Conflict of Interest

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Key word Conflict of interest

Conflict of interest refers to a “a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of research) is unduly influenced by a secondary interest (such as financial gain) [1].” Although most of the literature and commentary on this subject have focused on financial considerations, these are not the only interests that may affect physician behavior. Other potent influences include the desire for professional recognition and promotion, the ability to successfully compete for funding in the research environment, a physician's interest in the patient's well-being (in contrast to that of the community or employer), or even simply the quest for knowledge. Over the last two decades, complex relationships between industry, investigators, and academic institutions have evolved inevitably resulting in various ethical challenges. In this paper, we present an overview of the problems arising from such interactions and relationships.

Philosophical foundations

As noted by the Christian theologian Paul Ramsay, the foundational ethical challenge in medicine, research, and health care involves “the meaning of the faithfulness of one human being to another” [2]. In ethical discourse, this notion of faithfulness and its associated obligation of *fidelity* are

often described as a fiduciary relationship between the patient and the physician or in the context of research, the investigator [3]. In the corporate environment, business practices are based on contracts and marketplace interactions, whereas, in contrast, it is trust and confidence that center the patient–physician (investigator) relationship. As such, the physician, the clinical investigator, and the academic institutions where they work become trustees for the patient's welfare. Thus, when seen in these terms, conflicts of interest are, in their essence, conflicts of fidelity, arising inevitably from the pressures and divided loyalties that besiege those working in the modern health-care environment.

Incentives and professional conduct

The notion that financial and other incentives exert a significant influence over human behavior would seem intuitive based on observations from daily human experience. That such incentives do, from time to time, overpower professional judgment is beyond dispute. Yet, how often is professional judgment undermined in favor of such interests, and, when such indiscretions occur, what are the associated circumstances? Barnes and Florencio cite a number of principles that are likely important determinants [4]. These include that the potential for conflict of interest increases in step with as follows: the value of the secondary interest; as professional judgment becomes more specialized and less amenable to close supervision; as the decision-making process becomes less transparent; and when there is a long-standing relationship between the participants (i.e., manufacturer and the researcher) [4].

Evidence for these associations comes from both the clinical and research environments [4]. In the context of clinical practice, numerous studies have shown that financial incentives and gifts from industry do significantly influence physician behavior. Physicians so exposed are more likely to refer patients for laboratory tests and radiology, surgery, or hospital admission [5–8], to recommend that hospital pharmacies stock drugs having no

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appreciable advantages over existing medications [9], and to prescribe newer, more expensive medications having no clear advantage over well established, generic alternatives [10–13]. Furthermore, such incentives have also been shown to engender positive attitudes toward pharmaceutical representatives [14, 15] whose primary purpose is to influence physician prescribing practices.

In the research setting, similar observations have been made. With respect to the magnitude of the problem, Bekelman et al. [16] reported that 23–28% of academic investigators have received funding from industry, 43% have received gifts, discretionary funding, honoraria, and consulting fees, and one third have personal financial ties with industry sponsors. Furthermore, as a possible consequence of such relationships, industry sponsorship appears to correlate with potentially biased, proindustry clinical trial outcomes. This may result from study designs favoring positive conclusions such as the use of placebos (although this is sometimes a mandate by the FDA) or as a consequence of publication delays and data withholding (as in the case of negative trials).

Investigator–industry relationships

The fundamental impetus for these problems is industry support for biomedical research, which, in the United States, has increased dramatically in the last two decades. The following figures are illustrative. Industry's share of the total investment in biomedical research and development has grown from 32% in 1980 to 62% in 2000; currently, one fourth of biomedical investigators at academic institutions receive research funding from industry [16]. The origins of this remarkable transformation date to the Bayh–Dole Act [17] permitting intellectual property rights for federally funded research at extramural sites. Clearly, the Bayh–Dole Act succeeded in its goal of promoting and accelerating the transfer of scientific discoveries originating in academia into practice [18]. While increasing the revenue derived from patents and licensing and creating the incentive for the commercialization of intellectual property, this law has nonetheless increased the dependency on industry support for research in academic institutions, deepened the connections between academic institutions and industry, and fostered the development of the biotechnology industry in general. It has also produced an avalanche of conflict-of-interest dilemmas.

The recent interest in conflicts of interest in medical research has other origins as well, not the least of which was the tragic death of a participant in a gene transfer trial at the University of Pennsylvania in the late 1990s [19, 20]. In this study, researchers were not only out of compliance with federal regulations designed to protect human subjects, but also the substantial financial ties that existed between the principal investigator, his institution, and the study sponsor have further served to underscore and dramatize the problem of conflict of interest to the general public.

Physician–industry relationships

Because academic–industry relationships are perceived, for the most part, as generating information that enhances scientific knowledge, they are seen in the light of their potential societal benefit and are generally viewed favorably. In contrast, the relationship of the physician with investors and other members of the financial community at large has a different basis [21]. Generally, what is being sought from the physician is knowledge or insight about a given drug, device, or diagnostic procedure from which judgments concerning its success in the marketplace will lead to more or less investment in its development. For the individual physician, the primary incentive is financial gain, usually direct remuneration or, alternatively, profit in the form of stock or stock options. These relationships have been tolerated mainly because the distance between the physician (advisor) and the financial entity is seen as remote, an individual physician being unlikely to significantly influence the success of the product in the marketplace or the financial fortunes of its manufacturer or the investment firm. Nonetheless, as argued by Topol and Blumenthal [21], the potential negative impact of these relationships has been underappreciated, in both their legal and ethical dimensions. Here, some of the relevant considerations include: the risk (unwitting or otherwise) of violating securities law through the provision of “insider” information (this is clearly illegal and goes well beyond any purely ethical consideration); creating conflict of interest when there is either direct physician investment or, alternatively, when there is equity in companies manufacturing products related to the physician's work; and, last, when there is disclosure, an ethical requirement made difficult (if not impossible) by the dynamic nature of the stock portfolios of investment firms.

Conflicts of interest and the academic medical center

Although the conflict-of-interest considerations of the researcher and the institution where he/she works are intimately intertwined, it is noteworthy that existing federal law regulates only the conflicts of researcher. No comparable law, set of regulations, or oversight mechanism exist to manage institutional conflicts. Yet, important ethical dilemmas also confront academic institutions, their directors, and their boards of trustees, all of which result in specific challenges.

The Association of American Universities has defined institutional conflicts of interest, a definition that emphasizes several elements [22]. As summarized by Barnes and Florencio [4] in their review of this subject, this definition acknowledges a number of important considerations. These include that conflicts can arise from corporate (the institution) or individual (senior management, trustees, department chairs) relationships with or through financial holdings in industry; that there is no minimal threshold below which the conflict will be considered insignificant; that the appearance of bias is as important as actual bias; and if conflicts are not aggressively managed, they can lead to impaired decision making.

Further institutional conflicts of interest are not limited to financial considerations. In the context of the practicing physician or the individual investigator, nonfinancial conflicts of interest are widely acknowledged and have been the focus of discussion in the medical literature and elsewhere in this paper. In contrast, at the institutional level, nonfinancial conflicts of interest are also important and include the enhancement of institutional reputation, the origination of new technologies, and the development of effective therapies. Whereas institutional research oversight (i.e., IRB) is believed to manage such problems, nonfinancial conflicts are less easily identified than their financial counterparts and are therefore harder to regulate. Indeed, the relatively obscure nature of nonfinancial conflicts of interest may explain why the federal government regulates only the financial realm.

The central premise underlying the concept of institutional conflict of interest is the assumption that conflicts arising at the institutional level can influence researchers and institutional decision makers. This influence may be exerted at many levels including IRB members and staff, department chairs, deans, and other highly positioned administrators, all of whom may readily understand the potential commercial (and otherwise) value of the research that is under consideration. Such decision makers may therefore be influenced, either directly through financial incentives or perhaps more likely by their general awareness of the potential for benefit to their institution or their departments. That such influences and institutional conflicts can affect human subjects research has been extensively reviewed elsewhere [4].

Interest in these conflicts has been heightened by the recent disclosure that a venture fund established by the Cleveland Clinic owned significant equity in a company that manufactured a device that was used at the Cleveland Clinic for an indication for which the FDA had denied approval; needless to say, patients undergoing procedures utilizing this device were not informed of the financial stake of the institution [23].

Conflict of interest and journal publication

Medical journals remain an enduring, vital source of information, informing and shaping medical practice. Therefore, editors, reviewers, and the authors of manuscripts submitted for journal publication form another group who are susceptible to the influence of conflict of interest. Recognizing this vulnerability, the International Committee of Medical Journal Editors has set forth principles for the management of conflict of interest [24]. The guidelines of this organization emphasize considerations such as that all participants in medical publication, i.e., authors of original research as well as those writing review articles and individuals serving as journal reviewers, disclose all relationships that could be viewed as representing a conflict of interest. Furthermore, there is the requirement that authors confirm that they had full access to all data in the study and had final responsibility regarding the decision to publish the data. Journals, of course, may exercise their discretion to create their own guidelines,

and several have done so, often requiring even more stringent standards of disclosure [25, 26].

Conflict of interest in continuing medical education

One of the primary missions of the academic medical center is to provide continuing medical education (CME) to practicing physicians. Licensing requirements that include credits for continuing medical education in many states have bolstered the efforts of both academic medical centers and independent providers of medical education, and the potential for conflict of interest in medical education has grown accordingly. Leading physicians with expertise in an area of study may have relationships with the pharmaceutical industry that may bias their presentations. In addition, even unrestricted grants to institutions to support educational activities may lead to exclusion of speakers critical of a particular agent's use or inclusion of speakers with significant relationships with a manufacturer. Nonacademic continuing medical education providers often are supported by unrestricted educational grants as well, although support of a CME program may hinge upon inclusion of discussions of disease areas for which the granting company has a product indication. Although a regulatory body exists with a goal of maintaining the impartiality of these discussions, simply including discussions of a specific disease entity may permit discussion of the company's product.

Remedies for conflict of interest in the academic medical center

Paralleling the recognition that the potential for conflict of interest has increased in research and educational activities, efforts to control and manage these conflicts have increased as well. Initial efforts took the form of simple disclosure of potential conflicts. Investigators were expected to disclose their potential conflicts to their institutions and patients enrolled in trials, whereas speakers at meetings and courses were expected to disclose any outside financial interests. Committees were established to review potential conflicts of interest in research, and these committees have become increasingly prescriptive with respect to managing potential conflicts. Divestment of equities, termination of consulting relationships, assignment of new principal investigators, and the use of monitors are among the approaches used to manage the problem.

The need to manage potential conflicts of interest in continuing medical education has also spawned an enlarging and intrusive bureaucracy, although a central certifying officialdom promulgates the broad policies to be followed. It is now estimated that 80–90% of all CME is presented with pharmaceutical company support outside of academic centers, and clearly, the regulatory efforts are aimed primarily at independent providers of CME. In addition to disclosure of potential conflicts of interest, remedies for potential conflicts of interest recommended by the ACCME include

inviting speakers without conflicts of interest, vetting the slides for commercial content prior to the scheduled talk, and having another speaker present a counterpoint to commercial issues. Because of the increasing regulatory burden, it should be noted that the application of these recommendations at academic medical centers has the potential to diminish educational efforts and to inhibit the free flow of information (prior scrutiny of presentations does not permit addition of more recent data or findings) without demonstrably diminishing commercial influence on education.

Medical journals have also recognized the potential for conflict of interest to influence the medical literature in their own publications. Increasingly, journals request disclosure of financial arrangements by authors. Some journals have a strict policy of rejecting medical reviews by individuals with potential conflicts of interest. As with many of the other policies promulgated in the name of eliminating the taint of conflict of interest, the overly rigid application of these policies has resulted in the authorship of reviews by individuals who have not contributed to the primary literature on the subject and the exclusion of authors for associations that may have no effect on the topic under discussion (based on personal experience of B.N.C.).

Conclusion

In a relatively short frame of time, the problem of conflict of interest has come to occupy the forefront of the discourse pertaining to professional ethics in medicine. Broad in its influence, the boundary of the problem now encompasses the domains of the practicing physician, those involved in the conduct and the oversight of medical research, those responsible for medical publishing and for medical education, as well as the academic medical center itself. The problem has spawned an extensive literature, and opinions concerning how to best address the ethical dilemmas this issue engenders remain in evolution. As virtually no arena of the academic medical enterprise is not touched by its influence, it behooves all who work the medical environment to be well informed about this important subject.

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