

**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.**

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Key to Abbreviations

ADR	adverse drug reactions
ASH	American Society of Hematology (U.S.)
CAUT	Canadian Association of University Teachers
CFI	Canada Foundation for Innovation
CIBC	Canadian Imperial Bank of Commerce
CIHR	Canadian Institutes for Health Research
CMPA	Canadian Medical Protective Association
CoI	the present Committee of Inquiry
CPSO	College of Physicians and Surgeons of Ontario
DFO	deferoxamine
EAP	Expert Advisory Panel
EDR	Emergency Drug Release (programme of the HPB)
EMA	European Agency for the Evaluation of Medicinal Products
EPAR	European Public Assessment Report
FDA	Food and Drug Administration (U.S.)
HIC	hepatic iron concentration
HPB	Health Protection Branch
HSC	Hospital for Sick Children (Toronto)
IND	Investigational New Drug
LOR	loss of response
MAC	Medical Advisory Committee
MRC	Medical Research Council
MRI	magnetic resonance imaging
MSSA	Medical Scientific Staff Association
NCIC	National Cancer Institute of Canada
NSERC	Natural Sciences and Engineering Research Council
REB	Research Ethics Board
SCD	sickle cell disease
SQUID	superconducting quantum interference device
SSHRC	Social Sciences and Humanities Research Council
TTH	The Toronto Hospital
UTFA	University of Toronto Faculty Association

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Overview

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THIS CASE INVOLVES ISSUES of research ethics and academic freedom so important to the public interest that it has attracted national and international attention. It occurred in a context that quickly developed from the mid-1980s to the mid-1990s of increased pressures on universities, teaching hospitals and individual researchers to seek corporate sponsorship for projects. Public institutions were not conscious of the inadequacy of their policy infrastructures for protecting the public interest in this new environment, and policies and practices had not been changed to take into account the new circumstances.

It was possible for clinical investigators to sign contracts with industrial sponsors for research trials containing provisions that protected the sponsors' interests, but not the public interest or the safety of trial participants. This meant a dispute could arise between the ethical and legal obligations of an investigator to inform participants of unexpected risks, and the contractual right of a sponsor to insist that information on risks not be communicated and to terminate a trial without prior notice. The academic freedom of an investigator to publish adverse findings and inform the scientific community could be at issue.

Such a dispute arose in this case, and it was compounded by oversights, mistakes or misjudgments by individuals, public institutions, a private corporation, and inquiry panels. In some instances the mistakes were understandable, and are more clear with the benefit of hindsight and the full documentation available to us. In other instances, serious wrongs were committed. In these instances substantial redress and calling to account are appropriate.

Clinical research is essential to the health and well-being of Canadians. Industrial sponsors of trials are necessary in many instances, but they must not be allowed to infringe the rights of trial participants, or the rights and obligations of investigators. An important concern is that the policy inadequacies at the heart of this case remain in many institutions across Canada, and unless the lessons are learned and changes made, there will be repetitions.

The L1 research trials & Apotex involvements

Dr. Nancy Olivieri is a specialist in the treatment of hereditary blood diseases. In the early 1990s, she wished to further study an experimental iron-chelation drug, deferiprone (L1), 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 (HSC), one of the fully affiliated teaching hospitals of the University of Toronto. The level of funding required for the next stage of testing and development would only be available if she found a corporate sponsor. One of her scientific collaborators, Dr. Gideon Koren, a clinical pharmacologist and then Associate Director for Clinical Research in HSC, negotiated an arrangement with the pharmaceutical manufacturer Apotex Incorporated. Apotex agreed to acquire commercial development rights for L1 and to sponsor clinical trials of the drug. Dr. Olivieri and Dr. Koren signed a contract with Apotex in April 1993 to conduct a new randomized trial to compare L1 with the standard treatment, the drug deferoxamine (DFO). The already existing pilot study was continued with the support of Apotex as a separate long-term trial, although a contract for this trial was not signed with Apotex until October 1995.

It was the hope of the investigators and of Apotex that the trials would lead to the licencing of L1 for therapeutic use and subsequent marketing by Apotex, as an alternative to the onerous DFO treatment. Apotex funding meant the randomized trial was eligible for matching funds from the Medical Research Council (MRC) under its university-industry program. Dr. Olivieri's successful application to MRC, listing an Apotex subsidiary as co-sponsor, was approved by HSC and by the University of Toronto.

The new randomized trial was designed as the pivotal efficacy and safety trial for licencing. Continuation of the non-randomized pilot study that had been ongoing since 1989 was also considered important for assessment of long-term efficacy and safety of the drug. These two studies were the only clinical trials of L1 in any centre that included baseline assessments of liver iron concentration and liver histology, the most accurate measures of the long-term efficacy and safety of an iron-chelation drug. Because inefficacy of chelation would expose patients to chronic iron loading that damages major organs, a significant loss of sustained efficacy would also be a safety issue.

The 1993 contract for the randomized trial contained a confidentiality clause giving Apotex the right to control communication of trial data for one year after termination of the trial. This provision was fully in accordance with existing University of Toronto policy on contract research. There was no confidentiality clause in the 1995 contract for the continued pilot study.

Each of the two contracts specified that Apotex had the right to terminate the corresponding trial at any time. From 1993 until early 1996, the two trials proceeded with ongoing cooperation between the investigators and Apotex.

Trial terminations & legal warnings

In early 1996, Dr. Olivieri identified an unexpected medical risk in data of the patient cohort of the long-term trial: loss of sustained efficacy of the drug. 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) accepted that Dr. Olivieri had an obligation to inform patients of the risk she had identified. When Dr. Olivieri moved to inform patients in compliance with a directive from the REB Chair, Apotex terminated both trials abruptly on May 24, 1996. The company simultaneously issued warnings of legal consequences to Dr. Olivieri should she inform patients or anyone else of the risk.

The central issues

At issue was the right of participants in a clinical trial to be informed of a risk that had been identified during the course of the trial by the investigator, and the obligation of the investigator to inform them. Apotex maintained that there was a scientific disagreement, and said that it terminated the trials and issued legal warnings to Dr. Olivieri not to communicate about the risk because it "could not allow such information to be transmitted to patients." However, whether others disagreed or whether the identification 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. Also at issue was the academic freedom of Dr. Olivieri to publish her findings on L1 and thus inform investigators administering the drug in other centres. Consequently, the public interest was at stake.

Apotex donation discussions

The resulting controversy became linked to a much larger university-industry project. Since the early 1990s the University of Toronto and Apotex had been engaged in discussions for a multimillion-dollar donation, intended to allow a new biomedical research centre to be built that would benefit the University and its affiliated health care institutions. In the spring of 1998, agreement in principle was reached on what then would have been the largest donation the University had ever received. It was to have been matched by other sources to provide the approximately \$92 million needed for the new biomedical research centre. Later in 1998, after the controversy became public, the University and Apotex decided

to suspend discussions until the dispute involving Dr. Olivieri and Apotex was resolved.

Continued administration of the drug

Apotex's termination of the trials without prior notice left patients in an uncertain situation and some did not wish to return to the onerous standard treatment. In early June 1996, the University's Dean of Medicine, Dr. Arnold Aberman, mediated a new arrangement between Dr. Olivieri and Apotex, under the Emergency Drug Release program of Health Canada. Apotex agreed to reinstate the supply of its drug L1 for those patients who appeared to be benefiting. Dr. Olivieri agreed to administer it to those particular patients, on condition they were informed of and accepted the new risk, and agreed to monitoring tests for safety. Such patients were no longer in a research trial and so were not under the jurisdiction of the Hospital's Research Ethics Board. In the fall of 1996, Apotex stopped supplying the drug for the second time, again causing concern to the patients and their parents. Following another intervention by Dean Aberman, Apotex again agreed to reinstate the supply, but the supply of L1 nevertheless remained irregular into early 1997.

Continued associations between Apotex & Dr. Koren

It was agreed during Dean Aberman's June 1996 mediation process that Apotex would continue very substantial research funding to Dr. Koren. According to Apotex, prior to its termination of the L1 trials, Dr. Koren had stated that he agreed with the company's position that there was no risk of loss of sustained efficacy of its drug—contrary to his repeated assurances to Dr. Olivieri that he agreed with her finding of this risk. Unknown to Dr. Olivieri until after the fact, Dr. Koren subsequently re-analysed data from the terminated L1 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 L1 Dr. Olivieri identified, and did not acknowledge her contributions to generating the data he used. The company used Dr. Koren's statements to it and post-trial publications by him in communications with Health Canada to counter Dr. Olivieri's adverse findings on its drug.

Identification of a second risk of L1

In early February 1997, Dr. Olivieri identified a second unexpected risk, potentially more serious than the first, that the drug may cause progression of liver fibrosis. Despite further legal warnings from Apotex, she informed her patients and the regulatory authorities in a prompt way. She counselled 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 proper administration of DFO requires current test information for each patient. As the newly identified risk was not an acute one, there was time for a safe and orderly transition.

During this transition period, a dispute developed between Dr. Olivieri and Dr. Hugh O’Brodivich, HSC’s Pediatrician-in-Chief. His expertise is not in hematology and, following discussions with Apotex and Dr. Koren, Dr. O’Brodivich appears to have drawn the incorrect conclusion that the newly identified risk was one of acute toxicity. He also incorrectly supposed that the Hospital’s Research Ethics Board (REB) had jurisdiction over the matter and that Dr. Olivieri was obligated to notify the REB of the risk.

The dispute between Dr. Olivieri and Dr. O’Brodivich appeared to have been resolved through discussions and correspondence by early March 1997. At the same time, Apotex began efforts to persuade medical administrators and patients in Toronto, as well as regulatory agencies and the scientific community, that L1 was effective and safe and should be in wider use. Apotex proposed a new treatment arrangement for Toronto thalassemia patients in which annual liver biopsy, the test that had led to the identification of both of the unexpected risks of L1, would not be an integral part of the safety monitoring regime for all patients. Apotex’s proposal was not accepted by Dr. Olivieri who had phased out use of L1 in the clinics she directed. She had the support of hematologist Dr. Michael Baker, Physician-in-Chief of The Toronto Hospital, where adult thalassemia patients received their care under her supervision.

Lack of support for Dr. Olivieri

From May 1996 onward, Apotex repeatedly issued legal warnings to Dr. Olivieri not to communicate on the risks she identified. None of these warnings has been rescinded. 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 clearly ineffective requests to Apotex to desist made by Dean Aberman in 1996, the University did not take further action to meet this responsibility until early 1999. HSC officials took no effective action to support Dr. Olivieri, until early 1999 when the University and others intervened.

During the first two years of the dispute with Apotex, Dr. Olivieri had legal support through the Canadian Medical Protective Association (CMPA). The very substantial resources CMPA devoted to this case demonstrate both the seriousness

with which Apotex's legal warnings were taken by that physicians' mutual defence organization, and the ineffectiveness of any interventions the University and HSC might have made with Apotex. The primary mandate of CMPA legal counsel was to minimize Dr. Olivieri's legal exposure as an individual client, rather than to protect broad institutional or societal interests. There were instances when Apotex's legal warnings substantially impeded Dr. Olivieri in exercising her academic freedom. Defence of the institutional and societal interests at stake was the responsibility of the University and the Hospital.

In 1997 and 1998 increasing numbers of medical scientists expressed concerns over the lack of effective action by HSC and the University to assist Dr. Olivieri in contending with Apotex's actions. Their representations were not accepted and this led to calls for an independent inquiry into the controversy. In mid-August 1998, more than two years after it began, the controversy became public. During the 1997–1998 period, the HSC scientists who became Dr. Olivieri's principal supporters, Drs. Helen Chan, John Dick, Peter Durie and Brenda Gallie, began their involvement.

Apotex's licencing applications

Apotex submitted licencing applications for L1 in several jurisdictions in early 1998. In these applications, Apotex now alleged that the data from the terminated Toronto trials had been compromised by protocol violations by Dr. Olivieri. Conduct of a short-term safety trial had been one of the licencing requirements set out by the Federal Drug Administration (USA), and such a trial had been designed and organized for Apotex at sites outside Canada by Dr. Olivieri on a consulting contract. The company now maintained that this short-term trial, whose primary objective was an assessment of known acute-toxicity effects of L1, was the pivotal efficacy and safety trial for licencing purposes. Unlike the randomized and long-term trials in Toronto, the protocol for the short-term safety trial did not include baseline and annual determination of liver iron concentration and liver histology for all participants.

Criticism of Dr. Olivieri

Shortly after the L1 controversy became public, without first giving Dr. Olivieri an opportunity to respond, the HSC Executive issued a public statement repeating allegations made privately to it by Apotex against the quality of her scientific work. A week later, the Hospital unilaterally established a review of the controversy and appointed Dr. Arnold Naimark of the University of Manitoba as the Reviewer. The choice of Reviewer and structure of the Review became subjects of controversy and when efforts to resolve this controversy were unsuccessful, Dr. Olivieri and her supporters declined to participate in that Review.

During the Naimark Review, Dr. Koren and Dr. O'Brodovich put forward incorrect testimony against Dr. Olivieri on several topics. Dr. Aideen Moore, who became Chair of the HSC Research Ethics Board shortly after the Toronto trials were terminated, put forward incorrect testimony that a research trial of L1 continued after both trials had in fact been terminated. The Naimark Review accepted the testimony of these witnesses as true, and said that the patients on L1 were still in a research trial and that Dr. Olivieri had failed in the obligation to report the second risk she identified to the REB. These findings were incorrect: when that risk was identified, the patients were not in a research trial and she did not have that reporting obligation. In fact, the documentation shows Dr. Olivieri fulfilled all the reporting obligations she actually had, and put the patients' right to be informed ahead of concerns of possible legal action against her by Apotex.

During this period of the Naimark Review, Dr. Koren began sending anonymous letters to the media and to colleagues disparaging Dr. Olivieri and Drs. Durie, Gallie and Chan.

Disputes over resources for the sickle cell disease program

Because of demographic changes in the Toronto region, the number of patients with thalassemia and sickle cell disease (SCD) treated in the HSC hemoglobinopathy clinic directed by Dr. Olivieri grew substantially. This came at a time of erosion in health care funding by governments that caused resource problems in hospitals across Canada. In the mid-1990s the HSC administration selected the SCD program as one of several to be decentralized to regional hospitals, as part of a new regional pediatric care network. Dr. Olivieri opposed this move, citing evidence from outcomes in major American centres that patients with this disease are best cared for in tertiary hospitals by experienced specialists. Disagreements between her and HSC administrators over the proposed decentralization and other resource issues escalated in the spring of 1996. The correspondence shows that by the time Apotex terminated the L1 trials in May 1996, some HSC administrators viewed Dr. Olivieri as a demanding and challenging subordinate, while she viewed some of them as unreasonable and undeserving of deference.

The task of HSC administrators in realizing this decentralization objective was later complicated by opposition from SCD patient support groups, and by the view of administrators in The Toronto Hospital (where adult SCD patients received their care) that decentralizing SCD patient care might not be the best approach. Periodic flare-ups in the disputes over resources came to a head at the beginning of 1999, when HSC summarily removed Dr. Olivieri from her post as director of its hemoglobinopathy program, with no opportunity to respond to HSC charges against her.

Interventions by the University & others

On January 6, 1999, the same day HSC removed Dr. Olivieri from the directorship, it issued directives that Dr. Olivieri and Drs. Chan, Durie and Gallie were not to discuss their concerns publicly. As a result of these two HSC actions, legal counsel for Dr. Olivieri, distinguished scientists from abroad, the Canadian Association of University Teachers, the University of Toronto Faculty Association, and the University of Toronto administration intervened. University President Robert Prichard mediated an agreement that was signed on January 25, 1999 by HSC and Dr. Olivieri to resolve a range of issues. The agreement restored Dr. Olivieri's authority over research and clinical care of hemoglobinopathy patients in HSC, and affirmed the right to academic freedom for University faculty working at HSC. It also provided an assurance of HSC financial support for Dr. Olivieri in the event of legal action against her by Apotex. This was the first time HSC accepted responsibility to provide effective support to Dr. Olivieri, who since May 1996 had been subject to legal warnings by the company.

Despite this signed agreement, problems continued to arise between HSC and Dr. Olivieri. Dean Aberman, Dr. Baker and, later in 1999, President Prichard and Dr. David Naylor, the new Dean of Medicine, again became involved in mediative processes. These efforts have not yet been successful in resolving outstanding issues.

Further criticism of Dr. Olivieri

Upon receipt of the Naimark Report in December 1998, HSC's Board of Trustees declared (incorrectly) that Dr. Olivieri had "failed" in a reporting obligation, namely, to notify the REB of an unexpected risk in a timely way. The Board directed the Hospital's Medical Advisory Committee (MAC) to inquire into her conduct. During this inquiry, Dr. Koren and Dr. O'Brodovich introduced new allegations concerning Dr. Olivieri's care of thalassemia patients during the period in early 1997, when the second risk of L1 was identified and patients were being transferred to standard therapy. They alleged that a test Dr. Olivieri had performed on some patients, liver biopsy, was a risky procedure and was not clinically indicated. These allegations were based on incorrect information that could easily have been corrected if anyone on the MAC had checked the medical literature or well-established practice in the Hospital. In fact, Dr. O'Brodovich had been repeatedly advised in writing by Dr. Olivieri that these biopsies were being scheduled, and of the clinical indication for them, and he had not opposed them at the time.

Without disclosing the allegations and testimony of its witnesses to Dr. Olivieri, the MAC believed them, even though they were made by persons who did not have relevant medical expertise, no member of the MAC had the relevant expertise, and the MAC did not consult independent experts. Because she did not know the case against her, Dr. Olivieri was deprived of a fair opportunity to respond. The MAC issued a report based on the undisclosed information. It was not until after this, and legal representations on her behalf, that some of the allegations and testimony were disclosed to her.

In a press conference on April 27, 2000, the Hospital's Board and MAC announced they were referring the allegations against Dr. Olivieri, cast in the form of publicly enumerated concerns, to the College of Physicians and Surgeons of Ontario (CPSO) and to the University of Toronto for investigation.

Disciplinary action against Dr. Koren

The Hospital took its public action against Dr. Olivieri two weeks *after* the Presidents of the Hospital and the University had disciplined Dr. Koren for gross misconduct, namely, sending anonymous letters disparaging the personal and professional integrity of Dr. Olivieri and Drs. Chan, Durie and Gallie, and

persistently lying to conceal his actions. Dr. Olivieri *et al.* had lodged a complaint against Dr. Koren in May 1999 on the basis of substantial forensic evidence identifying him as author of the letters. He denied responsibility and lied for many months to frustrate and obstruct the Hospital's investigator, admitting responsibility only after Dr. Olivieri *et al.* obtained additional evidence (DNA) identifying him as the author. Dr. Koren was provided with full particulars of the case against him and a fair opportunity to respond, before the disciplinary action was imposed on April 11, 2000.

This dishonest conduct by Dr. Koren was ample reason to doubt, and to re-examine carefully, the information he and persons associated with him had brought forward to the Naimark and MAC inquiries, before taking such serious action against Dr. Olivieri in such a public manner. This apparently was not done by the MAC or the Board. If they had done so, they would have seen that Dr. Koren's allegations and testimony were contradicted not only by documents available to him, but by earlier correspondence written by him.

Allegations by Apotex

The two unexpected risks of L1 had been identified by Dr. Olivieri in data derived from liver biopsy specimens. Apotex subsequently claimed that liver biopsy was needless, risky and not generally accepted as a diagnostic guide to treatment for transfusion-dependent thalassemia patients. This claim is contradicted by the medical literature where it is clear that liver biopsy is extremely low risk, and is needed to guide appropriate dosage of medication for these patients and to assess possible adverse effects of treatment. The allegations and testimony by Dr. Koren and Dr. O'Brodovich to the MAC that liver biopsy was unnecessary and risky, and done by Dr. Olivieri only for research, came after the similar criticisms of this procedure by Apotex.

Apotex used the incorrect findings against Dr. Olivieri in the Naimark Report, and the public referral of the MAC allegations to the CPSO and the University, to defend the reputation of its drug L1 in legal proceedings.

Continued Apotex donation discussions

In 1999 the University of Toronto and Apotex had further discussions on the multi-million dollar donation which they had been discussing since the early 1990s and on which they had reached agreement in principle in 1998. Apotex requested assistance from University President Prichard in lobbying the Government of Canada against proposed changes to drug patent regulations that would adversely affect the company's revenues. President

Prichard wrote to the Prime Minister, stating that the proposed government action could jeopardize the building of the University's proposed new medical sciences centre. The President subsequently apologized to the University community, saying he had acted inappropriately. The lobbying efforts were unsuccessful, and later in 1999 Apotex withdrew from the 1998 agreement in principle on the donation. In 2000 it was announced that Apotex had made a smaller multi-million dollar donation to the University.

Ongoing controversy

Five years after Apotex terminated the Toronto trials and issued its first legal warnings to Dr. Olivieri, the controversy continues, widened and intensified. Several proceedings were initiated. Drs. Olivieri, Chan, Dick, Durie and Gallie lodged grievances against the University administration. HSC administrators initiated court action to quash summonses for documents issued by the University grievance panel. Dr. Olivieri initiated a libel suit against Apotex over public statements made by company officers. The company responded with a countersuit. Dr. Olivieri requested a judicial review in a European court through which she is contesting the validity of a restricted marketing licence for L1 granted to Apotex in 1999, on the basis of her claim that Apotex misrepresented data on the drug and incorrectly alleged that she had committed serious protocol violations.

The report of this Inquiry

A substantial amount of incorrect information on this case has been put into the public domain, and the central issues have often been obscured. Previous reviews were compromised by one-sided, sometimes incomplete, sometimes incorrect, and sometimes false information put forward to them. Perhaps not surprisingly, they arrived at incorrect conclusions regarding Dr. Olivieri's conduct. The Naimark Review had not been alerted to the possibility of misleading testimony by Dr. Koren's dishonest conduct being known, and neither it nor the MAC pursued inconsistencies and contradictions in the information before them.

The present Inquiry had several advantages over previous reviews. During the two years of our Inquiry, important documents became available that were not considered by the previous reviews. This is because the very extensive documentation available to us included for the first time not only the documentation of individuals and institutions participating in the Naimark Review, but also documentation of Dr. Olivieri and her supporters. We have had the advantage also of being able to take the time necessary to do the detailed analysis of the hundreds of primary documents we had available. As a result, we believe we have for the first time a complete picture of actions and events and have been able to arrive at an accurate understanding of this complex case. Our lengthy and detailed report relies principally on the documents we examined, and it lays out clearly the basis of our findings and conclusions, so that interested persons can follow our analysis. The facts of the case deserve to be known widely, in order that important lessons can be learned.

Our findings and recommendations follow, but in essence:

- **Apotex** should not have attempted to impede Dr. Olivieri from informing patients, regulators and the scientific community of the risks of the drug L1 she identified. This was against the public interest and was inappropriate conduct by the company.
- **The Hospital for Sick Children and the University of Toronto** could and should have effectively supported Dr. Olivieri in the exercise of her rights and obligations, as this was a matter of academic freedom and protection of the public interest, but they did not do so.
- **The Hospital for Sick Children** denied due process to Dr. Olivieri in several important matters, including the Medical Advisory Committee (MAC) proceedings.
- **Dr. Koren's** conduct as a witness in the Naimark Review and the MAC proceedings, and his conduct as author of certain publications on L1, was

unacceptable. He should be called to account by the Hospital for Sick Children and the University of Toronto.

- **The adverse findings** against Dr. Olivieri by the Naimark Review and the MAC allegations against her are incorrect.
- **The Hospital for Sick Children** should withdraw its referrals of allegations to the College of Physicians and Surgeons of Ontario and the University of Toronto.
- **Dr. Olivieri** should be given redress for the unfair treatment she has received.
- **The general features** of this situation are not unique to the Hospital for Sick Children and the University of Toronto, and given the current absence of the necessary protections, it could occur at many institutions across Canada. As we specify in our sections on recommendations and lessons to be learned, it is essential to put in place measures to ensure that, in the conduct of clinical research trials, the public interest is protected from inappropriate actions by trial sponsors.

Page 16 intentionally left blank

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Lessons to be Learned

FOR EVERYONE: There are important lessons to be drawn from this story. 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 (CAUT), 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, the researchers, the hospitals, the universities and the 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.

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 publication) findings of risk that may displease the sponsor.

FOR INVESTIGATORS: Clinical researchers should never sign contracts, protocols or agreements that allow sponsors to restrict communication (including publication) about risks they identify.

FOR RESEARCH ETHICS BOARDS: Research ethics boards should be vigilant against restrictions on communication in the wording not only of protocols but also of contracts and investigator agreements. In addition to reviewing protocols, they should review the wording of associated contracts and agreements, and should not give approval for the study if any of these documents contain wording that would restrict the investigators in communication (including publication) about risks they identify.

FOR INDUSTRY: Companies should not attempt to suppress or control results. This is in their long-term interest as the revelation of such actions will damage their reputation with the public, and with regulatory agencies. Any firm with a reputation for such suppression or control is unlikely to be viewed as a desirable sponsor of research by the best researchers or outstanding universities, or trusted by prescribing physicians, potential research participants and potential customers for the drugs they market.

FOR UNIVERSITIES: All universities should have a policy prohibiting clauses in contracts, investigator agreements or protocols restricting communication (including publication) of risks identified in research projects, particularly clinical trials. They should have procedures in place to ensure this policy is followed in practice. It is their duty to act strongly in support of their researchers if the researchers' independence or academic freedom is threatened by any sponsor. If they fail in this duty, the public interest and public safety are in jeopardy.

FOR HOSPITALS: All research hospitals should have in place a policy, and measures to ensure implementation, that prohibits agreements, contracts or protocols that have clauses that restrict communication (including publication) of risks identified in research projects, particularly clinical trials. They should act strongly in support of their clinical researchers if the researchers' independence or academic freedom is threatened by any sponsor, in order to fulfil their responsibility to protect the safety of their patients, whether or not the patients are enrolled in a research trial.

FOR UNIVERSITIES & HOSPITALS: 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 all hospitals affiliated with universities, should have policies on development to ensure that fund-raising possibilities do not have an adverse impact upon 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 put in place grievance and arbitration procedures for all persons holding academic appointments (including clinical researchers, bioethicists and biomedical scientists) who work in the hospitals, that encompass all important employment matters, including academic freedom, appointments and hospital privileges.

FOR GRANTING COUNCILS: All research granting councils should have a policy prohibiting 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 such policies and procedures 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 other institutions are known to be more lenient and available, pharmaceutical manufacturers could stop carrying out projects at institutions that ask for stringent patient protections and unrestricted disclosure of risks. A united stance would avoid any likelihood of a race to the bottom—such a race would be to the detriment of the public interest.

FOR THE ASSOCIATION OF UNIVERSITIES AND COLLEGES OF CANADA & THE CANADIAN ASSOCIATION OF UNIVERSITY TEACHERS: Both the AUCC and the CAUT should develop policies and procedures appropriate to the current environment of health research, in their own spheres, and they should cooperate in efforts to ensure that individuals, institutions, corporations and agencies of governments learn the lessons outlined in this report.

20 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.

FOR REGULATORS: If it is to maintain the public trust and safeguard the public interest, the federal regulatory agency should act in a way that strictly upholds the *Food and Drugs Act* and *Regulations* and should exercise its authority in the public interest. Health Canada should always put the public interest in safety above private corporate interests, and should review and where necessary revise legislation, regulations or policy to ensure this.

FOR FEDERAL & PROVINCIAL GOVERNMENTS: Because safeguards for independence of investigators are usually less robust in non-university settings, it is important that there 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 *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* is a valuable guide on many aspects, but it does not apply to research conducted in institutions or organizations which receive no funding from the three Canadian research granting councils (CIHR, SSHRC, NSERC). More broadly still, federal and provincial governments should work together to develop a way to regulate the conduct of research involving human subjects. They should consider and report back to the Canadian public on the option of legislating to govern the ethical conduct of *all* research involving human subjects conducted in Canada. In addition, the federal government should ensure that Health Canada has the human and financial resources, and the legislative powers, necessary to protect the public interest in the regulation (review, approval, and monitoring) of pharmaceuticals in Canada.

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Findings

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Contextual

1 | The Hospital for Sick Children (HSC) did not have an adequate policy infrastructure to protect patients and the public interest in the conduct of clinical trials, and this was a contributing factor in the development of the controversy.

2 | The University of Toronto Publication Policy in regard to contract research allowed industrial sponsors to impose confidentiality restrictions for one year following the termination of a project. This applied to sponsored research generally, including sponsored clinical trials. After the L1 dispute became public in 1998, the University stated that its policy would not have allowed such restrictions. This was not true. In 2001 the University announced that it and its affiliated health care institutions were changing their policies so as to disallow confidentiality clauses in research contracts that could be used to deter clinical investigators from disclosing risks to patients and others. By the act of announcing this important and necessary change, the University acknowledged that its prior policy was inappropriate for clinical research.

3 | The University of Toronto and Apotex had been engaged in discussions on a major donation since 1991. They reached agreement in principle on a multi-million dollar donation in the spring of 1998 (\$20,000,000 to the University and \$10,000,000 to the University for affiliated teaching hospitals). In the fall of 1998, after the L1 controversy received widespread media coverage, the University and Apotex agreed to suspend donation discussions until the matters in that dispute were “resolved” and Apotex “cleared of wrongdoing.” In 1999, while the L1 controversy continued, discussions on the major donation between the University and Apotex resumed. At the request of Apotex, the President of the University of Toronto wrote to the Prime Minister of Canada to delay action on proposed changes to drug patent regulations that could adversely affect Apotex’s business. The President later apologized for his letter. After the Federal Government proceeded with the changes, Apotex withdrew from the agreement in principle. In a list of donors published by the University in late 2000, Apotex was shown as having made a smaller donation to the University, between \$5,000,000 and \$9,999,999.

4 | The Medical Research Council (MRC), through its university-industry program, encouraged clinical researchers to seek industrial sponsors, but did not put in place adequate guidelines to ensure the safety of trial participants and disclosure of risks. For instance, MRC did not prohibit inappropriate confi-

dentiality clauses in contracts between investigators and industrial co-sponsors. Also, an industrial sponsor could unilaterally terminate a trial co-sponsored by MRC, without any MRC requirement being in place to ensure that patients were not adversely affected by the premature termination.

5 | HSC had no effective grievance procedure for its medical and scientific staff, and it has not yet put such a procedure in place.

Chronological

6 | After the drug L1 showed promise in an MRC-funded pilot study, Dr. Nancy Olivieri applied to MRC for a larger grant to conduct a randomized trial to compare the efficacy and safety of L1 with the standard iron-chelation therapy, deferoxamine (DFO). This application was not successful, but she was invited to re-apply in light of written comments of the reviewers. These included the suggestion that she apply under MRC's university-industry program.

7 | Dr. Gideon Koren, a co-investigator with Dr. Olivieri on the pilot study and Associate Director for Clinical Research in the HSC Research Institute, approached the pharmaceutical manufacturer Apotex Inc. through his long-time colleague in the University and in HSC, Dr. Michael Spino. Dr. Spino had recently joined Apotex as a full-time employee, while still retaining his status as a professor of pharmacy in the University and his laboratory facilities in HSC. Apotex agreed to acquire the commercial development rights for L1 and to sponsor clinical trials.

8 | Dr. Koren and Dr. Olivieri signed a contract in 1993 with Apotex Inc. for the randomized trial (LA-01). This contract contained a one-year, post-termination confidentiality clause. This was in accordance with existing University and Hospital policy. Nevertheless, Dr. Koren and Dr. Olivieri should have been more alert to the implications of this clause in the contract and should have refused to sign it without appropriate modifications.

9 | Apotex funding enabled Dr. Olivieri to re-apply to MRC under its university-industry program for co-sponsorship of the randomized trial. This application was successful.

10 | Apotex also agreed in 1993 to supply L1 free of charge for continuation of the pilot study as a long-term efficacy and safety trial (LA-03), but there was no formal contract for this trial until 1995.

11 | The Research Ethics Board (REB) of HSC approved protocols for both the Toronto L1 trials (LA-01 and LA-03) without reviewing the associated contracts to ensure that the contracts did not breach ethical standards or norms. The confidentiality clause in the LA-01 contract had an inappropriate confidentiality clause—it specified that Apotex had the right to suppress information during the trial and for one year after its termination. The REB also did not require inclusion of provisions in the protocol to protect the interests of trial participants in the event of premature termination by the industrial sponsor.

12 | Dr. Olivieri signed a consulting contract with Apotex in June 1995 for work on a short-term safety trial of L1 at international sites (LA-02), that the Federal Drug Administration (USA) had specified as a licencing requirement. This had a three-year, post-termination confidentiality clause that was not in compliance with University of Toronto policy. Dr. Olivieri had no patients enrolled in this trial, she was not an “investigator,” and this contract (including its confidentiality clause) was not relevant to the two Toronto trials (LA-01 and LA-03). However, it was nevertheless inappropriate for her (or any clinical investigator) to sign a contract containing such a clause.

13 | Confidentiality clauses of the type then allowed are not appropriate for clinical trials. They can be used by an industrial sponsor to suppress information it considers adverse to its commercial interests, including information concerning risks to trial participants, or to patients in a post-trial treatment arrangement. As invoked in this case by Apotex, such confidentiality clauses offend public policy.

14 | Dr. Koren and Dr. Olivieri signed a contract in October 1995 with Apotex Inc. for continuation of the pilot study as long-term efficacy and safety trial (LA-03). This contract had *no* confidentiality clause. The two unexpected risks of the drug L1 were identified by Dr. Olivieri in data of this trial.

15 | Apotex had the right under the LA-01 contract to terminate the LA-01 trial and it had the right under the LA-03 contract to terminate the LA-03 trial.

16 | In 1996 Dr. Olivieri identified an unexpected risk of L1—loss of sustained efficacy—in data of the LA-03 trial. She believed she was obligated to inform trial participants and the Research Ethics Board (REB), and she prepared a report on the risk for the REB. Apotex disputed this finding and opposed informing patients. On reviewing Dr. Olivieri’s report, the REB Chair Dr. Zlotkin agreed that trial participants should be informed and accordingly directed her to revise the information and consent forms for participants.

17 | Dr. Olivieri submitted the revised information and consent forms to the REB on May 20, 1996 and sent a copy to Apotex. On May 24, 1996 Apotex exercised its rights under the LA-01 and LA-03 contracts and terminated *both* trials.

18 | Apotex notified the Canadian regulatory agency, the Health Protection Branch (HPB) of Health Canada that it had terminated both Toronto trials, LA-01 *and* LA-03, on May 24, 1996.

19 | Dr. Olivieri notified the Hospital's Research Ethics Board (REB) in writing that both Toronto trials, LA-01 *and* LA-03, had been terminated by Apotex on May 24, 1996.

20 | Apotex showed disregard for the interests and concerns of patients when, without prior notice, it terminated both trials and stopped supplying its drug L1 in May 1996.

21 | Apotex terminated both Toronto trials (LA-01 and LA-03) in an attempt to prevent Dr. Olivieri from informing patients and others of a risk of L1 she identified, and it issued warnings of legal action against her should she inform patients or anyone of the risk without its prior written consent. Apotex has never consented to any disclosure by Dr. Olivieri of risks she identified.

22 | Apotex had no contractual basis for legal warnings in regard to LA-03 data, but this important fact does not seem to have been appreciated and did not play a role in the developing controversy.

23 | Against the wishes of Dr. Olivieri, and against the recommendation of its own Expert Advisory Panel, Apotex refused to reinstate either the LA-01 or the LA-03 trial. The Expert Advisory Panel urged that the trials be reinstated so that it could be clarified whether some patients benefited and what factors determined potential benefit. Only by continuing the trials could participants and thalassemia patients elsewhere have the benefit of knowing whether L1 was sufficiently effective and safe to be licenced as therapy for some patients.

24 | When Apotex terminated the trials without notice, Dr. Arnold Aberman, the University's Dean of Medicine, mediated a new arrangement under which those patients who wished to continue on L1, and in whom it appeared to be working, could do so, as patients of Dr. Olivieri and being monitored by her. This new treatment arrangement was under Health Canada's Emergency Drug Release (EDR) program and was not a research trial. The REB had no jurisdiction over this clinical arrangement.

25 | Those patients who wished to continue on L1, and for whom it was considered sufficiently safe and beneficial in their individual cases, were permitted to continue, provided they were informed of and accepted the new risk, and agreed to safety monitoring tests. Under EDR, Dr. Olivieri was required to monitor patients and report the results to Apotex and Health Canada.

26 | Apotex showed disregard for the interests and concerns of patients when it stopped supplying its drug a second time, in October 1996. Dean Aberman intervened again in an effort to have the supply reinstated, but the supply remained irregular into early 1997.

27 | The situation in regard to research fellows who had been engaged for fixed periods to work on the trials was left uncertain when Apotex terminated the trials without notice. It was agreed during Dean Aberman's mediation process that the fellows would continue to be employed for their contracted periods, under continuing supervision of Drs. Koren and Olivieri during the close-out of the terminated trials. Thereafter they would work under Dr. Koren's supervision on his research projects. Apotex provided additional funds for salary support for the research fellows during the post-trial period. Contrary to practice by other members in his Division in the University's Department of Pediatrics, Dr. Koren did not disclose that Apotex was the source of a \$250,000 research grant he received that year, that was listed in his University department's annual grant listing. Nor did he disclose the subject matter of the research this grant funded.

28 | Before and after Apotex terminated the Toronto trials in May 1996, Dr. Koren gave assurances to Dr. Olivieri that he agreed with her finding of a risk of L1 and her view that trial participants needed to be informed of it. Apotex stated that during the same period, Dr. Koren gave assurances to the company that he agreed with its contrary position on these matters.

29 | Dr. Koren was senior author of two abstracts based on analysis of data from the two terminated trials. These were presented at a conference in Malta in April 1997 by their first author, Apotex employee Dr. Tricta, who had not been involved in the work of either trial. They reported that L1 was effective and safe in the treatment of thalassemia patients. This was inconsistent with the findings Dr. Olivieri had published in two abstracts based on data from the same trials in December 1996. Dr. Koren's Apotex-funded research fellows were included among his co-authors on his abstracts for the Malta conference. The abstracts did not disclose the Apotex funding support for Dr. Koren or the fellows, did not acknowledge Dr. Olivieri's contributions to generating the

data, and did not note that she had already published abstracts based on this data.

30 | In communications with Health Canada in 1996 and 1997, to counter Dr. Olivieri's adverse findings on L1, Apotex used Dr. Koren's assurances that he supported its position on the drug, as well as publications by him supporting the company's position on the efficacy and safety of the drug.

31 | In early 1997, Dr. Olivieri identified a second unexpected risk of L1, when she and liver pathologist Dr. Ross Cameron conducted a historical review of charts of patients who had been in the long-term trial (LA-03). She informed in a prompt way all those she was obligated to inform: the patients, Apotex and Health Canada. She also promptly informed Dr. Koren. She initiated steps to inform the scientific community so that physicians prescribing L1 in other centres would learn of the newly identified risk.

32 | Apotex issued more legal warnings to deter Dr. Olivieri from communicating this second unexpected risk of L1 to anyone. However, she was legally and ethically obligated to communicate the risk to those taking, or prescribing the drug as there were potential safety implications for patients, and she fulfilled these obligations despite the legal warnings.

33 | Some of Apotex’s 1997 legal warnings to Dr. Olivieri were to deter her from presenting her findings on the two unexpected risks of L1 at the same April 1997 conference in Malta at which Dr. Koren’s abstracts were being presented. On CMPA legal advice, she initially withdrew her already submitted abstract, but upon learning that Dr. Koren was presenting abstracts with an Apotex employee, she re-submitted and presented her abstract, notwithstanding the legal warnings from Apotex.

34 | Apotex acted against the public interest in issuing legal warnings to Dr. Olivieri to deter her from communicating about risks of L1. None of the legal warnings has been rescinded.

35 | Apotex’s legal warnings violated Dr. Olivieri’s academic freedom.

36 | The representative of Apotex most prominent in the repeated and continuing legal warnings violating Dr. Olivieri’s academic freedom was its Vice-President, Dr. Michael Spino, who continues to hold the status of a professor in the University’s Faculty of Pharmacy. We have seen no evidence that his conduct in violating this fundamental freedom has been effectively addressed by the University.

37 | The Hospital for Sick Children and the University of Toronto did not provide effective support either for Dr. Olivieri and her rights, or for the principles of research and clinical ethics, and of academic freedom, during the first two and a half years of this controversy. After the controversy became public in 1998, the University stated publicly that it had provided effective support for Dr. Olivieri’s academic freedom, but this was not true.

38 | Notwithstanding Apotex’s legal warnings and the lack of support from the University and the Hospital, Dr. Olivieri complied with all of her ethical obligations, including reporting obligations, and she published her findings. During the period summer 1996–summer 1998, the only effective support she had in exercising her rights and responsibilities in the face of the Apotex legal warnings was from the Canadian Medical Protective Association (CMPA), although it was not always effective. In keeping with their mandate, the advice of legal counsel provided by CMPA was largely aimed at minimizing Dr. Olivieri’s legal exposure, not at protecting societal or institutional interests.

The University and the Hospital should have ensured defence, including legal defence, of these broader interests.

39 | The very substantial resources CMPA devoted to this case demonstrate the seriousness with which CMPA, and the lawyers CMPA engaged to represent her, viewed the Apotex legal warnings, and demonstrate the ineffectiveness of any support the Hospital and the University gave.

40 | HSC Pediatrician-in-Chief Dr. O’Brodivich put forward incorrect allegations and testimony, in addition to seriously incomplete testimony, against Dr. Olivieri to the Naimark Review and to the Medical Advisory Committee. In this he used information from Dr. Koren and cooperated with Dr. Koren. Dr. O’Brodivich was seriously neglectful in not checking the validity, or ensuring the completeness, of his testimony.

41 | Dr. Koren attempted to discredit Dr. Olivieri by dishonest means:

- He was the author of anonymous letters to the press and others against Dr. Olivieri and her supporters, for which he denied responsibility for many months.
- He put forward false allegations and testimony against Dr. Olivieri to the Naimark Review, and to the MAC inquiry that followed.

42 | In addition to false allegations and testimony, Dr. Koren put forward incorrect allegations and testimony against Dr. Olivieri to the Naimark Review and to the MAC inquiry that he should have known were incorrect, because they were contradicted in documents available to him. He was seriously neglectful in putting these forward.

43 | Dr. Koren lied persistently for many months about his responsibility for the anonymous letters, and did not admit responsibility until after he had been identified by DNA evidence.

44 | The University and the Hospital disciplined Dr. Koren on April 11, 2000 for the misconduct to which he admitted: his series of anonymous letters disparaging Dr. Olivieri and several colleagues; and lying persistently about responsibility for the letters.

45 | After Dr. Koren admitted to writing and sending anonymous letters against Dr. Olivieri and her supporters, Dr. O’Brodivich, the Medical Advisory Committee (MAC) and the HSC Board of Trustees had a responsibility to review and assess carefully all the allegations and testimony Dr. Koren had put forward both to the Naimark and MAC reviews, and all allegations and testimony by other witnesses which relied in any way upon

information given to them by Dr. Koren. We have no evidence that they fulfilled this responsibility.

46 | Neither the University nor the Hospital has properly addressed the conduct of Dr. Koren in putting forward false allegations and testimony against Dr. Olivieri to the Naimark Review and to the MAC, or taken any action to correct the resulting situation.

47 | Research Ethics Board (REB) Chair Dr. Aideen Moore put forward seriously incorrect testimony in regard to the period after Apotex terminated both Toronto trials of L1. Namely, she said that the long-term trial of L1 (LA-03) continued, and continued under REB jurisdiction, after May 1996 when both trials had in fact been terminated and never reinstated. She put forward this testimony despite the fact that the correct information was available to her as REB Chair in documentary form in the files of the REB. Her incorrect testimony was relied on by Dr. O’Brodivich, the Naimark Review and the MAC. It was also cited by Dr. Koren to bolster his allegations and testimony against Dr. Olivieri, despite the documented fact that he himself knew Dr. Moore was wrong. Dr. Moore was seriously neglectful in not checking REB records wherein it was documented that both trials had been terminated on May 24, 1996.

48 | The Naimark Review and the MAC inquiry apparently were not provided with some important, relevant information by persons they interviewed. For instance, the formal notice to the REB by Dr. Olivieri and her HSC Division Chief Dr. Freedman that the long-term trial (LA-03) had been terminated, a notice that had been received by the REB on August 1, 1996, and a centrally important document, was not cited in the reports of either the Naimark Review or the MAC and must be assumed not available to them.

49 | The adverse findings against Dr. Olivieri in the reports of the Naimark Review and HSC’s Medical Advisory Committee are incorrect and based on incomplete, incorrect and false testimony.

50 | The misconduct by Dr. Koren in putting forward false and seriously neglectful testimony against Dr. Olivieri to the Naimark Review and the Medical Advisory Committee, and the uncritical acceptance of his testimony, are significant factors in the L1 controversy being prolonged and widened.

51 | Dr. Koren violated accepted standards of conduct in regard to publication in biomedical journals, when he published an article in *Therapeutic Drug Monitoring* in 1999 on Apotex’s drug L1 without disclosing the company’s financial support for his research, without acknowledging the contributions of Dr. Olivieri and others to generating the data he used or giving them an

opportunity to review or participate in the publication, and without noting previous publications on risks of the drug. We have seen no evidence that either the University or the Hospital has yet taken appropriate action to address this improper conduct.

52 | The Hospital for Sick Children took actions that were harmful to Dr. Olivieri's interests and professional reputation, and disrupted her work. In each instance, the adverse actions were taken without providing due process. She was provided neither with the case she was expected to meet, nor a fair opportunity to respond, prior to the actions being taken. These included:

- wide dissemination on September 1, 1998, of unsupported allegations made privately to the HSC Executive by Apotex against the quality of her work;
- removal from her program directorship on January 6, 1999;
- completion by a subcommittee of the Medical Advisory Committee (MAC) in January 2000 of a report based on allegations and testimony that had not been disclosed to Dr. Olivieri, and endorsement of that report by the MAC; and
- public referral of allegations made by the MAC to external bodies on April 27, 2000.

The matter of the program directorship was resolved through the intervention of the University and other parties, but the other matters remain outstanding.

53 | The action taken by the HSC Board of Trustees and the MAC on April 27, 2000 to publicly refer the MAC allegations, cast in the form of enumerated "concerns," to the College of Physicians and Surgeons (CPSO) and to the University's Faculty of Medicine represented an abdication of responsibility and an abuse of process. The MAC investigation into Dr. Olivieri's conduct was directed by the Board on the basis of incorrect findings in the Naimark Report. The Board's directive did not instruct the MAC to provide due process, and due process was not provided to Dr. Olivieri. The MAC does not appear to have diligently reviewed the available evidence, and did not consult independent experts. The MAC was empowered to review conduct and report conclusions, but instead it brought forward allegations. The Board and the MAC referred the allegations without specifying which CPSO or University policies Dr. Olivieri was alleged to have breached. The action damaged Dr. Olivieri's reputation and imposed a substantial, unwarranted burden of defending herself before two different bodies, without knowing the case she

had to answer. Regardless of the intentions or purpose of these actions, they later were used by Apotex in efforts to discredit Dr. Olivieri and defend the reputation of its drug L1.

54 | Although Apotex’s own interests were served in 1998 when it put forward to regulatory agencies and to Dr. Olivieri’s employers *post hoc* reasons for why it terminated the Toronto L1 trials (alleged protocol violations), these reasons were materially different from the reason given in its own statements made at the time of the terminations in 1996 and during the following year. This was inappropriate conduct by the company.

55 | Apotex made statements to regulatory authorities about the relative significance of the two Toronto efficacy and safety trials (LA-01 and LA-03), and the safety trial at international sites (LA-02), that were contradicted by its own earlier documents. The protocol for the international trial specified that it was a short-term trial, the primary objective of which was to assess the occurrence of known acute-toxicity effects of L1. The information and consent form for patients enrolling in the international trial stated that its purpose was to determine the safety of L1. This nature of the international trial was acknowledged by Apotex’s Vice-President, Dr. Spino in 1996, when he wrote that it was a safety study of short duration (1 year). However, in later submissions to regulatory authorities in 1998, Apotex stated that the short-term toxicity trial at international sites (LA-02) was the pivotal efficacy and safety trial for licencing purposes, and that the randomized comparison trial (LA-01) and the long-term efficacy and safety trial (LA-03) in Toronto were supportive studies to the LA-02 study. We have seen no convincing evidence that would demonstrate why or how the public interest was served by Apotex’s claim that LA-02, rather than LA-01, was the pivotal trial of the drug.

56 | Attempts to discredit Dr. Olivieri and her work were an aspect of Apotex’s 1998 licencing submissions for its drug L1 to regulatory agencies. This information was not disclosed to Dr. Olivieri by the regulators or by Apotex. Subsequent to learning of its existence independently, she was only able to gain access to particulars of Apotex’s allegations against her work through court proceedings in Europe.

57 | Apotex’s attempts to discredit Dr. Olivieri with regulatory agencies, and with other scientists, included allegations that liver biopsy was not an accepted or appropriate diagnostic guide to therapy for transfusion-dependent thalassemia patients, but rather was a needless, risky procedure done by Dr. Olivieri for research purposes. A review of the relevant medical literature shows that this is not the case—liver biopsy is a safe procedure that is necessary to guide appropriate therapy for such patients, and to assess the efficacy and safety of their

iron-chelation treatment. Nevertheless, similar incorrect allegations were later put forward by Dr. Koren and Dr. O’Brodivich to the MAC, with specific reference to biopsies done on some of Dr. Olivieri’s patients in 1997 following identification of the risk that L1 could cause progression of liver fibrosis. The allegations were believed by the MAC.

58 | Dr. Olivieri sought a meeting with Health Canada officials in June 1999 to express concerns regarding Apotex’s licencing submissions. She was accompanied by Dr. Michèle Brill-Edwards who assisted her in her presentation. Shortly afterward, Dr. Brill-Edwards received two letters—one an anonymous letter disparaging Dr. Olivieri and others who were critical of Apotex’s drug L1 and of the HSC administration, and the other a signed letter from Dr. Koren offering her employment in his HSC Division. DNA evidence from envelope of the anonymous letter to Dr. Brill-Edwards identified Dr. Sergio Grinstein, a scientist at HSC and a public supporter of the HSC administration in the L1 controversy, as the author. DNA evidence from the envelope of the signed letter to Dr. Brill-Edwards identified Dr. Koren as the author of the series of anonymous letters against Dr. Olivieri and her supporters sent out in late 1998 and early 1999.

59 | Neither Dr. Olivieri nor the colleagues who tried to assist her during the first two years of the controversy (1996–1998) were aware that the University of Toronto Faculty Association (UTFA) and the Canadian Association of University Teachers (CAUT) could be approached for advice and assistance.

60 | UTFA and CAUT knew of the dispute and its implications for academic freedom and research ethics in August 1998, when it became public, yet they did not offer assistance to Dr. Olivieri until November 1998. However, both associations provided substantial assistance from November 1998 onward, to the present in the case of UTFA, and until this Committee of Inquiry commenced work in September 1999 in the case of CAUT.

61 | Sir David Weatherall of Oxford University and Dr. David Nathan of Harvard University, UTFA, CAUT, and President Robert Prichard of the University of Toronto, were instrumental in bringing about the agreement of January 25, 1999 that resolved the dispute concerning HSC’s removal of Dr. Olivieri from her program directorship. President Prichard has been rightly credited with having played an indispensable role in the mediation process on this occasion, a process that resulted in this very significant agreement.

62 | The agreement of January 25, 1999 also resolved a number of other important matters, including violations of the academic freedom of Dr. Olivieri and her colleagues, Drs. Chan, Durie and Gallie, by HSC through the

issuance of “gag orders” to them on January 6, 1999. Under this agreement, HSC withdrew the “gag orders.”

63 | The agreement of January 25, 1999 provided, for the first time, assurance that HSC would provide legal support for Dr. Olivieri, in the event Apotex took legal action against her and the CMPA declined to support her. This implied a belated acknowledgment by the Hospital that it had responsibilities in the dispute between Apotex and Dr. Olivieri.

64 | Given the Hospital’s previous treatment of Dr. Olivieri, the University, UTFA and CAUT should have made representations to the Hospital for Sick Children in January 1999 in an effort to ensure that Dr. Olivieri would be provided due process in the MAC inquiry. UTFA and CAUT did not do so and we have seen no evidence that the University did so. It became clear a year later that Dr. Olivieri had been very seriously denied due process by the MAC. The University, in particular, had publicly stated in December 1998 that it had a commitment from the Hospital that it would be consulted on actions adverse to Dr. Olivieri in matters arising from findings in the Naimark Report. We have seen no evidence that the University pursued this commitment to ensure it was fulfilled.

65 | Throughout this dispute, during which Dr. Olivieri was publicly and privately criticized by medical administrators of the Hospital for Sick Children, she has had the confidence and support of medical administrators in The Toronto Hospital where she treats adult patients, including Physician-in-Chief Dr. Michael Baker.

66 | Dr. Olivieri’s efforts during the past five years and more to exercise her rights and responsibilities, and to uphold principles of academic freedom and research and clinical ethics, have been at great personal cost to her.

67 | Drs. Chan, Dick, Durie and Gallie have actively supported the principles of academic freedom, research ethics, research integrity and fair procedures during the past several years. They have supported Dr. Olivieri in the exercise of her individual rights during this time. Without their active involvement, events in this case would likely have been still more unfortunate for the upholding of these general principles, and for Dr. Olivieri, than they have been. Their involvement has been at great personal cost to each of them, but they felt moved to intervene when the institutional leadership of the University of Toronto and the Hospital for Sick Children had failed to provide effective support either for the general principles or for Dr. Olivieri.

68 | Officers of the University of Toronto, including President Prichard and Dean David Naylor made substantial efforts during 1999 to mediate disputes between Drs. Olivieri, Chan, Dick, Durie and Gallie, and the Hospital for

Sick Children. Although these efforts have not yet been brought to a successful conclusion, they could still form the basis for resolving a number of outstanding issues.

69 | It is unfortunate the University did not effectively intervene to counter the legal warnings by Apotex or unfair actions against Dr. Olivieri by HSC prior to January 1999, or effectively address certain other relevant matters since then. However, it is the case that without some of the significant interventions the University has made, events in this case would likely have been still more unfortunate for the upholding of these general principles, and for Dr. Olivieri, than they have been.

General

70 | The central issue in both instances of identification of an unexpected risk was an ethical one. A drug manufacturer, Apotex, attempted through legal warnings to impede a clinical investigator and treating physician, Dr. Olivieri, from informing patients and others of the risks. By these actions, Apotex attempted to deprive patients of their right to give informed consent to a treatment that was unproven as to its efficacy and safety, and it thereby acted contrary to the public interest.

71 | The issue of academic freedom is related to the ethical issue: communication through presentations at scientific meetings and through other publications were essential to alert physicians around the world to risks of the drug. Speaking out on the actions of Apotex and on the failures by the Hospital for Sick Children and the University of Toronto to take any effective counter-action (until early 1999), was also important to the public interest.

72 | This case demonstrates the importance to the public interest that universities and their affiliated teaching hospitals act robustly to protect academic freedom, bringing to bear the full weight of their resources in cases where large private corporations attempt to infringe academic freedom.

73 | This case demonstrates the importance to the public interest of ensuring that in hospitals affiliated with universities, hospital staff who hold academic appointments have the right to academic freedom and its protection to ensure their independence.

74 | This case demonstrates the importance to the public interest of ensuring that in hospitals affiliated with universities, inquiries by Medical Advisory Committees into conduct of clinical professors be conducted with standards

of fairness and due process commensurate with the seriousness of the allegations under review.

75 | This case demonstrates the importance to the public interest of ensuring that in hospitals affiliated with a university, staff holding academic appointments in the university have access to grievance and arbitration procedures on all significant matters pertaining to their hospital employment, and that such procedures be comparable to and harmonized with the university grievance and arbitration procedures.

76 | This case demonstrates the importance to the public interest of ensuring that investigators conducting clinical trials do so in the context of strong guidelines, regulations, or legislation, that exist and are enforced to protect investigators' independence, and thus their ability to act in the interests of trial participants and patients.

77 | There are important gaps in the policies and procedures of the Canadian research granting councils and Health Canada to protect public safety in clinical trials. Nationwide rules, and mechanisms for enforcing the rules, to govern relationships among investigators, their institutions and industrial sponsors of clinical trials, are urgently required.

D

Recommendations

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General

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 risks 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.

The Hospital for Sick Children & the University of Toronto

2 | The Hospital and the University should address the professional misconduct by Dr. Gideon Koren in putting forward false and seriously neglectful allegations and testimony against Dr. Olivieri to the Naimark Review and the Medical Advisory Committee.

3 | The University and the Hospital should address the academic misconduct by Dr. Koren in regard to his article, “An Investigation Into Variability in the Therapeutic Response to Deferiprone in Patients With Thalassemia Major” in the journal *Therapeutic Drug Monitoring*, volume 21 (1999), pp. 74–81.

4 | The University and the Hospital should investigate the facts and circumstances pertaining to Dr. Koren’s actions in the following matters: his role as senior author of two abstracts presented by an Apotex employee at the 6th International Conference on Thalassaemia and the Haemoglobinopathies held in Malta in April 1997; and his failure to disclose the source or purpose a \$250,000 grant from Apotex in the academic year 1995–1996 for use in 1996–1997.

5 | The University should address the misconduct of Dr. Michael Spino, who holds the status of professor in the Faculty of Pharmacy, in repeatedly violating Dr. Olivieri’s academic freedom.

6 | The Hospital for Sick Children should immediately and publicly withdraw its April 2000 referrals to the College of Physicians and Surgeons of Ontario and the University of Toronto, of the enumerated “concerns” of the Medical Advisory Committee regarding Dr. Olivieri.

7 | Dr. Olivieri should receive redress from the Hospital for Sick Children and the University of Toronto for the unfair treatment she has received, including their lack of support to her in the exercise of her rights and obligations.

8 | Dr. Olivieri should receive redress from the Hospital for Sick Children for the damaging and unfair actions against her by its Medical Advisory Committee and Board of Trustees arising from the MAC proceedings.

9 | Dr. Olivieri, and Drs. Chan, Dick, Durie and Gallie believe that they were subjected to unfair treatment in certain matters of their employment and working conditions, for exercising their right to academic freedom in the matters outlined in this report. In the case of Dr. Olivieri, this was from 1996 onward—in the cases of Drs. Chan, Dick, Durie and Gallie, subsequent to their being identified as supporters of Dr. Olivieri. This Committee of Inquiry did not investigate and address all of these matters. We understand that some concerns of these five scientists were under consideration in the mediation process undertaken by the Dean of Medicine in the fall of 1999, and that other concerns are the subject of grievances lodged with the University of Toronto in late 1998 and augmented since then. Neither the mediation nor the grievance process has yet been brought to a resolution in the ensuing years. These processes should be brought to an expeditious and fair resolution.

Research Ethics Boards

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 protocols, 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.

11 | REBs should ensure that the guidelines in recommendation 10 are understood and followed by all sponsors and investigators. Insertion of the following text in the relevant documents is recommended:

a) *Consent form*

Throughout the research process, you will be given any new information that might affect your decision to participate in the research. In particular, you will be told of any unforeseen risks that may be identified.

b) *Protocol*

No agreements or contracts between researchers and sponsors that limit the right and the responsibility of the researchers to disclose relevant information about unforeseen risks that becomes known in the course of the research, to participants in the study, members of the research group, other physicians administering the treatment, research ethics boards, regulatory agencies, and the scientific community, have been or will be entered into by the researchers.

c) *Investigator agreements / contracts*

If I have concerns about the safety and/or efficacy of the study drug, X, I have the right and the responsibility to disclose relevant information that becomes known to me in the course of the research, to participants in the study, members of the research group, other physicians administering the treatment, research ethics boards, regulatory agencies, and the scientific community.

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.

13 | REBS should ensure that protocols and related contracts and agreements make express provision for management of patient care in the event of premature termination of a research trial, and should withhold approval of the study until such provision has clearly been made.

14 | REBS should review institutional policies and practices with respect to access to patient records for research purposes to ensure that they are in compliance with the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS)*.

Universities & Teaching Hospitals

15 | Each Canadian university with a faculty of medicine, and each affiliated health care institution, should put in place the policy in recommendation 1 together with procedures to ensure compliance, and ensure that their REBS comply with recommendations 10–14.

16 | Universities and affiliated teaching hospitals should implement appropriate policies and practices to ensure protection of the right to 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.

17 | Clinical and other researchers, and bioethicists, who are employees of teaching hospitals and who hold academic appointments in the affiliated university, should have access to grievance and arbitration procedures in matters pertaining to their hospital employment, as well as their university employment. The affiliation agreement between a teaching hospital and a university should require that the hospital grievance and arbitration procedures are comparable to, and compatible with, those available to faculty members employed full-time in the university. The affiliation agreement should specify the process with

jurisdiction, and the responsibility for remedies, in matters involving both hospital and university employment.

18 | Teaching hospitals affiliated with universities should put in place a policy of due process in such matters as: removal of administrative office from an employee; Medical Advisory Committee (MAC) investigations into conduct of a staff physician; and disciplinary proceedings. The policy should make clear that adverse MAC recommendations and adverse administrative or Board decisions arising from MAC recommendations are subject to grievance and arbitration.

19 | Provision should be made by each institution 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.

20 | 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 ensure they are managed in the public interest.

AUCC & CAUT

21 | To ensure a united stance and prevent any likelihood of companies moving research projects to institutions with less stringent patient protection, there should be a national, integrated approach for all research done in hospitals affiliated with universities. We recommend that the Association of Universities and Colleges of Canada (AUCC) develop, implement and enforce a policy governing industry-academy relationships that would apply to all faculties of medicine and affiliated teaching hospitals across Canada. Such a policy should include, at a minimum, the provisions outlined in recommendation 1. It should also include guidelines for determining whether a proposed university-industry contract qualifies as academic activity, or as consulting service—with different rules for pricing and overseeing the project for these two categories.

All industry/academy agreements and contracts for health research should be filed with an oversight body established by AUCC for the purpose of ensuring compliance. A surtax should be levied on all industry/academy health research agreements and contracts to fund the activities of this oversight body.

22 | The Association of Universities and Colleges of Canada, the Canadian Association of University Teachers and learned societies should undertake cooperatively an ongoing program to promote academic freedom and the ethical conduct of research. This should include development and implementation of an educational component to be included in all post-graduate and post-doctoral training programs in all fields where research on human subjects is conducted. It should also include an awareness program on these matters for all persons holding academic appointments who work in teaching hospitals affiliated with universities.

23 | The Canadian Association of University Teachers should develop policies and model clauses for grievance and arbitration procedures for medical and health-related faculty members and bioethicists who work in health care institutions affiliated with universities.

24 | The Canadian Association of University Teachers should review and revise its policies on:

a) action in regard to cases of infringement of academic freedom or other important rights or privileges brought to its attention, so as to be in a position to promptly intervene to ensure expeditious access to a fair and effective resolution process;

b) ensuring the independence of Committees of Inquiry into cases that are *prima facie* serious. In the present instance, CAUT agreed to changes to policy at the request of the Committee of Inquiry to ensure its independence.

Granting Councils

25 | In order to help ensure consistency in standards across the country, the Canadian Institutes for Health Research (CIHR), together with the Social Sciences and Humanities Research Council (SSHRC) and the Natural Sciences and Engineering Research Council (NSERC), should impose a requirement that universities and health care institutions receiving any funding from the granting councils have in place the policy in recommendation 1. The requirement should apply to all clinical research projects conducted at these institutions, whether or not such projects are funded by one of the granting councils. A means of ensuring compliance would be the withholding of all CIHR, SSRHC

and NSERC funds where such a requirement is not in place, or is not met, and the Councils should actively monitor compliance.

26 | The *TCPS* 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.

Government of Canada

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

28 | Health Canada should adopt a policy of establishing an independent inquiry whenever a clinical trial is prematurely terminated as a result of a disagreement between the sponsor and the investigator on identification of a risk.

29 | Health Canada should adopt a policy that whenever a manufacturer makes allegations against the work of a trial investigator in a regulatory submission, the investigator is immediately provided with full particulars by Health Canada and a fair opportunity to respond.

30 | The Government of Canada should ensure that Health Canada has adequate personnel and financial resources to protect the public interest in the regulation of pharmaceuticals.

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