Scientific Integrity, Fidelity and Conflicts of Interest

Teddy D. Warner; Laura Weiss Roberts

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Introduction

In 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research defined the core principles underlying ethically sound research as respect for persons, beneficence, and justice.[1] These concepts have served well in guiding the design, implementation, and oversight of human studies over the past 26 years.[2,3] Nevertheless, ethical controversies continue to arise, most recently in relation to challenges in fulfilling two other ethical ideals - scientific integrity and fidelity - in everyday research activities involving human volunteers.[4-7]

Scientific integrity has been characterized as a commitment to truthfulness, to personal accountability, and to vigorous adherence to standards of professional conduct (e.g., accuracy, fairness, collegiality, transparency).[8] Fidelity is the notion of faithfully living up to one's commitments.[9,10] Integrity and fidelity, taken together in the context of human research, thus represent the making and keeping of the promise to collaborate respectfully with study volunteers in a manner that is scientifically rigorous, seeks benefit for individuals and for society, is fair, is non-exploitative, and is truthful.[10] Conflicts of interest are important because they may threaten the ability of scientists to fulfill their obligations of scientific integrity and fidelity in their professional work.[5,6,8,11-15] In addition, conflicts of interest, and the appearance of conflicts of interest, undermine trust in the scientific integrity as perceived by key stakeholders.[8,12,14-15]

Scientists undertake many roles as researchers, clinicians, research reviewers, and institutional leaders in their professional activities. Each of these roles is accompanied by specific duties and fiduciary responsibilities, and at times these may conflict.[16] Conflicts of interest go beyond these natural role conflicts: conflicts of interest are arrangements in which a professional's ability to observe, judge, and act according to the moral requirements of their role are or will be compromised, often to an unacceptable degree.[17] Conflicts of interest in research theoretically relate to dominance of the personal advantage or values of the investigator over other important elements in the situation.[8]

Conflicts of interest may be very diverse in their character and effects.[12,13,18] For example, potential conflicts may occur when a large incentive is paid to a researcher who very rapidly enrolls volunteers into a protocol. In this case, the researcher may be tempted to recruit briskly and, perhaps, to take short-cuts or to interpret entry criteria in a biased way, albeit often unknowingly.[4,19,20] Subtle but important non-financial conflicts of interest may also relate to academic promotion, inappropriate data interpretation, or expression of personal political or religious values in interactions with participants or patients.[4,13-15,20-22] Conflicts of interest may also emerge in relation to overlapping roles, such as an investigator who sits on an institutional review board (IRB) or who leads a clinical research initiative and whose judgment may be affected by the desire for personal power or institutional resources.[23] Finally, conflicts of interest that threaten scientific integrity may occur in situations in which approval for publication of data resides with an 'interested party' upon whom the researcher depends for resources (e.g., funds, access to participants).[13,24-27] Hypothetical examples of these conflicts range from the pharmaceutical company that seeks to publish only positive findings to the small community IRB that seeks to prevent the publication of stigmatizing study results.[4,12,13]

Financial conflicts of interest in clinical research have grown in their salience for investigators and institutions alike as funding has increased and has shifted to a different balance between private and federal sources.[4,13-15,24-28] Between 1980 and 2001, support for research by pharmaceutical companies grew from US$1.5 billion to US$22 billion.[29,30] Research support by federal sources also rose, although not so dramatically, during this period. The United States National Institutes of Health (NIH) research expenditures increased from US$4.5 billion to US$13.9 billion between

1985 and 1999 (website: http://grants2.nih.gov/grants/award; May 31, 2002), for example, and the US National Science Foundation (website: http://ntalpha.bfa.nsf.gov/nsffundhist_files; May 31, 2002) increased its research support from US$1.4 billion to US$3.5 billion between 1985 and 2001. With these changes conflicts of interest pertaining to financial arrangements in research became much more powerful. Expectations of the private and federal paradigms regarding conflicts of interest and professionalism in the conduct of research evolved or, some argue, eroded.[13,28]

Recent US Policy Documents

Numerous policy documents have been created to assist researchers and research institutions to manage and minimize conflicts of interest.[13-15,23,31] A key example is the set of recommendations recently released by an NIH Blue Ribbon Panel intended to increase the protections for human subjects from potential harms created by financial conflicts of interest.[23] At the institutional level, for instance, it was suggested that the responsibility for research activities should be separated from management of the institution's financial interests. The establishment of conflict of interest committees was encouraged to help in the identification of both institutional and individual conflicts. The panel further suggested that clear criteria should be created to determine what constitutes a conflict and which associated behaviors are allowed and disallowed. For IRB, the panel suggested that policies be created to ensure that board members do not have potential or actual conflicts that compromise rights and welfare of human research participants. Educational initiatives to sensitize IRB members to conflicts of interest were also endorsed. Finally, at the level of the individual investigator, other recommendations were made. Investigators should consider the possible effects that a financial relationship might have on their relations with research participants and the decisions that researchers make. Investigators should include sources of funding and funding arrangements in the informed consent document, including information about financial arrangements with an investigator and institution, and how that arrangement is being managed.[23] A second major resource and policy document was prepared by the Institute of Medicine. The authors of the report emphasized how academic institutions may serve to minimize conflicts of interest and to foster appropriate conduct of research, or they may indirectly 'collude' with negative practices of their faculty and staff, ultimately undermining scientific integrity within the institutional environment.[8] Examples of features of institutions that support ethical conduct include providing leadership and encouraging respect for all involved in the research endeavor; developing policies that are attentive to integrity issues and promoting adherence to these policies; offering educational opportunities related to scientific integrity and protection of human study volunteers; anticipating institutional conflicts of interest and disclosing and managing them effectively; and investigating allegations of misconduct.[8]

Recent Empirical Reports

While a great many commentaries have been published on the topic of conflict of interest in research, relatively few empirical papers exist to help inform our understanding of the many complex issues in this area. Here we briefly summarize key papers and their major results in three areas: indirect evidence on the prevalence of conflicts of interest; scientific bias as an impact of conflicts of interest; and institutional policies on conflict of interest. The interested reader may also wish to refer to other recent reviews of empirical studies concerning conflicts of interest.[18,24,32,33]

Prevalence of Conflicts of Interest: Indirect Evidence

Potential financial conflicts of interest among researchers at academic medical centers have been suggested through indirect forms of evidence in a few studies. Krimsky *et al.*[34] carefully reviewed 789 published papers (a total of 1105 authors) in 14 medical and scientific journals. One-third of the principal authors had at least one type of financial interest (e.g., officer of a company related to the research). A survey of 2052 basic science faculty at 50 NIH-funded institutions indicated that a substantial minority (28%) received research funding and nearly half (43%) had received a research-related gift from for-profit companies.[24-27] In this study, researchers with industry support

were found to differ from those who did not, in terms of academic productivity, impact and research topics. By examining the reported personal financial relationships of 225 academic researchers at a single institution, Boyd and Bero[35] found that the number of principal investigators with personal financial ties to a private research source increased from 3 to 8% between 1985 and 1999. From 1985 to 2002, the self-reports of conflicts of interest increased substantially (10-32%) across all forms of scientific presentations in orthopedic professional meetings.[36]

Physicians believe that patients' concerns about conflicts of interest are increasingly impairing the doctor-patient relationship, but that patients rarely ask about conflicts.[37] In an extremely interesting web-based survey by Kim *et al.*,[38] 5478 persons with known illness were asked about their attitudes toward physician conflict of interest. Participants were presented with several conflict of interest scenarios, and a large majority of respondents (64-87%) expressed the importance of routine disclosure of the conflicts to patients. The respondents indicated that they would generally be wary of participation in activities with such conflicts. In another study involving physicians, it was found that physicians also are often unaware of the specific aspects of their institution's conflict of interest policy and they have quite diverse attitudes about conflicts of interest. They recognize the general risks associated with such conflicts, although they feel they are personally not at risk.[39]

A number of papers have examined scientific journal policies and publications in relation to conflict of interest issues. In a small study of 48 basic science and medical journals, only 43% required the disclosure of financial conflicts of interest by authors. In a much larger study involving 1396 prestigious basic science and medical journals in 1997, only 13% published conflict of interest disclosure requirements and only 0.5% of 61 134 publications that year provided disclosure of any existing conflict. Hussain and Smith[40] examined a sample of published articles in five leading medical journals in the US and UK in 1989, 1994, 1996, and 1999, discovering that authors documented conflicts of interest in very few articles (1.4% rate across all 4 years; 4% rate in 1999). In 2001 the authors with colleagues performed an analysis of 424 published educational research projects, finding that 25% disclosed financial sources in 1988-1989 and 28% in 1998-1999, and only 47% provided no documentation of any safeguards protecting student participants.[41] On the other hand, Gross *et al.*[42] reviewed 268 published randomized clinical trials, finding that 238 did disclose their sources of funding.

Bias Attributable to Conflict of Interest

Scientific bias associated with financial conflicts of interest has been identified in several recently published empirical papers related to cancer[43] and multiple myeloma medications,[44,45] non-steroidal antiinflammatory drugs,[46] calcium-channel antagonists,[47] tobacco use,[24-27,48] and medical and surgical randomized trials.[49] Articles published in industry-sponsored journal supplements have been assessed to be of lower quality overall, to be based on less rigorous study designs, and to have inadequate disclosure of research funding sources.[50] In addition, almost 90% of authors of clinical practice guidelines report some financial relationship with for-profit enterprises.[51] Few clinical practice guidelines authors think that their recommendations are influenced by their industry relationships, but they are almost three times as likely to think that their coauthors' recommendations are so influenced.[51] Interestingly, the psychological issues in recognizing and guarding against potential conflicts of interest and their possible impact on the research decisions have received little direct study, and it must be emphasized that awareness of all sorts of influences on one's own behavior are often far less than ideal.[4,19,52,53]

Beyond active pressures that permit bias in the scientific process, delayed publication of data associated with industry-sponsored trials was documented in a large study (n=2167) of basic science faculty at 50 universities.[24-27] A minority (20%) of researchers acknowledged that they had deferred publication at least 6 months to allow for advantageous arrangements in relation to specific data (e.g., dealing with patent or intellectual property right issues, minimizing publication of undesired or negative results).[26,27] In a survey of 210 life-science companies, over half (58%) required investigators to delay publishing research results for six or more months.[25]

Institutional Policy Implementation

Nearly all (94%) medical schools and research institutions in the US in a survey study (*n*=250) reported having a policy on conflict of interest related to research.[54] Nearly all (91%) also used the federal standard of US$10 000 of annual income (or 5% equity) as the threshold for disclosure and management of conflicts of interest. Very few (9%) employed stricter standards. In a similar study focusing on 10 medical schools, financial conflict disclosure was required for faculty, but only four institutions required disclosure by staff members.[55] In a third study, the conflict of interest policies at the 100 top US research institutions were analyzed.[56] Policies were very diverse, with variable elements and rigor. Only two institutions required disclosure of all financial interests, and no consistency or optimal practices for reviewing disclosures and managing conflicts emerged across the set of schools. Beyond academic centers, 16 large federal agencies participated in a study of conflict of interest policies, and it was revealed that only four had explicit internal policies to help guide their staff.[54]

Conclusion

It is clear that conflict of interest is an important issue in international research, with tremendous attention in the US and UK literature. It is a topic amenable to empirical study and a subject of many valuable guideline documents and policies. Nevertheless, it is important to note that most of the data have been generated from small, self-report survey or literature review projects, the accuracy of which is almost entirely untested. In addition, there is little evidence that rigorous policies and guidelines have been widely adopted. Efficacy and effectiveness of these measures are unknown.

It is our hope that future efforts in this area will stimulate rigorous investigation of questions amenable to empirical study, will integrate evidence-based best practices with appropriate outcome measures, and will remain attentive to the fundamental concepts of respect for persons, beneficence, justice, integrity, and fidelity. We further hope that the international community will choose to build realistic, non-judgmental approaches to the natural conflicts that arise from the multiplicity of roles that scientists undertake in their efforts to contribute to society.

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Reprint Address

Correspondence to Teddy D. Warner, PhD, Department of Family and Community Medicine MSC 9 5040, 1 University of New Mexico School of Medicine, Albuquerque, NM 87131, USA E-mail: twarner@salud.unm.edu

Abbreviation Notes

IRB = institutional review board; NIH = National Institutes of Health

Teddy D. Warner[a] and **Laura Weiss Roberts**[b]

[a]Department of Family and Community Medicine, 1 University of New Mexico School of Medicine, Albuquerque, New Mexico and [b]Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin, USA