Constraints of interest: lessons at the Hospital for Sick Children

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Editorial

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As you now [sic], paragraph 7 of the LA-02 Contract provides that all information whether written or not, obtained or generated by you during the term of the LA-02 Contract and for a period of three years thereafter, shall be and remain secret and confidential and shall not be disclosed in any manner to any third party except with the prior written consent of Apotex. Please be aware that Apotex will take all possible steps to ensure that these obligations of confidentiality are met and will vigorously pursue all legal remedies in the event that there is any breach of these obligations.

Excerpt from a letter dated May 24, 1996, from Dr. Michael Spino, Vice President of Scientific Affairs, Apotex Research Inc., to Dr. Nancy Olivieri.

The truly remarkable thing about this paragraph is that it came to be written at all. That an internationally renowned children's hospital would have no formal mechanism to scrutinize contracts and that seasoned researchers at the hospital, faculty members at one of Canada's most prestigious medical schools, would sign a contract containing a 3-year gag clause to prevent the unauthorized release of any findings is astounding. What happened and why?

In April 1993 Dr. Gideon Koren and Dr. Nancy Olivieri of the Hospital for Sick Children (HSC) in Toronto signed contracts with Apotex Research Inc. to evaluate the use of deferiprone in the treatment of iron overload in patients with thalassemia major. Although by April 1995 Olivieri and her colleagues had reported some positive findings,[1] not long after, she became concerned that the drug lost effectiveness with long-term use.[2] In December 1996 Olivieri and Dr. Gary Brittenham of Case Western Reserve University in Cleveland began to suspect that the drug might worsen hepatic fibrosis. They voiced their concerns to Apotex, who took the position that their interpretation was incorrect.[3] Olivieri subsequently approached the hospital's Research Ethics Board (REB) and was mandated to change the consent form to ensure that patients were informed of new safety concerns, to inform all of the clinicians participating in the trial and to report the findings to the regulatory agencies. Olivieri sent a copy of the revised consent form to Apotex on May 21, 1996.[3] Apotex responded by informing Olivieri and Koren that trials of the drug were being terminated in Toronto (they were continued at study sites in Philadelphia and in Italy) and firing Olivieri as chair of the steering committee of the Italian trial.

Olivieri asked the HSC administration to provide legal assistance. They declined. As for her other employer, the University of Toronto, Dr. Arnold Aberman, dean of the faculty of medicine, states that all contracts involving the use of university resources must be signed by the university and that no contracts involving "secret or classified research" are ever agreed to. However, research contracts undertaken by faculty members at affiliated institutions are not governed by university policy (Dr. Arnold Aberman, Faculty of Medicine, University of Toronto: personal communication, 1998). A spokesperson for the HSC says that the hospital was not aware of the contracts until after they had been signed, at which point it was too late to intervene (Ms. Cindy DeGiusti, Public Affairs, Hospital for Sick Children, Toronto: personal communication, 1998).

Undaunted by Apotex's warnings of legal action and the lack of support from her sponsoring institutions, Olivieri, with Brittenham and others, published the controversial findings in the *New England Journal of Medicine* in August of this year.[4,5]

Government funding for health care and medical research has deteriorated significantly in Canada in recent years. Federal and provincial governments have

encouraged universities, hospitals and research institutes to seek commercial funding for their activities. Funding for the Medical Research Council (MRC) of Canada has been severely cut in recent years. Although funding cut from its budget was restored last year, MRC funding is still approximately 5 times less than federal funding for health research in the US.[6] Among the G7 countries, Canada is next to last in terms of the proportion of gross domestic product devoted to research and development.[7] Pharmaceutical firms have increased their spending on research; member companies of the Pharmaceutical Manufacturers Association of Canada now spend $624 million annually on research.[8] Researchers have turned to pharmaceutical firms to fund their clinical research: that's where the money is.

Because of the importance of industry as a funder for clinical investigation, it is essential that we understand the issues in the Apotex–Olivieri dispute. Are the pressures to seek funds from nontraditional sources forcing academic administrators to lose sight of the primary goals of protecting patients' health, teaching, and advancing scientific knowledge? Recruiting research funds and donations must always be secondary to patient safety and the integrity of research.

The expenditure of substantial sums by pharmaceutical firms can put executives and researchers under considerable pressure. The stakes are high: a successful new product can result in a huge return on investment for shareholders and may, through profit-sharing plans, result in windfall gains for employees. Researchers stand to benefit financially through consulting contracts with sponsoring companies. The goal for company-funded research is to maintain or increase profit. If governments continue to abdicate their responsibility to fund health research of international standing, profit will become the major force driving the research agenda, and we must worry whether such company-funded research addresses the issues that are most important in treating disease.

Financial concerns aside, research publications are essential for academic promotion, and researchers have a compelling interest in attracting research funding for their projects. As MRC and other government funding wilts, there is increasing pressure on academics to seek industry support and to sign contracts that, in less constrained circumstances, would not be tolerated. As private industry accounts for a growing proportion of research dollars, greater vigilance by universities and a re-examination of existing ethical guidelines will be required.

The 3 main research funding councils in Canada recently published their *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*.[9] A useful component of the new guidelines is the attention it devotes to the functioning of REBs in the face of potential conflicts of interest. The policy states:

> The REB must act independently from the parent organization. Therefore, institutions must respect the autonomy of the REB and ensure that the REB has the appropriate financial and administrative independence to fulfil its primary duties. . . . [T]he public trust and integrity of the research process require that the REB maintain an arms-length relationship with the parent organization and avoid and manage real or apparent conflicts of interest. (4.2)

The guidelines also state:

> Institutions must respect the authority delegated to the REB. The institution may not override negative REB decisions reached on grounds of ethics without a formal appeal mechanism. (1.3)

An important question is whether the REB at the hospital had sufficient authority and autonomy to enforce ethical standards. It is disturbing that the hospital undermined the REB by standing on the sidelines in what the hospital's chief of research, Dr. Manuel Buchwald, described as simply a "scientific dispute."[3] If there *are* situations in which institutions can ignore the recommendations of their REBs, we need careful and generally accepted guidelines for doing so. The Tri-Council policy statement addresses the issue of exceptions as follows:

> Good ethical reasoning requires thought, insight and sensitivity to context, which in turn helps to refine the roles and applications of norms that govern relationships. Thus, because principles are designed to guide ethical reflection and conduct, they admit flexibility and exceptions. To preserve the values, purpose and protection that they attempt to advance, the onus for demonstrating a reasonable exception to a principle should fall on those claiming the exception. (i.9)

We need to understand fully why Apotex and the hospital did not support Olivieri in carrying out the recommendations of the hospital REB. To date, no adequate explanation has been given.

We should not underestimate the seriousness of Apotex unilaterally stopping a clinical trial for other than scientific reasons. Their May 24, 1996, letter to Olivieri did not give reasons for stopping the trial. Previous communications indicated that they did not agree with her interpretation of the findings. Furthermore, in a letter dated June 17, 1996, to Brittenham, Spino stated that they "could not justify Nancy as the Principal Investigator in studies of a drug that she does not believe works," a condition that would eliminate most clinical trial researchers. Trials are done precisely to discover if drugs are efficacious, not to prove that they are. In fact, in a letter of Sept. 15, 1995, to Spino, Olivieri had recommended a new protocol that would have allowed investigation of the anomalies observed; continuation of the trial and initiation of the new studies suggested by Olivieri might have led to the identification of conditions under which the drug could be used safely and effectively.

But what about the patients who consented to participate

in the initial trial? Patients accept the risks of participation on the understanding that the trial will be carried to completion. Both the investigators and the funders of trials have a moral contract with study participants to do their best to obtain an answer to the research question. To stop a trial prematurely without just cause violates this moral contract.

A related issue is the publication and discussion of data collected during a trial. Can investigators fulfil their moral contract with research subjects if data, analyses and conclusions generated by a trial remain secret? How can the information needs of the patients whose lives are on the line in a clinical trial be balanced against the desire of commercial sponsors to restrict disclosure to maintain their competitive advantage? All academic institutions have policies that allow them to delay publication of new data for a short period, usually around 90 days, in order to file patent applications. The secrecy requirements in the Apotex contracts were excessive and indefensible. The Tri-Council code emphasizes the duty of researchers

> to disseminate the analysis and interpretation of their results to the research community. Unfortunately, negative results and outcomes of research frequently are not published or disseminated. Silence on such results may foster inappropriate and potentially harmful clinical practices or needless and wasteful duplication. Researchers and REBs may exert pressure to alleviate this deficiency in the dissemination of research results by resisting publication bans proposed in research protocols, on the basis of ethical obligations of truthfulness and the integrity of research. Research journalists, journal editors, members of editorial peer review boards, sponsors and regulators should address this as an issue of scientific and ethical urgency. (7.5)

These guidelines and the principle of informed consent seem to demand that in this case the need to communicate the concerns of the investigators should override the secrecy clause in the Apotex contract. Why were the hospital and the university apparently not concerned that the warnings of legal action by Apotex would inhibit proper scientific debate and potentially compromise the safety of patients in the trials? Was this not contrary to proper ethical conduct?

The controversy surrounding the deferiprone trial illustrates the need for public disclosure of all funds received by institutions and investigators from commercial sources. Recent studies have suggested that research funded by drug companies is more likely to report favourable results than research funded by independent agencies.[10] Acting as paid consultants to drug companies, as many researchers do, can potentially impede ethical conduct. Many medical and scientific journals require that all authors disclose any such association with a company, regardless of whether that company funded the trial being reported. All universities and hospitals in Canada should require similar public disclosure of involvement with commercial enterprises, including positions held, ownership, honoraria and research funding. Given the potential for bias to be introduced by such associations, it is essential that we develop guidelines for their disclosure and for monitoring and enforcing disclosure.

It is likely that conflicts between the ethical concerns of researchers and the business concerns of their sponsors will arise in future. We need to develop better procedures for resolving such disputes before they become *causes célèbres*. In many situations the parties involved will not hold positions of equal power within an institution. Given the difficulty of settling disputes between scientists of different standing in the power structure, perhaps we need to establish a third-party mechanism to ensure unbiased, fair evaluation of the issues with the ultimate goal of protecting patients in clinical trials and promoting good science.

Finally, we need to learn from this mess. If a properly constituted inquiry can sort out the issues and analyse carefully what went wrong and why, then it may be that the entire Canadian research community can benefit from the resulting awareness and reforms.

After a good deal of foot-dragging, HSC has named Dr. Arnold Naimark to investigate what went wrong with these contracts and their administration and to report to the hospital's board of directors by the end of November. This review process is welcome. However, Naimark's associations with private industry, while providing a unique perspective on the relation between the commercial and academic sectors, may make it more difficult for his report to be seen as unbiased. The complexity and importance of this issue requires an open, public review by multiple reviewers. We urge Naimark to recruit others to the review team and to make the process public to ensure a review that can develop recommendations useful to all Canadian health research institutions.

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