Unraveling the conflicts to preserve research integrity

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For decades, constructive collaborations between investigators and industry have benefited patients and the public. Recently, high-profile lawsuits (1), public interest groups, and politicians (2) have raised concerns that financial and other interests may unduly influence professional judgment and threaten the integrity of scientific research.

As a result of the attention regarding payments to physicians, a sense of urgency has arisen to better detect and deal with conflicts. Multiple efforts have emerged to mitigate the conflicts and promote objectivity in research. Individual states (3), professional organizations (4), and even industry (5) promote more rigorous reporting and restrictions. In addition to the Food and Drug Administration (FDA) regulations (6), the Public Health Service (PHS) National Institutes of Health (NIH) proposed new, more stringent guidelines in May 2010 aimed at preventing financial conflict of interests among researchers who receive federal research funding (7).

Starting September 30, 2013, the Physician Payment Sunshine Act (8), a provision of the Patient Protection and Affordable Care Act, will require manufacturers of drugs, devices, biologicals, and medical supplies to post payments or other transfers of value over \$10 (or lesser-value items when the aggregated amount exceeds \$100 during the calendar year to a single provider) that are made to physicians. This applies to payments made for research funding and grants. The information will be posted on a public website that is searchable and in a format that is easy to understand.

The goal of these regulations and the internal policies implemented by institutions (including Baylor Health Care System) is to protect research participants, maintain the integrity of professional judgment and science, and preserve trust in research. When bias occurs in research, there is the potential of harm to participants, damage to the reputations of researchers and institutions, and possible distrust of the research findings. Well-formulated institutional policies for addressing conflicts can assist the institution in mitigating bias by identifying potential conflict of interests and prospectively determining whether the conflicting relationships should be allowed, managed, or eliminated.

WHAT IS A CONFLICT OF INTEREST IN RESEARCH?

Conflicts arise when a researcher's personal interests have the potential to compromise the researcher's professional judgment

and independence in the design, conduct, or publication of research. Almost anything with the potential to affect judgment presents a concern and is considered a conflict. Simply the perception that a conflict may exist creates the need for review of the interest.

While many varieties of conflicts exist, spanning a wide range of circumstances, it is important to note that conflict of interest is not research misconduct. Research misconduct involves fabrication, falsification, or plagiarism in proposing, performing, or reviewing research or in reporting research results (9). A conflict of interest involves the potential use of personal authority for private gain. It may be possible for a conflict to result in misconduct, or misconduct may have at its basis a conflict, but conflicts do not automatically equal research misconduct.

Financial interests are the most obvious type of conflict and often the easiest to identify. Researchers may have an array of financial ties to drug, device, and biotech companies. Researchers are commonly compensated for a wide range of activities including consulting, speaking, instructing, and serving on advisory boards. Compensation includes gifts, research equipment, computers, trips, and discretionary funds from industry. Researchers may also own intellectual property, potentially resulting in licensing and royalty fees. Serving on a company's board of directors or as an officer of the company presents conflicts that may be financial or motivated by other factors. Regardless of the monetary amount involved, all these situations present the potential for conflict.

Financial conflicts are not the only type of conflict present in the research setting. The desire for notoriety, publications, media attention, increased patient referrals, job security, promotion, tenure, and the ability to secure government grants and future research funding of research projects may all present opportunity for conflicts and potential research misconduct.

Some interests may not be considered a conflict in one research project and may be a conflict in another research project. Generally, there must be a relation between the research

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Table. Comparison of financial disclosure rules

Topic	Proposed Public Health Service	Current Public Health Service	Current Food and Drug Administration
Significant “financial interest” (PHS) or “payments” (FDA) required for disclosure	Minimum threshold of \$5,000 for payments and/or equity interests; excludes income from seminars, lectures or teaching, and service on advisory or review panels for government agencies or institutions of higher education	Minimum threshold of \$10,000 for payments and/or equity interests; excludes income from seminars, lectures or teaching, and service on advisory or review panels for public or nonprofit entities	Monetary value of >\$25,000; excludes the cost of conducting the clinical study or other clinical studies
Significant equity interest required for disclosure	Any equity interest in nonpublicly traded entities	Minimum threshold of \$10,000 and/or >5% ownership interest in any single entity	Any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices or any equity interest in a publicly traded corporation >\$50,000
Applicable time	In the 12 months preceding the disclosure	Over the next 12 months	During the time the clinical investigator is carrying out the study and for 1 year following completion of the study

project and the potential conflict. For example, consulting fees of \$25,000 received from a device company may not be a conflict in a research study on a drug sponsored by a different company, but would be considered a conflict in a research study sponsored by the same device company that pays the researcher to consult or speak on its behalf.

Federal regulations provide some guidance regarding what may be considered a significant conflict of interest. However, FDA regulations (10) differ from the PHS regulations (11), resulting in additional complications. The FDA regulations apply to investigational new drugs and devices, while the PHS regulations apply to federally funded research. It is possible for both regulations to apply to a research project that involves an investigational product and funding from PHS. The FDA (12) and PHS (13) require disclosure of financial interests by research personnel as well as their spouses and dependent children. Both sets of regulations provide monetary thresholds for what is considered a significant conflict (*Table*).

REPORTING POTENTIAL CONFLICTS OF INTEREST

Transparency is touted as the key to mitigating conflicts and preserving reputable research. Transparency requires public disclosure of any and all private financial arrangements and other interests that are directly or indirectly related to professional responsibilities. Public disclosure of any and all interests related to a research project is believed to allow research participants to become more informed and medical research as a whole to be more transparent. When a researcher is uncertain regarding the relation of an interest to a research project, disclosure is always the correct action.

At Baylor Health Care System, the research conflict of interest process begins with disclosure. Disclosure of interests that may be related to research activity is essential to achieving transparency. The disclosure occurs at three points during

the research project. The first disclosure is made at the initial submission of a research project to the institutional review board (IRB) or when the funding application is submitted. Next, disclosures are made at each IRB periodic review of the project or annually. Finally, it is the obligation of all research personnel to provide an updated disclosure when a previously unreported activity arises or a significant change occurs in previously reported activities. This obligation continues throughout the research project and for 1 year following completion of the project for FDA-regulated research (14). Currently, PHS-funded research requires reporting of funds that would be expected to exceed the thresholds over the next 12 months (15).

MANAGING AND RESOLVING RESEARCH CONFLICTS

Baylor Health Care System established the Research Conflict of Interest Committee to review financial disclosure statements from all research personnel. The committee consists of physicians and scientists appointed by the Baylor Research Institute president and administrative representatives as designated in Research Conflict of Interest Committee policy. The committee meets monthly or as may otherwise be scheduled to address research-related conflict issues. Members do not receive compensation for their participation on the committee.

Disclosure triggers the conflict resolution process. In 2010, 318 new research protocols were initiated, and all research personnel involved submitted a conflict of interest disclosure statement. Researchers on 573 continuing projects also submitted disclosures for evaluation. Disclosures with potential conflicts were reviewed by the committee.

The committee evaluates and acts on the information disclosed by the researchers in order to determine whether to manage or to eliminate real and perceived conflicts. Factors considered by the committee include the monetary value of a conflict, the scope of the interest or relationship, the duration

of the interest or relationship, the likelihood of undue influence, and the seriousness of harm. By providing detailed information on the disclosure forms, the researchers assist the committee in making appropriate decisions.

Committee actions may include requiring additional disclosure to research participants, patients, or even the public. Most scientific journals require disclosure of conflicts when publishing research results, and the committee may require this disclosure as well. Other restrictions may be established by the committee for participation in the research by the researcher with the conflict, such as not personally providing informed consent, not personally analyzing the research data, or instituting monitoring by external sources.

Some solutions require actions before the research begins in order to mitigate the conflict. These actions may include modifying the research plan or restricting the conflicted researcher from participation in portions of the research where conflicted.

These are only examples of resolutions the committee may utilize to manage real or perceived conflicts. There are conflicts that will not allow for any method of mitigation. Divestiture of the conflict or severance of the relationship creating the conflict may be the only alternative to allow the research project to continue. The committee makes every effort to reach a resolution allowing continuation of research while avoiding opportunity for undue influence from any real or perceived conflicting interests, but there are instances when the research cannot continue due to the nature of the conflict.

The committee presents its recommendations to the researcher with identified conflicts in the form of a resolution for the researcher to accept and implement. The resolution from the committee is approved by the Baylor Research Institute IRB. IRB approval of the research project is not released until the resolution has been accepted by the researcher and all elements of the management plan have been implemented.

Baylor Health Care System Research Compliance conducts monitoring to ensure the implementation of the resolution. Monitoring is used to determine whether each aspect of the management plan has been followed. Failure to implement the management plan can result in suspension or termination of the research project, or other actions by the institution as appropriate.

Each situation presents unique circumstances for consideration and careful weighing of the potential harm and benefits of actions that may be taken to avoid conflicts. The committee

makes its best determination based on the information disclosed. Extenuating circumstances may exist that could potentially override the committee's recommendation and therefore result in an appeal. Researchers may appeal the decision in writing and present additional information for review.

Conflicts of interest will always be present in the conduct of research. Both the tangible and intangible conflicts will always exist, and the types of conflict are certainly becoming more complex. Developing new strategies to manage, reduce, or eliminate conflicts of interest will continue to be a challenge. By making the process transparent and by carefully addressing any potential conflicts, the trust of the public and integrity of scientific research can be preserved.

1. *Gelsinger v Trustees of the University of Pennsylvania; Robertson v McGee; William Lee Wright et al v The Fred Hutchinson Cancer Research Center et al.*
2. Senator Charles E. Grassley (R-Iowa) and Senator Herb Kohl (D-Wisconsin).
3. Vermont, Maine, West Virginia, and Washington, DC, require disclosure of payments to physicians, but not in a public database. Minnesota and Massachusetts have public databases for physician payments, but they are not searchable.
4. AAMC-AAU Advisory Committee on Financial Conflicts of Interest in Human Subjects Research. *Protecting Patients, Preserving Integrity, Advancing Health: Accelerating the Implementation of COI Policies in Human Subjects Research*. Washington, DC: Association of American Medical Colleges, February 2008. Available at https://www.aamc.org/download/157386/data/aamc-aau_coi_report.pdf; accessed May 9, 2011.
5. Pharmaceutical Research and Manufacturers of America. *Code on Interactions with Healthcare Professionals*. Washington, DC: PhRMA, January 2009. Available at http://www.phrma.org/sites/default/files/108/phrma_marketing_code_2008.pdf; accessed May 9, 2011.
6. 21 CFR Part 54 (revised April 1, 2010).
7. Responsibility of Applicants for Promoting Objectivity in Research for Which Public Health Service Funding Is Sought and Responsible Prospective Contractors; Proposed Rule, 75 *Fed Reg* 28688 (May 21, 2010).
8. Patient Protection and Affordable Care Act, HR 3590, §6002. Transparency Reports and Reporting of Physician Ownership or Investment Interests. Available at http://www.healthcare.gov/center/authorities/title_vi_transparency_and_program_integrity.pdf; accessed March 25, 2011.
9. 42 CFR 93.103 (revised October 1, 2010).
10. 21 CFR 54.1-6 (revised April 1, 2010).
11. 42 CFR 50.603 (revised October 1, 2010).
12. 21 CFR 54.3(d) (revised April 1, 2010).
13. 42 CFR 50.603 (revised October 1, 2010).
14. 21 CFR 54.2(b), (f) (revised April 1, 2010).
15. 42 CFR 50.603(6) (revised October 1, 2010).