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Journal Discussion

Maintaining Integrity in Industry-Sponsored Research

Many ethical and legal issues arise when academic medical research is sponsored by pharmaceutical companies.

Alison Bickford

Parks, MR, Disis ML. Conflicts of interest in translational research. [J Translational Med.] 2004;2:28. Available at: http://www.translational-medicine.com/content/pdf/1479-5876-2-28.pdf. Accessed October 26, 2004.

In recent years, a growing number of academic researchers have looked to private industry for funding. Ideally, both parties can benefit from this kind of exchange—the researcher receives resources and funds while the company can utilize highly skilled workers and functioning laboratories to conduct its research. Research can progress swiftly and efficiently by combining the intellectual resources of academia and the financial resources of industry.

This kind of relationship can be particularly important in translational research—the process of moving drugs and procedures from bench to bedside—where developments must be tested for safety and efficacy. Companies that are developing treatment protocols may not have access to human subjects for a clinical trial, but they can provide both financial resources and a supply of their drug to academic researchers who interact with patients at academic tertiary care facilities. From one perspective this situation offers tremendous promise: accelerated research means that successful treatments will benefit patients sooner. Unfortunately, there is also a drawback to this sort of partnership: the ethical problems that arise in privately funded research are only aggravated when patients and clinical trials are involved.

One of the best-known cases that combines questions of biomedical ethics with translational research involves Dr. Nancy Olivieri and Apotex, Inc, a major Canadian manufacturer of generic drugs. While the Olivieri case is both lengthy and complex, it is the perfect case study for an applied understanding of the benefits and pitfalls of academic-industry partnerships. Consequently, much of this discussion will use the Olivieri saga to illustrate the general principles raised by Malcolm Parks and Mary Disis in their 2004 article in the *Journal of Translational Medicine*.

In 1991, leading hematologist Nancy Olivieri applied to the Medical Research Council of Canada for funding of a clinical trial to compare deferiprone (L1) with current iron-chelating treatments for thalassemia. Her application was rejected, and she was advised to seek funding from the pharmaceutical industry. She finally found funding in 1993 from Apotex. Dr. Olivieri signed a 3-year contract with the company, agreeing, among other things, not to disclose or publish any information or knowledge about L1 without the express consent of Apotex.

By early 1996, Dr. Olivieri became concerned that in certain patients the efficacy of L1 was decreasing over time. When she reported her findings to Apotex, the company argued that no drug could be universally effective and that there was no risk to her patients. But Olivieri thought that some patients taking L1 might respond better to the standard treatment while avoiding the risk of neutropenia, a side effect previously associated with L1.

Olivieri sent a report to the ethics board of her hospital. Apotex sent their own report, outlining their interpretation of her results. The ethics board concluded that Olivieri needed to change her consent forms and publish her conclusions. She drew up new consent forms, but when her grant came up for renewal in May of 1996, Apotex terminated the trials and reminded Olivieri that all information generated by her research under their grant was to remain confidential.

In June 1996, Olivieri agreed to continue administering Apotex-supplied L1 to informed patients who appeared to be benefiting from the drug and to monitor the risk. But by early 1997 Olivieri had data suggesting that L1 increased liver fibrosis. At the same time, Apotex began planning treatment using University of Toronto patients without liver biopsy, claiming the drug was safe and effective. Olivieri felt that concealment of her data would be unethical. Apotex saw her movement to publish as a violation of contract and issued legal warnings to Olivieri.

The University of Toronto acknowledged that Apotex was wrong to try to suppress Olivieri's data, but never took any decisive action to stop the pharmaceutical company's plans. At the time, the university was anticipating a multimillion-dollar donation from Apotex for a new biomedical research center. When the controversy went public, the university issued a statement repeating Apotex's allegations about the quality of Olivieri's research.

For the next 2 years, Olivieri fought Apotex, her own hospital, and the university. On January 6, 1999, the Hospital for Sick Children (HSC) removed Olivieri from her position as director of the hemoglobinopathy program, after a further disagreement regarding plans to move the program for the treatment of sickle cell disease into regional pediatric centers. The university intervened, and Olivieri was reinstated on January 25, with a promise of legal support from the HSC. But in April 2000, the hospital issued a complaint against Olivieri regarding her treatment of patients during initial clinical trials in 1996. The complaint was referred to the College of Physicians and Surgeons of Ontario, and the charges were only dismissed after a period of 2 years.

The prolonged drama of the Olivieri case is an example of the potential for conflicts of interest and ethical dilemmas whenever industry funds clinical trials. Misinformation and miscommunication delayed resolution of the issue, and many reviews and reports were necessary to vindicate Olivieri (the main report, published by the Canadian Association of University Teachers, can be found at www.caut.ca/en/issues/academicfreedom, and an external review from the Hospital of Sick Children at www.sickkids.ca/l1trials).

While worthy of study in its own right, the Olivieri case also serves as an illustration of a basic question facing the medical research community: should universities allow their researchers to receive private funding? In their article, Malcolm Parks and Disis address several issues related to this fundamental question. Given the potential problems associated with industry funding—so clearly demonstrated in the Olivieri case—blanket prohibition may seem like the easiest solution. Parks and Disis point out, however, that this kind of blunt approach can leave other biasing interests in place and eliminate the resources and communication that can accelerate clinical advances [1]. Some authors argue that funding from industry has not improved clinical research, but the fact remains that nearly 75 percent of funding for clinical trials in America comes from corporate sponsors [2]. It is therefore important to examine the problems with industrial funding for translational research and find regulations that can minimize these ethical dilemmas.

The issue of academic freedom is central to the Olivieri case. Understandably, industrial sponsors would like to ensure that publications reflect their interests, but the investigator must be free to analyze and publish all findings, even if there is a legitimate difference of opinion about the interpretation of the data. Parks and Disis recommend allowing the sponsor to review material prior to publication without the power to limit distribution of information [1]. Other writers suggest appointing an independent review committee acceptable to both parties, or creating a national review center under the National Institutes of Health or equivalent bodies [3]. It is important that research sponsors never have the right to control publication and that both investigators and review boards ensure this as a standard of practice.

Other problems arise when an investigator stands to profit personally from the success or failure of a treatment. An investigator may profit directly from the sale of a drug, receive a higher payment from an industrial source if results are positive, or receive payments for each patient recruited into the trial [4]. Parks and Disis suggest that investigator bias can be minimized by assigning certain problematic activities (like recruitment of subjects, acquiring consent, and analysis of data) to disinterested team members; assigning independent committees to review the data; conducting multisite research to lessen the bias of any one investigator; and requiring all researchers to disclose their financial interests [1]. Other authors point out that institutional review board members and other institutional decision makers like presidents or trustees may also have extensive financial ties with industry and suggest that those without a declared legitimate justification for these financial ties should either give up these interests or remove themselves from the decision-making process [4]. This kind of institutional bias is illustrated by the financial connection between the University of Toronto and Apotex in the Olivieri case. In this situation, however, the responsibility of an academic

institution is to support its researchers and not to protect its financial interests.

Research may actually be limited and slowed by outside funding because of the regulation necessary to avoid conflicts of interest. Parks and Disis note that extra time and resources will need to be allocated for institutional and extra-institutional review processes [1]. One review found that industry-sponsored academic researchers were more likely to experience delays in publication, often because of the need for confidentiality while filing for a patent [5]. Assigning all positions involving contact with human subjects to disinterested third parties increases the cost of research and assumes that disinterested parties exist and are available. As investigators become increasingly involved in patenting and licensing drugs, they may even disqualify themselves from participation in their own clinical studies [1].

Both academic investigators and industrial sponsors must be aware of the impediments to research that can arise when financial interests are involved. Parks and Disis point out that universities are not designed to be as secure or secretive as industrial laboratories, a fact that is to their advantage. Communication between investigators and exchange of information can lead to increased creativity and focused research, but it can also be construed as an information "leak" by an industrial sponsor. Yet if industry sponsors need to reconsider their collaborative research frameworks, universities too must be realistic in their expectations. Many tested drugs will not be safe and efficacious, and many joint ventures with industry will not return large profits for the university [1].

Although a connection between academia and industry can accelerate and improve clinical research through increased access to resources and increased communication between researchers, we can only avoid the ethical conflicts apparent in the Olivieri case through strict regulation. Unfortunately this regulation can impede the very research we want to accelerate. However, when the rights and safety of all patients are considered to be of paramount importance in the final cost-benefit analysis of academia-industry partnerships, such regulations must be clearly delineated and strictly enforced. Consequently, both academic institutions and the medical industry must be aware of potential pitfalls when they initially pursue a relationship.

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Questions for Discission

1. What should Olivieri have done to avoid conflict with the pharmaceutical company Apotex? What should Apotex have done? What was the role of the university and the Hospital for Sick Children?
2. Parks and Disis point out several ways in which industrial funding can impede clinical research. Are there others? Is it possible to modify their recommendations to lessen their impact on research?
3. What do you think when you see that a drug company funded the clinical trials for one of its drugs? What are some ways that a researcher can manipulate the clinical setting, patient population, or data in order to change the outcome of a trial? What can be done to minimize this kind of manipulation?

Alison Bickford is a graduate of Amherst College where she majored in neuroscience. She is currently a second-year student in the Medical Scientist Training Program (MD/PhD) at Northwestern University's Feinberg School of Medicine. Prior to beginning medical school, she spent a year working with Partners in Health in Siberia.