Special Report

Conflicts of Interest in Research— Towards a Greater Transparency

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Abstract

Recently, substantial undisclosed financial Conflicts of Interest (COI) by researchers at academic medical centers have been discovered and reported in US Senate investigations, prompting large research institutions to take a close look at policies and procedures associated with the reporting and with the management of researcher COI. This article defines COI, reviews the background, describes the problems that arise, and offers solutions.

Background

Researcher conflicts of interest (COI) have received considerable attention in professional journals¹⁻⁴ and the national popular press,⁵⁻⁷ as well as various federal government reports.^{8,9} Recently, substantial undisclosed financial COI by researchers at academic medical centers have been discovered and reported in US Senate investigations,¹⁰ prompting large research institutions to take a close look at policies and procedures associated with the reporting and management of researcher COI.¹¹ Kaiser Permanente (KP) is no exception.

In 2009, approximately \$156.3 million worth of research was funded in KP. Of that total, \$28.6 million came from industry, \$80.3 million from the federal government, \$37.8 million from internal KP funding, and the balance of \$9.6 million from foundations and associations, and state and local governments. In federal fiscal year 2004, the latest period for which figures are available, KP was the recipient of \$24.7 million in grants from the National Institutes of Health (NIH), placing KP among the top 200 recipients of NIH funding that year.¹² One hundred nineteen million dollars (the total research funding less internal KP funding) is a large amount of money from industry and other sponsors, and the risks associated with researcher COI to KP and research participants—putting the interests of the sponsor ahead of the interests of participants or of KP—is

one of the reasons research receives such scrutiny. In all KP Regions, for example, institutional review boards (IRB) review proposed human research for ethical and regulatory compliance, and some Regions utilize scientific review committees before proposed research makes it to the IRB in the first place.

KP researchers have been required for many years to declare COI associated with individual research proposals submitted to IRBs. Since 2002, KP has had a policy on the *Minimum Standards on Financial Conflicts of Interest in the Conduct of Research*,¹³ based on US Public Health Service regulations, to which all researchers are held by KP IRBs when an application for initial human subjects research is reviewed.

In response to heightened concern about the potential for severe reputational damage to the institution, KP has recently increased its compliance reporting requirements regarding researcher COI. In 2009, national leaders at The Permanente Federation and Kaiser Foundation Health Plan and Hospitals (KFHP/H) directed that all KP physician and nonphysician researchers (investigators and co-investigators) annually identify investments, relationships, and other situations that might reasonably present or appear to present possible COI with their accountabilities at the Permanente Medical Groups, KFHP/H, and any other KP entity. This year, the *Conflicts of Interest Questionnaire for Researchers* and associated attestation will be completed by approximately 2000 KP researchers. To assist KP researchers in understanding their responsibilities related to COI, an online tutorial, *Conflicts of Interest in Research: A Tutorial for Kaiser Permanente Researchers*, is available from KP LEARN (<http://learn.kp.org>).

What is a Conflict of Interest?

COI is defined as anything that can create a divided loyalty—or the appearance of one—between the researcher, the institution, and the individuals enrolled in

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the research.¹³ Another way of defining COI would be a situation in which circumstances that create a risk that a researcher's professional judgments or actions regarding a primary interest (KP and the participant) will be unduly influenced by a secondary interest (a research sponsor, or the desire for professional advancement, for example).¹⁴

Interests are broadly characterized into two types: financial, and conflicts of commitment. A *financial interest* is anything of monetary value, including but not limited to salary and other payments for services, equity interests, and intellectual property rights from companies and/or institutions that are sponsoring research. Financial interests include consulting fees and honoraria, stock,^a stock options and other interests, patents, copyrights, and royalty rights.¹³ This definition is necessarily broad, as it is meant to encompass the totality of possibilities that could give rise to a COI, that is, a divided loyalty, or the appearance of a divided loyalty, on the part of the researcher.

Financial interests are further separated by identifying *significant* financial interests.

KP follows the US Public Health Service definition of significant COI, a financial interest that is an equity interest that when aggregated for the researcher and the researcher's immediate family,^b exceeds \$10,000 in value, or is more than 5% ownership interest.¹⁵ *Immediate family*, for purposes of determining COI for KP researchers, is defined as including the following individuals, whether or nor they live in the researcher's household: current spouse or domestic partner, children or step-children and their spouses or domestic partners, and any related or unrelated individuals living in the researcher's household whose financial holdings are known to the researcher.¹³ KP researchers are not permitted to participate in research that is funded by a sponsor in which they or a member of their immediate family hold a significant financial interest. In some KP entities, no financial interest of any kind is permitted.

A *conflict of commitment* occurs when a divided loyalty exists because of nonfinancial ties. For example, this would exist if a researcher was conducting research with an investigational agent, and at the same time was sitting on the scientific advisory board of the agent's manufacturer, even if the researcher did so without pay.

Although a number of institutions address conflicts of commitment in research, COI policies generally focus on financial gain because it is a relatively objective,

fungible, and quantifiable construct, as opposed to conflicts of commitment, which may not be.¹⁴

What's the Problem?

A judgment that a researcher has a COI does not imply that the individual is unethical or has committed a wrongdoing. Such judgments assume only that some situations are generally recognized to pose an unacceptable risk that decisions may be unduly influenced by considerations that should be irrelevant. After having been identified, institutions manage or eliminate these situations in order to preserve the integrity of the research process.

Problems can arise, however, when a COI exists and the conflict is not declared and dealt with in some way by the institution to which the individual owes primary allegiance. At institutions other than KP, there have been a number of instances in the recent past in which researcher COI has figured prominently. In addition to actually or potentially harming research subjects, as well as calling into question research results, the COI and resulting inherently negative publicity have put both the individual researchers involved, and their home institutions, in an unwelcome spotlight. Two examples illustrate this:

- Harvard University child psychiatrist Joseph Biederman, MD, earned at least \$1.6 million in consulting fees from drug makers from 2000 to 2007 but did not report much of this income to Harvard officials, which may have violated internal university policy, as well as federal regulations.⁶
- Between 2000 and 2007, Emory University psychiatrist Charles Nemeroff, MD, the principal investigator on an NIH study of five GlaxoSmithKline antidepressives, received at least \$2.8 million in consulting fees from pharmaceutical companies, including GlaxoSmithKline. He failed to report a third of these fees to Emory.⁵

Senator Charles E Grassley (R-Iowa), the ranking member on the Senate Finance Committee, who initiated the Nemeroff investigation, took the trouble to have read into the Congressional Record of the US the letter he sent to James Wagner, PhD, the President of Emory University, regarding Dr Nemeroff's alleged lack of compliance with federal COI regulations and Emory University policy.¹⁶

At Harvard and Emory, allegations of researcher COI resulted in reputational damage to both the individual physicians involved and their institutions. In addition, in situations like this, civil and criminal charges may attach.

KP and KP members' data have been instrumental

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in correcting at least one egregious situation that came about partly as a result of COI, that of rofecoxib (Vioxx). Manufactured by Merck and Company, Vioxx, a COX-2 inhibitor, was approved by the Food and Drug Administration (FDA) for the relief of chronic and acute pain.¹⁷ A study published in the *New England Journal of Medicine*¹⁸ soon after the drug's approval reported that Vioxx caused fewer gastrointestinal (GI) complications than naproxen. Minimizing GI complications was a driving force behind the development of the COX-2 inhibitor class of drugs. Disturbingly, all 13 authors of the study had financial ties to Merck or were employed by the company.¹⁹ In addition, in yet another study, Merck had deliberately withheld information from the FDA concerning the increase in total mortality of patients on Vioxx compared with patients on placebo.²⁰ It is obvious that significant patient harm can occur when hidden COIs exist.

Vioxx was removed from the marketplace about five years after its introduction because KP data had shown that its use increases the risk of serious coronary heart disease compared with celecoxib (Celebrex) when used for arthritis pain.²¹

From an ethical point of view, it is essential that *any* involvement a researcher or his/her immediate family may have with sponsors must be transparent and declared. Compliance with federal regulations and institutional policies concerning COI is essential to avoid the type of damage that occurred at Harvard, Emory, and Merck.

What's the Solution?

COI policies throughout academia and in academic research institutions are varied in terms of how COI is both defined and managed.²² Journal requirements for authors to report COI are not uniform.¹⁴ Arriving at a set of COI policies and standards to which research institutions in the US could subscribe has proven to be elusive. This variability is frustrating both to researchers and to those charged with ensuring compliance with COI policies. The International Committee of Medical Journal Editors (ICMJE), however, has established a uniform format for disclosure of competing interests for authors.²³ Although only a dozen journals are members of ICMJE, over 600 journals have requested inclusion on the list of publications that follow the ICMJE's Uniform Requirements for manuscripts submitted to biomedical journals, including this one.²⁴ Even so, the format concerns itself with reporting at one point in time, and does not address institutions' ongoing requirements for COI disclosure.

Closer to home, although KP's *Principles of Responsibility* addresses COI in general terms,²⁵ as does KP's National Policy on COI,²⁶ and the annual COI attestation for researchers is now in place, there is still some variation across KP in practices dealing with declaration of COI at the individual research study level.

Nationally, the Association of American Medical Colleges and the Association of American Universities together have called for a general rule that researchers may not conduct research involving human participants if they have *any* financial interest in the outcome of the research, for example, if they hold a patent on an intervention being tested in a clinical trial. Exceptions would be allowed only if an individual's participation is judged to be essential for the safe and appropriate conduct of the research.²⁷

In addition, Senator Grassley, along with Senator Herb Kohl (D-Wisconsin), has authored and introduced the Physician Payments Sunshine Act into the US Senate, requiring annual public reporting by drug, device and biologic manufacturers of payments made to physicians nationwide. In anticipation of being forced to comply with such disclosure legislation, pharmaceutical companies such as Pfizer²⁸ and Eli Lilly²⁹ have already begun to publicly release such data on their Web sites, while others, such as GlaxoSmithKline,³⁰ have promised to do so. Although all pharmaceutical companies are not yet jumping on the transparency bandwagon, having these data will allow institutional officials concerned with COI to cross verify individual researcher attestation data against these records for the companies that currently provide them.

Given the skepticism of "Big Pharma" by politicians like Senator Grassley and by the public generally, it is virtually certain that considerable attention will continue to be paid to researcher COI, and that transparency and uniformity with respect to oversight will likely increase. In addition, the combined efforts at transparency being made by government, industry, the professional and popular media, and academic and other health care institutions such as KP, will also result in increased self-scrutiny by individual researchers and others involved in the research enterprise. Although this introspection may be forced, in some cases anything that enhances transparency regarding COI is to be extolled. ♦

^a For KP physicians and employees, shares of any value in diversified mutual funds held by a researcher or his or her immediate family do *not* constitute a financial interest or significant financial interest.

^b This *de minimis* standard for researchers is espoused by, among others, the Institute of Medicine.

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