-financial conflicts need to be regulated in a comparable fashion to financial interests for several reasons: the very similar social and psychological influences resulting from such interests that result in bias; the synergistic interaction of financial and non-financial conflicts; and the importance of both as threats to public trust [18••]. More systemic responses to these challenges [18••, 36], the discussion of which is beyond the scope of this essay, may be required in the future to address these problems, and further research is merited to determine whether these approaches or selected aspects of proposed strategies are feasible and effective.

Conclusions

Conflicts of interest are pervasive in medical research but must be managed effectively to maintain the integrity of research and public trust. Although most of the focus on conflicts and their management has been on financial conflicts, it is likely that non-financial and intrinsic conflicts have similar potential for creating bias and exerting undue influence on the judgment and actions of the investigator. Further efforts are needed to develop and test methods for effectively identifying conflicts of interest, and strategies for their management should be evaluated for their capacity to promote high quality research, protection for research subjects, and public trust in medical research.

Compliance with Ethics Guidelines

Conflict of Interest Paul L. Romain declares that he has no conflict of interest.

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