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Financial Conflict of Interest and Medical Research: Beware the Medical-Industrial Complex

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It has been a generation since the foundations of medical research in the United States have been shaken to the point of necessitating reform in the system of oversight. The sentinel event at that time was the Tuskegee Syphilis Study; the ethical lapses threatened the system of trust between patients, their physicians, and the medical research system. In response to the egregious actions of the Tuskegee scientists, Congress passed the National Research Act, which requires the establishment of Institutional Review Boards (IRBs) to review federally-funded research. The Act also created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This commission subsequently issued the Belmont Report, which detailed the ethical principles upon which the systematic protection of research participants is based.

Although the same ethical principles pertaining to the protection of research subjects apply, new challenges have also arisen. While fortunately there has been no recent event that is comparable to Tuskegee, there are increasing concerns that the current system of human subject protection is inadequate. What happened? Research has become a for-profit industry, and the resulting financial conflicts of interest jeopardize human subjects, patients, and the future role of academic medical institutions. It is time to reconsider the clinical research system.

Medicine, and the medical research endeavor, has changed considerably over the past 25 years. Although the NIH budget has increased substantially, there has been an even greater increase in industry sponsorship of clinical research.[1] This increase in research funding, in combination with pressures to ensure that clinical trials are efficient and organized, has produced a new, for profit research industry. This industry consists of contract research organizations, which perform nearly every aspect of the research process, and do so at rates that are competitive with academic institutions. Unfortunately for academic institutions, this new competition for research funding comes at a horrible time – when clinical revenues have fallen substantially in the setting of managed care. Clinician-scientists need industry sponsorship more than ever. Institutions themselves, in a similar position – since the passage of the Bayh-Dole act in 1980, have stood to yield substantial financial gains from the discoveries of their faculty members.

Unfortunately, prior work has demonstrated that investigators can be unduly influenced by a financial connection to an industry sponsor, resulting in biased science. In a prior review of 107 controlled clinical trials, Davidson reported that 89% of the industry supported trials had a positive outcome, in comparison to only 61% of the non-industry supported trials.[2] More recently, another review of 136 randomized trials found that industry sponsored trials were not only more likely to yield positive results (74% vs. 47% for non-industry studies), but also more likely to use placebo rather than active agent as the treatment for the comparison group.[3] A similar analysis found that industry-sponsored cost effective studies were significantly more likely than non-industry funded studies to yield positive results.[4] Academic scientists who were supported by industry reported that they were more likely to have their areas of inquiry influenced by the interests of their funding source.[5]

Clearly financial conflicts need to be addressed. In the most recent update to the federal human protections system, the DHHS regulations for IRB participation and function were modified and eventually adopted by 17 other federal agencies. Financial conflicts of interest received scant attention. The section on IRB membership states that "*No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB*."[6] The threshold for disclosure of financial conflicts set by regulations is quite specific - investigators are required to disclose "significant" (>$10,000 in equity, $10,000/year in fees, or >5% ownership in the company) financial interests in companies that might be affected by their research.[7] These interests are disclosed to the scientists' own institutions, which are then required to "manage, reduce, or eliminate them".[8]The approach to this problem is highly variable across institutions, however.[9]

Disclosure alone is inadequate. This is not only because the response to the disclosed information can vary dramatically between institutions, but also because it is difficult to assess the nature of complex relations between scientists and their sponsors based on financial data alone. Further guidance regarding managing financial conflicts and ensuring subject safety and research integrity are warranted. A recent joint editorial co-authored by the editors of a dozen of the highest impact general medical journals, represents an important first step in this direction.[10] The editors acknowledge that industry sponsors have a powerful position, but that scientists must be accountable for key aspects of the investigations over which they reportedly preside.[11] As such, the joint editorial states "we strongly oppose contractual agreements that deny investigators the right to examine the data independently."[12] For instance, JAMA will require authors to sign a statement attesting that they "…had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis."[13]Other journals are expected to follow suit.[14] The editors also addressed concerns about squelching negative studies by stating that the "sponsor must impose no impediment, direct or indirect, on the publication of the study's full results, including data perceived to be detrimental to the product."[15]

This action by the journal editors is a welcome and essential first step in addressing investigator conflicts. But what about institutional conflicts? If a university holds equity

stake in a “start-up company”, the existence of which depends on a successful clinical trial, can institutional officials evaluate the financial conflicts presented by that trial objectively? They should not be in that position in the first place. Institutional officials cannot evaluate themselves; they need external guidance just like individual investigators do. It is time to create an external oversight system for institutional conflicts. The American Association of Medical Colleges is currently drafting a proposal to address financial conflicts of interest; whether institutional conflicts receive their due notice remains to be seen. Not only can financial conflicts jeopardize those who participate in the studies, but they can affect the validity of the scientific research enterprise as well. It is time to take action to ensure that the public’s trust in medicine and medicine research is not further eroded.

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[1] R. Rettig, “The industrialization of clinical research,” *Health Affairs*, 2000;19:129-146.

[2] R. Davidson, “Source of funding and outcome of clinical trials,” *J Gen Int Med*, 1986;1:155-58.

[3] B. Djulbegovic, M. Lacevic, A. Cantor, K. Fields, C. Bennett, and R. Adams, “The uncertainty principle and industry-sponsored research,” *Lancet*, 2001;356:635-8.

[4] M. Friedberg, B. Saffran, T. Stinson, W. Nelson, and C. Bennett, “Evaluation of conflict of interest in economic analyses of new drugs used in oncology,” *JAMA*, 1999;282:1453-7.

[5] D. Blumenthal, “University-industry research relationships in biotechnology: implications for the university,”*Science*, 1986;232:1361-6.

[6] Code of Federal Regulations, Title 45: Public Welfare, Part 46: Protection of Human Subjects, June 18, 1991.

[7] Responsibility of applicants for promoting objectivity in research for which PHS funding is sought, 1999.

[8] Id.

[9] B. Lo, L. Wolf, and A. Berkeley, “Conflict of interest policies for investigators in clinical trials,” *N Engl J Med*. 2000;343:1616-20.

[10] F. Davidoff, C. DeAngelis, and J. Drazen, “Sponsorship, authorship, and accountability,” *Ann Int Med*. 2001;135(6):463-5.

[11] Id.

[12] Id.

[13] “Instructions for authors,” *JAMA*, 2001;286:101-8; C. DeAngelis, P. Fontanarosa, and A. Flanagin, “Reporting financial conflicts of interest and relationships between investigators and research sponsors,” *JAMA*, 2001;286(1):89-91.

[14] See note 10.

[15] Id.