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# Industry and the Academy: Conflicts of Interest in Contemporary Health Research

Jocelyn Downie

# Industry and the Academy: Conflicts of Interest in Contemporary Health Research

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## I. Introduction

The case of Dr. Nancy Olivieri, the Hospital for Sick Children (HSC), the University of Toronto, and Apotex Inc. (hereinafter the "Olivieri case") is critically important to an understanding of the issues central to contemporary health research and the safety of research participants. First, the case illustrates the huge stakes in such research – not only billions of dollars, but the health of Canadians. Second, the case played out at a crucial time in the history of the regulation of health research. Like other recent high-profile cases, it challenged the ways in which research is governed at the local and national levels and fuelled calls for significant governance reform.[1] Finally, it is relevant not only nationally but in individual communities right across the country. What happened in Toronto could have happened (and could still happen) anywhere in Canada. To pursue the promises and avoid the perils of contemporary health research, it is essential to attend to the lessons of this case.

Full consideration of the Olivieri case was a daunting task. The Committee of Inquiry into it reviewed thousands of documents, conducted many hours of interviews, and produced a report with 540 pages of text and 1230 footnotes.[2] In this paper, the three committee members summarize the facts of the Olivieri case and highlight some of the most significant lessons to be learned, particularly in relation to the obligation of investigators to disclose risks to trial participants and

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[1] Other such cases include those of Dr. David Healy, see e.g. Bruce Charlton, *The David Healy Affair*, online: Pharmapolites <http://www.pharmapolitics.com> (last modified: October 2001), and of Dr. Jamie Cuticchia, see "Sick Kids Fires Top Genomic Scientist" (December 2001) CAUT Bulletin Online, *online: CAUT <http://www.caut.ca/english/bulletin/2001_dec/news/genome.asp> (date accessed: 16* May 2002). Calls for reform are found, for example, in "The Governance of Health Research Involving Human Subjects (HRIHS)" Law Reform Commission Report (2000) online: LRC, <http://www.lcc.gc.ca/en/themes/gr/hrish/macdonald/macdonald.pdf> (last modified: May 2000).

[2] J. Thompson, P. Baird & J. Downie, *The Olivieri Report: The complete text of the report of the independent inquiry commissioned by the Canadian Association of University Teachers* (Toronto: Lorimer, 2001) [*hereinafter The Report*]. *Online: Committee of Inquiry* <http://www.dal.ca/committeeofinquiry>.

to the academic freedom of researchers, whether or not their findings are adverse to their sponsors' interests.[1]

## II. Overview

In this paper, we review the facts of the Olivieri case relevant to the issues we wish to highlight, the issues raised by these facts, and the recommendations made by the Committee of Inquiry. Our message is that the research ethics community (Research Ethics Boards (REBs) and research ethics experts), the research community, hospital and university administrators, Health Canada, and everyone else involved in research, must work together to protect the public interest. We must raise our colleagues' awareness, work with our institutions' administrations, lobby funding councils, lobby the federal, provincial, and territorial governments, and encourage public involvement. We must actively seek the realization of the considerable promises of research while just as actively seeking to avoid its perils.

## III. The Facts

### The Committee of Inquiry

*Appointment*

In 1999, the Canadian Association of University Teachers (CAUT) commissioned a Committee of Inquiry into the case of Dr. Nancy Olivieri, HSC, the University of Toronto, and Apotex Inc.. They asked us – Dr. Jon Thompson (Chair of the Mathematics and Statistics Department at the University of New Brunswick), Dr. Patricia Baird (University Distinguished Professor at the University of British Columbia and member of the Department of Medical Genetics) and Dr. Jocelyn Downie (Associate Professor of the Faculties of Law and Medicine at Dalhousie University) – to serve on this Committee. We did not seek appointment to the Committee and we served without any remuneration.

In our initial discussions, we decided that we would serve only if we could be independent of CAUT and any other person or organization. We therefore asked CAUT to make special arrangements to ensure our independence. For example, we were provided with our own office in Toronto, our research assistants reported only to us, and independent legal counsel was retained. CAUT also agreed to refrain from comment on the case until the Committee completed its inquiry and published its report. CAUT also undertook to have the report published as submitted and in

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[1] To avoid replicating the elaborate and detailed citations in *The Report*, we have limited citations in this paper to *The Report* itself. Where appropriate, we refer the reader to the sections of *The Report* that not only offer elaborated description, but noted citations to all primary materials relied upon. Unless otherwise stated, all subsequent references in this paper are to *The Report*.

its entirety, in fact, the report was delivered to CAUT at the same time as it was released to the public on October 26, 2001.[4]

*Terms of Reference*

The Terms of Reference for this Committee of Inquiry were as follows:

1. *To investigate the sequence of events leading to and subsequent to the* crisis at the Hospital for Sick Children and the University of Toronto involving Apotex Inc. and Dr. Nancy Olivieri, her colleagues, students, and others who may have been connected with her in this matter.
2. To determine whether there were breaches of medical research ethics and clinical ethics.
3. To determine whether there were breaches of or threats to academic freedom.
4. To determine whether changes in Dr. Olivieri's working conditions during this period impaired her and her colleagues' ability to conduct their scientific research and treat their patients.
5. To make any appropriate recommendations.

*The Process*

The Committee received from CAUT an initial collection of relevant documents. On the basis of these documents and the experience each member brought to the Committee, we contacted a large number of people who had been involved and invited them to meet with us, provide us with documents, and suggest the names of other individuals who might have relevant information. Additional people were *contacted as their involvement became known to us.*

It is important to note that the administrators of the University of Toronto and of HSC, Apotex Inc., and a number of other individuals, declined our invitation to participate. However, it is equally important to note that the potential disadvantage of these gaps in participation was substantially offset by our access to a large quantity of relevant correspondence and documents originating with the administrations of the University, HSC, Apotex, and other non-participants. These thousands of documents included the Naimark Report[5] – a prior report on the case which the board of HSC had engaged Dr. Naimark and two associates to carry out over a three month period. While the HSC, the University, and Apotex participated in it, neither Dr. Olivieri nor her supporters did. We closely examined the Naimark Report, those of its documents deposited in the HSC library archives, and a number of additional documents relied on by the Naimark Report but not deposited in the

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[4] See Appendix D, "Motions Passed by CAUT at the request of the Committee of Inquiry" at 501.

[5] A. *Naimark, B.M. Knoppers & F.H. Lowy, "Clinical Trials of L1 (Deferiprone) at the Hospital for Sick* Children: A Review of Facts and Circumstances" (1998), online: The Hospital for Sick Children <http://www.sickkids.on.ca/L1trials/revcontents.asp> (last modified: 28 Feb 2000).

archives. In addition, our base of information included a large number of documents written by those who chose not to participate in our inquiry. We therefore believe we had a comprehensive set of relevant information regarding all players in the dispute.

Beginning on October 31, 1999, the Committee visited Toronto several times to conduct interviews. Persons interviewed typically brought documents with them and forwarded additional ones later. Additional interviews were conducted by telephone. We also requested additional documents and received substantial quantities of materials in response.

On March 26, 2001 we sent letters to a number of individuals and organizational heads providing, in each case, a summary of the information we had pertaining to their involvement (letters were sent to those about whom we were intending to make significant findings of fact). We invited them to comment on this and to provide us with any corrections or further information. Some, but not all, of the recipients of these letters had previously declined to participate. The letters again invited their participation and invited them to provide information to the Committee. Some recipients of these letters replied and we included copies of these replies in our Appendix (mostly they were reiterations of the desire not to participate or warnings that legal action might be taken against us).[6]

The inquiry process had two main phases. The investigation phase extended from September 1999 to June 2001. This phase was followed by an evaluation phase where each Committee member conducted their own separate final review of the relevant documents and of information gathered through the investigation phase. This was done to further ensure that each member of the Committee reached his or her own independent conclusions. We reached the same conclusions and the report issued on October 26, 2001 is the unanimous report of the Committee.[7]

## Background and Context

### *National Context*

The Olivieri case arose in a particular national context that developed quickly from the mid-1980s to the mid-1990s. Universities, teaching hospitals, and individual researchers were under increasing pressure to seek corporate sponsorship for research. Public institutions were not sufficiently attentive to the inadequacies of their policy infrastructures to protect the public interest in the face of these new

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[6] See Appendix G, "Letters Received in Reply to Letters Sent 26 March 2001" at 513.

[7] The central conclusions of our report were later independently corroborated by the report issued on December 19, 2001 by the College of Physicians and Surgeons of Ontario (CPSO): Complaints Committee, CPSO, "Complaints Committee Decision and Reasons, Respondent: Dr. Nancy Olivieri" (2001), online: CAUT <http://www.caut.ca/english/issues/acadfreedom/olivieri_CPSO.pdf> (date accessed: May 21, 2002) [hereinafter *CPSO Report*]. It is of note that CPSO had the participation of HSC officials who declined to participate in our inquiry.

pressures. Policies and practices had not changed to take into account the new ethical challenges at the institutional level in addition to the traditional challenges of research ethics at the researcher-participant level.[8]

*Local Context*

Since the early 1990s, the University of Toronto and Apotex had been discussing a major multi-million-dollar donation intended to allow a new biomedical research centre to be built at the University. It would have been the largest donation the University had ever received ($20 million to the University and $10 million to the University for affiliated hospitals). This donation was to have been matched by other sources to provide the approximately $92 million needed for the new centre.[9]

## The L1 trials and contracts

In the early 1990s, Dr. Nancy Olivieri (a specialist in the treatment of hereditary blood diseases) wanted to further study deferiprone (L1), an experimental iron-chelation drug that had shown promise in a pilot study. It appeared to reduce tissue iron loading in a group of transfusion-dependent thalassemia patients at the Hospital for Sick Children. This iron loading leads to tissue damage and eventually may be fatal. The level of funding required for the next stage of testing and development would be available only through a corporate sponsor. One of her scientific collaborators on the original pilot study, Dr. Gideon Koren, negotiated an arrangement with a longtime colleague of his (Dr. Michael Spino) who was a Senior Vice President of Apotex. Apotex agreed to acquire the commercial development rights for L1 and to sponsor clinical trials of the drug. Although three trials were set up, only two were conducted in Toronto and Dr. Olivieri was an investigator only on these two, so we discuss only these two trials in this paper.

One trial was a new randomized comparison trial (LA-01) designed as the pivotal safety and efficacy trial to compare L1 with the standard treatment deferoxamine (DFO). This study was co-sponsored by Apotex and the Medical Research Council of Canada (MRC). The contract for this study contained a confidentiality clause giving Apotex the right to control communication of trial data for one year after termination of the trial. Contrary to assertions made by the University, this provision was fully in accordance with existing University of Toronto policy on contract research.[10]

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[8] See Chapter 3, "Policy Context" at 67.

[9] See Chapter 4(2), "The Context of Associations Between Apotex Inc. & the University of Toronto–A possible Major Donation by Apotex" at 94 notes 3 and 4.

[10] In fact, in 2001, the University of Toronto made policy changes that were deliberate attempts to distinguish new policy from old. At the time, the Dean of Medicine was quoted as saying that had the new policy been in place at the time, "the whole Olivieri-Apotex conflict would likely have been avoided." See Chapter 5A(3) "The Toronto L1 Trials–Confidentiality Provisions in the LA-01 Contract" at 113 note 38.

The other trial, LA-03, was a continuation of the pilot study as a long-term trial. This was a compassionate use trial – it was for patients who were unwilling or unable to take the onerous standard therapy – and it was not funded by either Apotex or MRC from 1993 until late 1995 when Apotex began to fund it.

The contract for LA-03 contained no confidentiality clause. It is particularly important to note this, as LA-03 produced the data that led to Dr. Olivieri's concerns about risks. Unfortunately this important fact seems to have escaped the notice of lawyers and others involved until 2000.

## Trial terminations and legal warnings

In early 1996, Dr. Olivieri identified an unexpected risk in the data from the patient cohort of the long-term trial: loss of sustained efficacy of the drug.[11] This had implications for patient safety as it meant the tissue-damaging iron was not being removed. She informed Apotex that she needed to disclose this risk to patients in both trials. Apotex disputed the risk and the need to inform patients, but HSC's Research Ethics Board (REB) agreed that Dr. Olivieri had an obligation to inform patients of the risk. When Dr. Olivieri moved to inform patients in compliance with a directive from the REB Chair, Apotex unilaterally terminated both trials on May 24, 1996. The company simultaneously issued warnings of legal consequences to Dr. Olivieri if she informed patients or anyone else of the risk.

In the letter terminating the trials, Apotex warned Drs. Olivieri and Koren not to disclose information "in any manner to any third party except with the prior written consent of Apotex," and warned that it would "vigorously pursue all legal remedies in the event that there is any breach of these obligations" it claimed under "the LA01 Agreement and the LA01 and LA03 Protocols." In a telephone message left on Dr. Olivieri's voice mail on the same day, Dr. Spino of Apotex said "You must not publish or divulge information to others about the work you have done with Apotex...without the written consent of Apotex. Now, should you choose to violate this agreement you will be subject to legal action."[12]

Repeated legal warnings were issued not to disclose the risks to patients, as well as with regard to reporting on the research through presentations at scientific

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[11] Chapter 5D of *The Report*, "Concerns Arising in 1995", reports the concerns Drs. Olivieri, Brittenham and Koren had in 1995 about the possibility of reduced efficacy over time. During 1995 Dr. Olivieri sought greater resources from Apotex in order to support the increased monitoring of subjects she felt her concerns warranted. Apotex responded that because of Dr. Olivieri's reported findings of efficacy (based on earlier data), monitoring should in fact be scaled down to include measures only of safety, and no longer efficacy, thereby ignoring the relationship between efficacy and safety in the risk of iron loading over time. Dr. Olivieri refused to accept Apotex's proposal to scale down monitoring, and withdrew several patients from the long-term trial and returned them to standard therapy because the continued monitoring showed serious loss of efficacy of L1 in these patients. A revised protocol dated September 1995 noted the need for an increase in monitoring.

[12] See Chapter 5F "Trial terminations and legal warnings" at 143.

conferences and publication of articles in the scientific literature. These warnings raised questions of both research and clinical ethics, and academic freedom.

It is important to note that Dr. Olivieri wanted to continue to study the drug to determine whether it was safe and efficacious for a subgroup of patients. She felt that she could not continue, however, without the participants being informed of the unexpected risk of loss of efficacy so that they could make an informed choice about whether they wished to continue in the trials.[13] It was Apotex who cancelled the trials.

## Ongoing administration of the drug post-termination

Apotex's sudden termination of the study left patients in an uncertain situation; some of them did not want to return to the onerous standard treatment which involves subcutaneous infusion by a pump for several hours, often several times a week. In early June 1996, arrangements were made to have some patients under Dr. Olivieri's care receive L1 through Health Canada's Emergency Drug Release (EDR) program. Apotex agreed to reinstate the supply of the drug and Dr. Olivieri agreed to administer it to those patients who appeared to be benefiting, on condition that they were informed of and accepted the new risk and agreed to monitoring tests for safety. These patients were no longer in a research trial and, as recipients of an unlicensed drug through the EDR program, were not under the jurisdiction of the HSC REB.[14]

## Identification of a second risk of L1

In early February 1997, Dr. Olivieri believed that she had identified a second unexpected risk, potentially more serious than the first. She believed that the drug might be causing progression of liver fibrosis (thus in addition to the risk of loss of efficacy, it might also be toxic over time). Despite further legal warnings from Apotex, she informed her patients and the regulatory authorities promptly. She counselled her patients to discontinue use of L1 and began making arrangements to transfer them back to the standard treatment, a complex process that takes a number of weeks since setting the proper dosage of the standard drug requires current test information for each patient. As the new risk was chronic rather than acute, there was time for a safe and orderly transition.

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[13] Dr. Olivieri's position on this and her reasons for it are documented in the notes drafted for her by the Canadian Medical Protective Association in preparation for a mediation meeting held with the Dean of Medicine as mediator, discussed at Chapter 5G(1) "Post-termination events–The new L1 treatment arrangement under EDR" at 152 note 3.

[14] See discussion, *infra* "Criticisms of Dr. Olivieri" note 17. It is critical to note that while we may wish it to be otherwise, EDR was not then subject nor is it now subject to REB review.

## Early lack of support for Dr. Olivieri and the principles at stake

From May 1996 onward, Apotex repeatedly issued legal warnings to Dr. Olivieri not to communicate the risks she believed that she had identified. To date, none of these warnings has been rescinded. It is surprising and disturbing that neither HSC nor the University provided effective support to Dr. Olivieri or took effective action to defend principles of research ethics, clinical ethics and academic freedom. University officials acknowledged that Apotex was acting inappropriately and that the University had a responsibility to defend her academic freedom. However, except for the Dean of Medicine's clearly ineffective 1996 requests to Apotex to desist, the University did not take further action to meet this responsibility. HSC officials also took no effective action to support Dr. Olivieri during these events.[15]

In 1997 and 1998, increasing numbers of medical scientists expressed concern over the lack of effective action by HSC and the University to assist Dr. Olivieri in contending with Apotex's actions. Still no effective support was provided and so calls for an independent inquiry into the controversy were made. In mid-August 1998, more than two years after it began, the controversy became public.

## Criticisms of Dr. Olivieri

Not only was there a lack of support for Dr. Olivieri, but there were also considerable efforts made to undermine her, as is shown by the following three examples.

One criticism lodged against Dr. Olivieri was that she was wrong about the risks that she had identified. However, whether others disagreed or whether the identification of risk would be borne out by other studies was not relevant: when a trial investigator has a reasonable basis to believe she has identified a risk, she must ensure that trial participants are informed about the risk. Otherwise, they are not giving informed consent to continue in the trial.[16]

A second criticism was that she had failed to meet her obligation to report the second risk (liver toxicity) to the REB. However, this was untrue.[17] When the toxicity risk was discovered, the patients were *not* in a research trial under REB jurisdiction, and so Dr. Olivieri did not have a reporting obligation to the REB. In fact, the documentation shows that Dr. Olivieri fulfilled all of the reporting obligations that she actually had, including informing the patients directly.

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[15] See Chapter 5G(4) "Post-termination Events–Lack of involvement by senior HSC administrators" at 155.

[16] See Chapter 5K(4) "Identification of the second risk–Fulfilling reporting obligations" at 191.

[17] This criticism was founded in both misinterpretations of REB documents and misunderstandings of REB jurisdiction by the REB chair Dr. Moore, and Dr. O'Brodovich; see Chapter 5K(6) "Identification of the second risk–Interventions by Dr. O'Brodovich & Dr. Moore" at 195.

A third criticism was that Dr. Olivieri performed a test (liver biopsy) on some patients and that this test was risky, was conducted for research purposes (without going through the REB) and was not clinically indicated. Dr. Olivieri had identified both unexpected risks of Apotex's drug in liver biopsy data. Apotex subsequently made efforts to discredit not only Dr. Olivieri, but the procedure of liver biopsy itself. In written statements to HSC Pediatrician-in-Chief Dr. Hugh O'Brodovich, Dr. Naimark and others, the company said that the procedure was risky and unnecessary, and that Dr. Olivieri's use of the procedure in 1997 was unauthorized research. Later, Drs. Koren and O'Brodovich put forward similar allegations to the Hospital's Medical Advisory Committee (MAC), despite their being contradicted by the medical literature. These were prominent among the allegations that HSC's MAC and Board of Trustees referred to the College of Physicians and Surgeons of Ontario (CPSO) in the spring of 2000. Shortly thereafter in a court proceeding in the European Community, Apotex used evidence of HSC's action to support the granting of a restricted licence for its drug and against Dr. Olivieri, who had challenged the legitimacy of the licence. However, all of these allegations were contradicted by the medical literature where liver biopsy is established as a low risk, necessary way of monitoring transfusion-dependent patients for iron overload and for histology in order to adjust therapy. Liver biopsy was an established practice for such patients in the HSC thalassemia clinic. The test was clinically indicated and was not conducted for research purposes, but rather for clinical management purposes. The CPSO exonerated Dr. Olivieri in 2001, and termed her use of liver biopsies "commendable."[18]

## Actions taken against Dr. Olivieri

Several adverse actions were taken by individuals and the HSC against Dr. Olivieri. First, during the period of the Naimark review in the fall of 1998, Dr. Gideon Koren sent anonymous letters to colleagues and the media disparaging Dr. Olivieri and some of her supporters, calling them "unethical" and a "group of pigs."[19]

Second, following the release of the Naimark Report in December 1998, the Board of Trustees of the HSC declared that Dr. Olivieri had failed in an alleged obligation to report the unexpected risk to the REB in a timely way, and directed the Hospital's MAC to inquire into her conduct. The MAC was given incorrect

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[18] *CPSO Report*, *supra* note 7.

[19] See Chapter 5R(3) "The Central Role of Dr. Koren in the L1 Controversy–Dr. Koren's anonymous letters" at 397. After forensic evidence identified him as the author in May 1999, he continued for many months to deny responsibility for the letters. Dr. Koren admitted to having sent the letters only after DNA evidence identified him more conclusively in December 1999. He was suspended with pay pending disciplinary hearings. Four months later, in April 2000, the Presidents of the UofT and HSC wrote to Dr. Koren and stated that "your actions constitute gross misconduct and provide sufficient grounds for dismissal." However, the Presidents did not dismiss Dr. Koren. Rather, they continued his suspension for a further two months (without pay), removed him from the CIBC-Wood Gundy Children's Miracle Foundation Chair in Child Health Research, removed him from a University administrative position, and imposed a $35,000 fine as partial restitution for the cost of the investigation.

testimony, including allegations about Dr. Olivieri's obligations to report to the REB, as well as allegations about liver biopsy and unauthorized research. Drs. Gideon Koren and Hugh O'Brodovich were the principle sources of this testimony that was contradicted by documents available to them, in some instances documents written earlier by Dr. Koren himself. When charged by Dr. Olivieri's counsel with failing to follow due process, the MAC terminated its proceedings without reaching specific conclusions. Instead, it referred an enumerated list of allegations framed as "concerns" to the CPSO and the University in a press conference.[20] These "concerns" were based on false and neglectful testimony by Dr. Koren and incorrect and neglectful testimony by Dr. O'Brodovich provided to Dr. Naimark and the MAC. After investigation, the CPSO completely exonerated Dr. Olivieri. To date, HSC has refused to give the same prominence to the exoneration and its decision not to pursue the matter any further, as it did to the referral of the allegations which damaged Dr. Olivieri's reputation.[21]

Third, in January 1999, the HSC removed Dr. Olivieri from the directorship of the hemoglobinopathy program and issued directives that she and her supporters were not to discuss their concerns publicly.[22] After Drs. David Nathan of Harvard University and David Weatherall of Cambridge University (two internationally renowned experts in the field) and others made representations to the University, these moves were rescinded by an agreement mediated by University President Robert Prichard.[23]

## The ongoing relationship between the University of Toronto, the Hospital for Sick Children, and Apotex

All of this developed against a backdrop of discussions that began in 1991 between the University of Toronto and Apotex about a major donation that could also benefit the University's teaching hospitals, including HSC. This donation was intended to be the basis for large government matching grants that would allow the building of a new biomedical research complex.

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[20] See Chapter 5P(1) "The Medical Advisory Committee Proceedings–Overview" at 330.

[21] In December 2001, the College of Physicians and Surgeons of Ontario (CPSO) released its decision on the complaints laid against Dr. Olivieri arising out of the MAC "concerns", *supra* note 7. The CPSO exonerated Dr. Olivieri. The HSC, responding to an inquiry from the media, stated that it did not plan to appeal the decision.

[22] See Chapter 5M(2), "Removal of Dr. Olivieri as Program Director–HSC's removal of Dr. Olivieri from her directorship & 'gag orders'" at 231 note 31. Both the preamble to the motion at the Combined Chiefs' Meeting in the Department of Pediatrics in which it was recommended that Dr. Olivieri be replaced as Director of the Hemoglobinopathy Program, and the removal letter subsequently issued to Dr. Olivieri cited the public statements by Dr. Olivieri's counsel as particular concerns. It is noteworthy that the statements at issue (about a substantial reduction in hemoglobinopathy clinic staff and the composition of Sickle Cell Disease and thalassemia patient populations) were statements of fact that were indisputable and well known.

[23] This did, in fact, produce the University's first open criticism of the Hospital since the L1 controversy began. *Ibid.*, Chapter 5M(2) at 233.

*Donations*

Agreement in principle on the major donation was reached in the spring of 1998. Discussions on this donation were suspended after the controversy involving Apotex and Dr. Olivieri became public later in 1998. However, in 1999, the University and Apotex had further discussions on the major donation. Apotex also requested assistance from University President Prichard in lobbying the Government of Canada not to make proposed changes to drug patent regulations that would adversely affect the company's revenues. President Prichard wrote to the Prime Minister saying that the proposed government action could jeopardize the building of the University's proposed new medical sciences centre, because "the adverse effect of the new regulations would make it impossible for Apotex to make its commitment to us."[24] After a Toronto newspaper obtained a copy of President Prichard's letter and published excerpts, he apologized to the University community for this action, saying that he had acted inappropriately. The lobbying efforts were unsuccessful, and later in 1999 Apotex withdrew from its 1998 agreement in principle.[25] In late 2000, it was announced that Apotex had made a smaller (5-10 million dollar) donation to the University.[26] In late 2001, it was announced that Apotex had made a further multi-million dollar donation to the University.[27]

*Dr. Spino*

Throughout all this, Apotex's Vice-President of Scientific Affairs, Dr. Michael Spino, held (and continues to hold) the status of professor in the University's Faculty of Pharmacy and, until the summer of 1998, continued to use laboratory facilities in the Hospital for Sick Children.[28] This was in spite of the fact that he had issued legal warnings from Apotex to Dr. Olivieri that violated her academic freedom.

*Dr. Koren*

It was agreed after the trials were terminated in 1996 that Apotex would continue very substantial research funding for Dr. Koren.[29]

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[24] See Chapter 4(8), "The context of associations between Apotex Inc. & the University of Toronto–Donation Discussions Resumed" at 99 note 27.

[25] *Ibid.*, note 32.

[26] *Ibid.*, note 33.

[27] "Apotex Gift Funds New Facilities" *The Bulletin* (29 October 2001) 1, online: University of Toronto <http://www.newsandevents.utoronto.ca/bulletin/10-29-01/10-29-01.pdf> (date accessed: 18 February, 2003).

[28] See Chapter 4(3), "The Context of Associations Between Apotex Inc. & the University of Toronto–Apotex Vice-President Dr. Spino & Dr. Koren" at 94 note 9, and Chapter 5N(11), "Events at the University of Toronto–Dr. Spino" at 264 note 89.

[29] See Chapter 5G(3) "Post-Termination Events–Continued Apotex Support for Dr. Koren's Research" at 154.

Unknown to Dr. Olivieri until after the fact, Dr. Koren subsequently reanalyzed data from the terminated trials and published findings that the drug was effective and safe. Dr. Koren's publications did not disclose Apotex's financial support for his research, made no reference to the risks of the drug that Dr. Olivieri had identified (and published), and did not acknowledge her contributions to generating the data he used. The company used Dr. Koren's statements and post-trial publications in communications with Health Canada to counter Dr. Olivieri's adverse findings on its drug.[30]

In 1999, the website of the Faculty of Medicine listed a research grant for Dr. Koren of $250,000 for use in 1996-1997 but, contrary to standard practice for the listing, neither the source nor purpose of this large sum was specified. After repeated inquiry, it was ascertained from the University that the source was Apotex. The purpose remains undisclosed.[31]

## Conclusion

Several serious breaches of research ethics and academic freedom occurred *in this case. A research project was terminated by a commercial sponsor when a* researcher (on direction from her REB) moved to tell the research participants about an unforeseen risk. A researcher was given legal warnings by the industrial sponsor *against disclosure of the risk. There was a lack of support from the hospital and* university where the researcher had appointments. Criticism and actions were launched against the researcher by individuals and official bodies within the *hospital and university.*

Additionally, the Olivieri case raised issues concerning due process and grievance procedures. There are other examples of serious academic and professional misconduct, and there are serious lapses of institutional responsibility. These associated issues are fully described, and recommendations made in *The Report* and *The Supplement* we issued on January 30, 2002.[32] However, our aim in this article was to give a summary of the facts sufficient to engage in a discussion of two of the key issues raised by the case, namely, the obligation of investigators to disclose risks to trial participants; and the academic freedom of researchers to publish their findings, whether or not these are adverse to their sponsors' interests.

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[30] See Chapter 5H(3), "Expanded Disclosure–Informing the Scientific Community" at 169, and Chapter 5I(1), "Ongoing Legal Warnings–The Series of Legal Warnings by Apotex in 1996 and 1997" at 176.

[31] See Chapter 5G(3), "Post-Termination Events–Continued Apotex Support for Dr. Koren's Research" at 154.

[32] For all recommendations listed throughout *The Report* see Section D, "Recommendations" at 39. J. Thompson, P. Baird & J. Downie, *Supplement to the Report of the Committee of Inquiry on the Case Involving Dr. Nancy Olivieri, the Hospital for Sick Children, the University of Toronto, and Apotex Inc.* (2002), online: Committee of Inquiry <http://www.dal.ca/committeeofinquiry> (last modified: 30 January, 2002) [hereinafter *The Supplement*].

## IV. The Issues

At issue was the right of participants in a clinical trial to be informed of a risk that an investigator had identified during the course of the trial, and the obligation of the investigator to inform them. Apotex maintained that there was a scientific disagreement about the risk, and that it terminated the trials and issued legal warnings to Dr. Olivieri because it "could not allow such information to be transmitted to patients." However, whether others disagreed with Dr. Olivieri and whether the existence of the risk would be borne out by other studies was not relevant: when a trial investigator has a reasonable basis for identification of a risk, she must ensure that trial participants are informed about the risk. Otherwise, they are not giving informed consent to continue in the trial.

The goals of industrial sponsors and academic researchers are not identical. When Dr. Olivieri believed that she had identified an unexpected risk, she had an obligation to act to protect the research subjects even though the findings were contrary to Apotex's interests. She did just this. The University and Hospital in turn had an obligation to protect both her academic freedom and the rights of trial subjects. By not doing so, they put the public interest at risk.

## V. Recommendations

In a Canada-wide context of increasing reliance on corporate sponsorship, where the largest proportion of research funding for medical research and clinical trials is now provided by private companies, this dispute holds important lessons for investigators, university faculties, Research Ethics Boards, administrators of hospitals and universities, the Canadian Association of University Teachers, the Association of Universities and Colleges of Canada (AUCC), research granting councils, industrial firms and regulatory agencies. Unless the lessons are learned, everyone will lose – the public, researchers, hospitals, universities, and private companies – as they have in this case. It is important to recognize that the circumstances that gave rise to this case are not isolated; they illustrate a system-wide problem.

### A. For everyone

The pharmaceutical industry is very powerful, and has substantial resources to promote its interests. Unless governments, granting councils, universities, hospitals, research ethics boards and researchers work in concert to protect the independence of investigators with nation-wide, well-publicized and effectively implemented regulatory mechanisms, the public interest is likely to suffer.

A principle of the highest priority is at stake: namely, that the safety of research subjects in clinical trials and the integrity of the research process are more important than corporate interests. In an era of increasing reliance on corporate funding of research, university and hospital administrations need to be doubly vigilant in protecting this principle. If university/hospital-industry partnerships are to bring benefits (other than to the partners), then there must be clear rules governing

the relationships, rules that protect the right of researchers to communicate (including publish) findings of risk that may displease the sponsor.

In light of this, as our first recommendation we said that:

1. All contracts, protocols and investigator agreements for industrial sponsorship of clinical trials should expressly provide that the clinical investigators shall not be prevented by the sponsor (or anyone) from informing participants in the study, members of the research group, other physicians administering the treatment, research ethics boards, regulatory agencies, and the scientific community, of risk to participants that the investigators identify during the research. The same provisions should apply to any risks of a treatment identified following the conclusion of a trial in the event there are patients being administered the treatment in a non-trial setting.
   Certain circumscribed confidentiality restrictions may be appropriate, for example, those pertaining to information on the chemical structure, or synthesis of a drug, or its method of encapsulation. However, restrictions on disclosure of risks to patients are not appropriate, subject only to the condition that the investigator believes there is a reasonable basis for identification of the risk. Under the term "risk" we include inefficacy of the treatment, as well as direct safety concerns.

## B. For investigators

We concluded that clinical researchers should never sign contracts, protocols or agreements that allow sponsors to restrict communication (including publication) about risks they identify.

## C. For research ethics boards

We concluded that research ethics boards should be vigilant against restrictions on communication in the wording not only of research protocols but also of all associated contracts and investigator agreements. In addition to reviewing protocols, REBs should review the wording of associated contracts and agreements, and should withhold approval for the study if any of these documents contain wording that would restrict communication (including publication) about risks.

More specifically, we recommended that:

10. Not only all protocols but also all associated research contracts and investigator agreements should be reviewed and approved by Research Ethics Boards (REBs) to ensure, among other things, that they comply with recommendation 1. The REBs should ensure that the wording of protocols is congruent with their associated contracts and investigator agreements. REBs should have, and should exercise, the power to withhold approval of any proposed study if any of the associated proto-

cols, contracts and investigator agreements contain inappropriate confidentiality clauses.
REBs should be permitted to delegate the authority to conduct reviews of contracts and investigator agreements to the institutional office of research services. However, such delegation should only be done if:
a) the office is given clear instructions that contracts and investigator agreements must comply with recommendation 1, with the protocols approved by the REB, the ethical standards articulated in the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS) and other norms of research ethics; and
b) there is an annual process of auditing by the REB of a representative sample of contracts and investigator agreements to ensure consistency between the protocols (and ethical standards) and the contracts and investigator agreements.

12. REBs should review project budgets as well as the research protocols and associated contracts and agreements, in order to ensure that all actual and potential conflicts of interest are managed in an ethical fashion.

## D. For universities and hospitals

We concluded that all universities and hospitals should have in place a policy prohibiting clauses in contracts, investigator agreements or protocols that restrict communication (including publication) of risks identified in research projects, particularly clinical trials. Universities and hospitals should also have procedures in place to ensure this policy is followed in practice. Universities and hospitals have a duty to support their researchers if their independence or academic freedom is threatened by any sponsor. If universities and hospitals fail in this duty, public safety and the public interest are in jeopardy. In addition, if hospitals fail in this duty, they fail to meet their responsibility to protect the safety of their patients, whether or not the patients are enrolled in a research trial.

We also concluded that universities and their affiliated hospitals should strongly support the independence, authority and ability of their research ethics boards to help them ensure all research involving human subjects being conducted in their institutions meets ethical standards.

All universities and their affiliated hospitals should also have policies that ensure that fund-raising does not adversely affect the institution's willingness or ability to protect and promote academic freedom and the public interest. If senior administrators are involved in discussions on major donations, it may be difficult for them to maintain their objectivity when a potential donor becomes engaged in a dispute with a researcher. Effects of donations on institutions may be pervasive and subtle due to a natural wish to oblige donors and it is important to discuss such influences openly.

Universities and their affiliated hospitals should establish grievance and arbitration procedures for all persons holding academic appointments (including

clinical researchers, bioethicists, and biomedical scientists) who work in the hospitals. These procedures should encompass all important employment matters including academic freedom, appointments and hospital privileges.

Universities and affiliated teaching hospitals should implement appropriate policies and practices to ensure the protection of academic freedom of clinical and other researchers and bioethicists who work in teaching hospitals and who hold academic appointments in affiliated universities. Relevant provisions should be included in affiliation agreements.

It is important that each institution make provisions for training and briefing new members and Chairs of Research Ethics Boards on matters relevant to their work. This briefing should include familiarization with: the TCPS and other relevant legal and ethical norms, guidelines and policies; and accurate information on the status of all active research protocols and recently terminated protocols. REB Chairs should have adequate independence and authority, as well as adequate release time and administrative support, to carry out their mandate to protect the safety of research participants and the public interest. At present, in most institutions across Canada, REBs are under-resourced and overstretched. They do not have adequate resources to do this important job.

The nature and importance of scientific independence, academic freedom, and of putting patient safety first in interactions with drug companies or other sponsors of research, should be incorporated into training programs for students in all medical schools and affiliated health care institutions. Students should be made aware of potential conflicts of interest, and of the need and ways to manage them in the public interest.

## E. For granting councils

We concluded that all research granting councils should prohibit clauses in contracts, investigator agreements or protocols, that could be used to restrict communication (including publication) of risks to human health identified in research projects, particularly clinical trials. The councils should make compliance with this a requirement for all research carried out in any institution to which they award funds, and the councils should actively monitor compliance. If this is done, it will not be possible for industrial sponsors to move funding to institutions that allow them to control disclosure of results. If this is not done and some institutions are known to be more lenient than others, pharmaceutical manufacturers could move their projects from the institutions that ask for stringent patient protections and unrestricted disclosure of risks to more lenient institutions. Appropriate council regulations would help prevent any race to the bottom; such a race would be to the detriment of the public interest.

Furthermore, we concluded that the TCPS (a joint policy of the three national funding councils) should be amended so as to give further explicit and prescriptive direction to REBs on the need and ways to identify and manage conflicts of interest.

### F. For federal and provincial governments

We recommended that, because safeguards for independence of investigators are usually less robust in non-university settings, there should be oversight of the conduct of clinical trials run outside university teaching hospitals. There has been a significant increase in the number of such trials in North America. The TCPS is a valuable guide in many respects, but has limits in that it does not apply to research conducted in institutions or organizations which receive no funding from the three Canadian research granting councils.

We recommended that federal and provincial governments work together to develop a way to regulate the conduct of research involving human subjects. Within its own activities, the federal government should ensure that Health Canada has the human and financial resources, and legislative powers, necessary to protect the public interest in the regulation (review, approval, and monitoring) of pharmaceuticals in Canada. They should consider and report back to the Canadian public on the option of using legislation to govern the ethical conduct of all research involving human subjects conducted in Canada.

Furthermore, Health Canada should impose a requirement, by statute or regulation, that a clinical investigator neither be asked to, nor agree to, limit his/her freedom to disclose any risks identified in an Investigational New Drug application, Emergency Drug Release, or other unproven treatment where Health Canada has jurisdiction.

Finally, the Federal Minister of Health, working with Provincial Ministers where appropriate, should thoroughly review the current regulation of health research in Canada and use legislation or regulations to ensure that the safety of Canadians is adequately protected.

## VI. Conclusion

The Olivieri case brought to attention gaps in the protection of the public with regard to clinical trials in Canada. There is an urgent need to protect the public interest by putting into place the measures we recommend. The promise of highly profitable developments in pharmaceutical, biotechnology, and genomics research in conjunction with the tighter fiscal realities of universities and hospitals makes appropriate and transparent resolution of conflicts of interest very important. No matter what our roles – as researchers, health law experts, ethicists, policy makers, health care providers, regulators, or health care consumers – we must take steps to ensure that we will not have more "Olivieri cases" in our local contexts. Nor can we allow what would be worse, that is, unexposed suppression of negative research results. As members of the larger Canadian community, we must take steps to ensure that these issues are addressed right across the country. The integrity of contemporary health research and the safety of the public rests on our doing so.

## Postscript

A number of relevant events occurred around the time of, as well as subsequent to, the release of our report on October 26, 2001, and we briefly note them here.[33] Several of these are discussed in more detail in a Supplement to the Report that we issued on 30 January 2002.[34]

1. In late October 2001, it was announced that Apotex Inc. had made a further major donation of $5,000,000 to the University of Toronto.[35] This brought the total donations to the University by Apotex in the period since May 1995 into the $10,000,000 to $24,999,999 category.[36]

2. It became public on 22 November 2001[37] that the Health Professions Appeal and Review Board of Ontario had issued a report in October 2001 regarding Dr. Gideon Koren's conduct on the matter of his anonymous letters against Dr. Olivieri and her supporters.[38] The Appeal and Review Board found that the Complaints Committee of the College of Physicians and Surgeons of Ontario (CPSO) had erred in not imposing discipline on Dr. Koren and referred Dr. Koren to the CPSO Discipline Committee for action. In addition, the Appeal and Review Board directed the CPSO Complaints Committee to investigate allegations of misconduct in clinical research that had also been made by Drs. Helen Chan, Peter Durie and Brenda Gallie, the complainants in the matter of Dr. Koren's anonymous letters.

3. Dr. Arnold Naimark and his Associates wrote a Commentary on our report that was posted on the HSC website on 18 December 2001.[39] In

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[33] Readers are also referred to articles published subsequent to the release of *The Report*. The following articles are of particular relevance: P. Baird, J. Downie, & J. Thompson, "Clinical trials and industry" (2002) 297: 5590 Science 2211; J. Thompson, P. Baird, & J. Downie, "Independent Inquiry" (2002) 167:1 CMAJ 12; 167(1): 12-3; J.M. Drazen, "Institutions, contracts, and academic freedom" (2002) 347:17 NEJM 1362; E. Gibson, F. Baylis, & S. Lewis, "Dances with the pharmaceutical industry" (2002) 166:4 CMAJ 448; M. Litman & L. Sheremeta, "The Report of the Committee of Inquiry on the Case Involving Dr. Nancy Olivieri: A Fiduciary Law Perspective" (2002) 10:2 *Health L. Rev.* 3; D.G. Nathan & D.J. Weatherall, "Academic freedom in clinical research" (2002) 347:17 NEJM 1362; C.D. Naylor, "The deferiprone controversy: time to move on" (2002) 166:4 CMAJ 452; C.D. Naylor, "Early Toronto experience with new standards for industry-sponsored clinical research: a progress report" (2002) 166:4 CMAJ 453; N. Olivieri, "I beg to differ" (2002) 167:1 CMAJ 11; M. Shuchman, "The Olivieri dispute: no end in sight?" (2002) 166:4 CMAJ 487; and M. Somerville, "A postmodern modern tale: the ethics of research relationships" (2002) 1:4 *Nat. Rev. Drug Discov.* 316.

[34] *Supra*, note 32.

[35] *Supra*, note 27.

[36] "University of Toronto National Report - Donor listing by amount" *The Globe and Mail* (7 December 2001) insert.

[37] Heather Sokoloff, "College Censured" *National Post* (22 November 2001) A4.

[38] *Decision and Reasons Regarding the [CPSO] Member Gideon Koren, M.D.* (11 October 2001; issued to the parties to the complaint 26 October 2001), Health Professions Appeal and Review Board of Ontario.

[39] A. Naimark, B.M. Knoppers & F.H. Lowy, "Commentary on Selected Aspects of the Report of the

*this they endeavoured to defend the 1998 Naimark Report against* criticisms in our report. As discussed in our supplement issued 30 January 2002, their conclusions are contradicted by the abundant documentary record, much of it available to them when writing their 1998 report and listed in their report's index of documentation. By June 14, 2002, the HSC had removed the Naimark Commentary from its website.

4. On 19 December 2001, the Complaints Committee of the CPSO issued its report on the allegations against Dr. Olivieri referred to it by HSC's Board of Trustees and Medical Advisory Committee.[40] The Complaints Committee, and the panel of medical experts it had commissioned for *the purpose, exonerated Dr. Olivieri on all counts. This report provided* independent corroboration of the findings of our report on all matters discussed in common.

5. On 7 January 2002, Dean David Naylor of the Faculty of Medicine of the University of Toronto dismissed all allegations against Dr. Olivieri referred to the Faculty of Medicine by HSC's Board of Trustees and Medical Advisory Committee – a referral made at the same time (April 2000) as HSC's referral of similar allegations to the CPSO. In dismissing the allegations, Dean Naylor relied on the report of the CPSO Complaints Committee noted above. A specific charge dismissed by the Dean was the central adverse conclusion against Dr. Olivieri in the *1998* Naimark Report.

6. On 22 April 2002, in a meeting of the Faculty Council, Dean Naylor read into the record a statement that Dr. Koren had been found to have committed research misconduct in the matter of his 1999 article on Apotex's drug deferiprone published in the journal *Therapeutic Drug Monitoring*.[41] The Dean reported that a Committee of Investigation had found that Dr. Koren had used data from the long-term trial of deferiprone without obtaining consent, review or participation by Dr. Olivieri and other research collaborators. As disciplinary action, Dean Naylor directed that Dr. Koren arrange with the journal's editor to have the article deleted from the scientific record, and directed him to send letters of apology to Drs. Olivieri and others.[42]

7. In his statement to the Faculty on 22 April 2002, Dean Naylor did not address additional research misconduct with regard to Dr. Koren's 1999

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Committee of Inquiry on the Case Involving Dr. Nancy Olivieri, the Hospital for Sick Children, the University of Toronto and Apotex Inc." (December, 2001), online: HSC <http://www.sickkids.on.ca/mediaroom/CAUTfinal2ed.pdf> (date accessed: 21 May, 2002).

[40] *CPSO Report, supra* note 7.

[41] O. Diav-Citrin, G. Atanackovic & G. Koren, "An investigation into variability in the therapeutic response to deferiprone in patients with thalassemia major" (1999) 21:1 Ther. Drug Monit. 74.

[42] Minutes, Faculty Council Meeting, University of Toronto Faculty of Medicine, 22 April 2002.

article identified in our report. For instance, nowhere in the article on Apotex's drug did Dr. Koren disclose that his work had been funded by the company. As discussed in our report, he received hundreds of thousands of dollars of research funding from Apotex after the company terminated the Toronto trials of this drug, in addition to the hundreds of thousands he received during the trials. Failure to disclose sponsorship in publication is contrary to University policy. In the 1999 article, Dr. Koren also failed to cite already published findings that the drug presents a risk of chronic liver toxicity, although he himself had been in possession of an extensive report on this risk since early 1997.

8. In his statement to the Faculty on 22 April 2002, Dean Naylor did not address the conduct of Dr. Koren in agreeing to be senior author of 1997 conference abstracts favorable to the drug that had been drafted and co-authored by company staff, and in not disclosing the source or purpose of a grant of $250,000 he is now known to have received from Apotex in the academic year 1995-96 for use in 1996-97. These are matters requiring investigation in the public interest, as noted in our report.

9. Dean Naylor also did not address the misconduct of Dr. Koren in putting forward false and seriously neglectful allegations and testimony against Dr. Olivieri to the Naimark Review and the Medical Advisory Committee.

10. On November 12, 2002, just over a year after our report was published, the parties to the dispute in Toronto said in a joint public statement:

> Dr. Nancy Olivieri, The Hospital for Sick Children and the University of Toronto are pleased to announce a resolution of all outstanding disputes arising from the clinical drug trials conducted by Dr. Olivieri at The Hospital for Sick Children which were terminated by Apotex in 1996. ... The settlement that has been reached is comprehensive and will resolve all outstanding litigation and arbitrations pending between the parties. The terms of the settlement are to be kept confidential by agreement. Dr. Olivieri is pleased with the settlement. ... The agreement that has been reached is fully supported by the University of Toronto, The Hospital for Sick Children, UTFA and CAUT. In light of the need to address more fully the resolution of the difficult issues raised in this case, the University and UTFA will appoint a joint working group to make recommendations on changes to university policies on the dissemination of research publications and conflict of interest and the relationship of these issues to academic freedom. The working group will report by June 30, 2003.[43]

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[43] Canada News Wire, <http://www.newswire.ca/releases/November2002/12/C1119.html>