The Olivieri Case: Lessons for Australasia

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Abstract

The case of Dr. Nancy Olivieri, the Hospital for Sick Children, the University of Toronto, and Apotex Inc. vividly illustrates many of the issues central to contemporary health research and the safety of research participants. First, it exemplifies the financial and health stakes in such research. Second, it shows deficits in the ways in which research is governed. Finally, it was and remains relevant not only in Toronto but in communities across Canada and well beyond its borders because, absent appropriate policies, what happened in Toronto could have happened (and could well still happen) elsewhere.

In Part One of this paper, we review the facts of the Olivieri case relevant to the issues we wish to highlight: first, the right of participants in a clinical trial to be informed of a risk that an investigator had identified during the course of the trial and the obligation of the investigator to inform participants (both her own and those of other investigators); and second, the obligation of institutions to protect and promote the well-being of research participants as well as academic freedom and research integrity, the obligations of research sponsors to inform participants, research regulators, and others about unforeseen risks, and the obligations of research regulators to ensure that participants are informed of unforeseen risks and to otherwise protect and promote research integrity. In Part Two, we relate these facts and issues to New Zealand and Australia. We also make detailed recommendations for changes to the various instruments used for the governance of research involving humans in Australasia.

Keywords
Ethics; research; research support; confidentiality; conflict of interest; guidelines, New Zealand; Australia

Introduction

The case of Dr Nancy Olivieri, the Hospital for Sick Children (HSC), the University of Toronto, and Apotex Inc. vividly illustrates many of the issues central to contemporary health research and the safety of research participants. First, it exemplifies the financial and health stakes in such research. Second, it shows deficits in the ways in which research is governed. Finally, it was and remains relevant not only in Toronto but in communities across Canada and well beyond its borders because, absent appropriate policies, what happened in Toronto could have happened (and could well still happen) elsewhere.

In Part One of this paper, we review the facts of the Olivieri case relevant to the issues we wish to highlight: first, the right of participants in a clinical trial to be informed of a risk that an investigator had identified during the course of the trial and the obligation of the investigator to inform participants (both her own and those of other investigators); and second, the obligation of institutions to protect and promote the well-being of research participants as well as academic freedom and research integrity, the obligations of research sponsors to inform participants, research regulators, and others about unforeseen risks, and the obligations of research regulators to ensure that participants are informed of unforeseen risks and to otherwise protect and promote research integrity. In Part Two, we relate these facts and issues to New Zealand and Australia. We also make detailed recommendations for changes to the various instruments used for the governance of research involving humans in Australasia.

Our message is that the Olivieri case could also happen here. In many ways, the threats to the safety of research participants in Canada that became so evident through the Olivieri case are also present in New Zealand and Australia. The research ethics committees, researchers, hospital and university administrators, research funding councils, ministries of health, and everyone else involved in research, should therefore work together to protect the public interest. We must raise awareness, work with our institutions' administrations, lobby funding councils, lobby the national (and, where relevant, state and territorial) governments, and encourage public involvement to put in place the appropriate protections to ensure that what happened in the Olivieri case does not happen again.

Part One – The Facts of the Olivieri Case[i]

Background Context

The Olivieri case arose in a national context that developed quickly from the mid-1980s to the mid-1990s. Universities, teaching hospitals, and individual researchers were under increasing pressure to seek corporate sponsorship for research as well as corporate donations. Public institutions were not sufficiently attentive to the inadequacies of their policy infrastructures to protect the public interest in the face of these new pressures. Policies and practices had not changed to take into account the new ethical challenges at the institutional level in addition to the traditional challenges of research ethics at the researcher-participant level.(1: 72)

At a local level, since the early 1990s, the University of Toronto and Apotex (the largest Canadian-owned pharmaceutical company in Canada) had been discussing a major multi-million-dollar donation intended to allow a new biomedical research centre to be built at the University. It would have been the largest donation the University had ever received ($20 million to the University and $10 million to the University for affiliated hospitals). This donation was to have been matched by other sources to provide the approximately $92 million needed for the centre.(1: 98)

The Deferiprone (L1) Trials and Contracts

In the early 1990s, Dr Nancy Olivieri wanted to further study deferiprone (L1), an experimental iron-chelation drug that had shown promise in a pilot study. It appeared to reduce tissue iron loading in a group of transfusion-dependent thalassemia patients (iron loading leads to tissue damage and eventually may be fatal). The funding required for the next stage of study would be available only through a corporate sponsor. Apotex agreed to acquire the commercial development rights for L1 and to sponsor clinical trials of the drug. Although three trials were designed at HSC, only two were conducted in Toronto and Dr Olivieri was an investigator only on these two, so we discuss only these two trials in this paper.

One trial was a new randomized comparison trial (LA-01) designed as the pivotal safety and efficacy trial to compare L1 with the standard treatment deferoxamine (DFO). This study was co-sponsored by Apotex and the

Medical Research Council of Canada (MRC). The contract for this study contained a confidentiality clause giving Apotex the right to control communication of trial data for one year after termination of the trial. Contrary to assertions made by the University, this provision was fully in accordance with existing University of Toronto policy on contract research.(1: 118)

The other trial, LA-03, was a continuation of the pilot study as a long-term trial. This was a compassionate use trial – it was for patients who were unwilling or unable to take the onerous standard therapy – and it was not funded by either Apotex or MRC until late 1995 when Apotex began to fund it. The contract for LA-03 contained no confidentiality clause. It is particularly important to note this, as LA-03 produced the data that led to Dr Olivieri's concerns about risks.

Trial Terminations and Legal Warnings

In early 1996, Dr Olivieri identified an unexpected risk in the data from the patient cohort of the LA-03 trial: loss of sustained efficacy of the drug.(1: 129-134) This had implications for patient safety as it meant the tissue-damaging iron was not being removed. She informed Apotex that she needed to disclose this risk to patients in both trials. Apotex disputed the risk and the need to inform patients, but the Chair of HSC's Research Ethics Board (REB[ii]) agreed that Dr Olivieri had an obligation to inform patients of the risk. When Dr Olivieri moved to inform patients in compliance with a directive from the REB Chair, Apotex unilaterally terminated both trials on May 24, 1996. The company simultaneously issued warnings of legal consequences to Dr Olivieri if she informed patients or anyone else of the risk.

In the letter terminating the trials, Apotex warned Drs Olivieri and Koren (her HSC collaborator) not to disclose information 'in any manner to any third party except with the prior written consent of Apotex', and warned that it would 'vigorously pursue all legal remedies in the event that there is any breach of these obligations' it claimed they had under 'the LA01 Agreement and the LA01 and LA03 Protocols'. In a telephone message left on Dr Olivieri's voice mail on the same day, Dr Spino of Apotex said 'You must not publish or divulge information to others about the work you have done with Apotex ... without the written consent of Apotex. Now, should you choose to violate this agreement you will be subject to legal action'.(1: 145)

Repeated legal warnings were issued not to disclose the risks to patients, as well as with regard to reporting on the research through presentations at scientific conferences and publication of articles in the scientific literature.

It is important to note that Dr Olivieri wanted to continue to study the drug to determine whether it was safe and efficacious for a subgroup of patients. She felt that she could not continue, however, without the participants being informed of the unexpected risk of loss of efficacy so that they could make an informed choice about whether they wished to continue in the trials.(1: 152) It was Apotex that cancelled the trials.

On-going Administration of the Drug Post-termination

Apotex's sudden termination of the study left patients in an uncertain situation; some of them did not want to return to the onerous standard treatment which involves subcutaneous infusion by a pump for several hours, often several times a week. In early June 1996, arrangements were made to have some patients under Dr Olivieri's care receive L1 through Health Canada's Emergency Drug Release Program (EDRP).[iii] Apotex agreed to reinstate the supply of the drug and Dr Olivieri agreed to administer it to those patients who appeared to be benefiting, on condition that they were informed of and accepted the new risk and agreed to monitoring tests for safety. These patients were no longer in a research trial and, as recipients of an unlicensed drug through the EDRP, were not under the jurisdiction of the HSC REB.(1: 191, 195, 342-344)

Identification of a Second Risk of L1

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

Early Lack of Support for Dr Olivieri and the Principles at Stake

From May 1996 onward, Apotex repeatedly issued legal warnings to Dr Olivieri not to communicate the risks she had identified. It is of note that neither HSC nor the University provided effective support to Dr Olivieri or took effective action to defend principles of research ethics, clinical ethics and academic freedom. University officials acknowledged that Apotex was acting inappropriately and that the University had a responsibility to defend her academic freedom. However, except for the Dean of Medicine's clearly ineffective 1996 requests to Apotex to desist, the University did not take further action to meet this responsibility (even though it was clear that the requests were ineffective as the Dean continued to be copied on further letters warning of legal action). HSC officials also took no effective action to support Dr Olivieri during these events.(1: 159)

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

Criticisms of Dr Olivieri

Not only was there a lack of support for Dr Olivieri, but considerable efforts were made to undermine her.

One criticism was that Dr Olivieri was wrong about the risks. However, whether others disagreed or whether the identification of risk would be borne out by other studies was not relevant: when a trial investigator has a reasonable basis to believe she has identified a risk, she must ensure that trial participants are informed about the risk. Otherwise, they are not giving informed consent to continue in the trial.(1: 191)

A second criticism was that she had failed to meet her obligation to report the second risk (liver toxicity) to the REB. However, this was untrue.(1: 195, 342-344) When the toxicity risk was discovered, the patients were not in a research trial under REB jurisdiction, and so Dr Olivieri did not have a reporting obligation to the REB. In fact, the documentation shows that Dr Olivieri fulfilled all of the reporting obligations that she had, including informing the patients directly. Nevertheless, this criticism was accepted in the report published in December 1998 by an inquiry commissioned and paid for by HSC's Board of Trustees and led by Dr Arnold Naimark.

A third criticism was that Dr Olivieri performed a test (liver biopsy) on some patients and that this test was risky, was conducted for research purposes (without going through the REB) and was not clinically indicated. Apotex subsequently made efforts to discredit not only Dr Olivieri, but the procedure of liver biopsy itself. In written statements to HSC Pediatrician-in-Chief Dr Hugh O'Brodovich, Dr Naimark and others, the company said that the procedure was risky and unnecessary, and that Dr Olivieri's use of the procedure in 1997 was unauthorized research. Later, Drs Koren and O'Brodovich put forward similar allegations to the Hospital's Medical Advisory Committee (MAC), despite their being contradicted by the medical literature. These were prominent among the allegations that HSC's MAC and Board of Trustees referred to the College of Physicians and Surgeons of Ontario (CPSO) in the spring of 2000. Shortly thereafter in a court proceeding in the European Community, Apotex used evidence of HSC's action to support the granting of a restricted licence for its drug and against Dr Olivieri, who had challenged the legitimacy of the licence. However, all of these allegations were contradicted by the medical literature where liver biopsy is established as a low risk, necessary way of monitoring transfusion-dependent patients for iron overload and for histology in order to adjust therapy. Liver biopsy was an established practice for such patients in the HSC thalassemia clinic. The test was clinically indicated and was not conducted for research purposes, but rather for clinical management purposes. The CPSO exonerated Dr Olivieri in 2001, and termed her use of liver biopsies 'commendable'.(2)

Actions Taken Against Dr Olivieri

Several adverse actions were taken by individuals and the HSC against Dr Olivieri. First, during the period of the Naimark review in the fall of 1998, Dr Koren sent anonymous letters to colleagues and the media disparaging Dr Olivieri and some of her supporters, calling them 'unethical' and a 'group of pigs'.(1: 397)

Second, following the release of the Naimark Report in December 1998, the Board of Trustees of the HSC declared that Dr Olivieri had failed in an alleged obligation to report the unexpected risk to the REB in a timely way, and directed

the Hospital's MAC to inquire into her conduct. The MAC was given incorrect testimony, including allegations about Dr Olivieri's obligations to report to the REB, as well as allegations about liver biopsy and unauthorized research. When charged by Dr Olivieri's counsel with failing to follow due process, the MAC terminated its proceedings without reaching specific conclusions. Instead, it referred a list of allegations framed as 'concerns' to the CPSO and the University in a press conference.(1: 324-325) These 'concerns' were based on false and neglectful testimony by Dr Koren and incorrect and neglectful testimony by Dr O'Brodovich. After investigation, the CPSO completely exonerated Dr Olivieri. To date, HSC has not given the same prominence to the exoneration and its decision not to pursue the matter any further, as it gave to the referral of the allegations which damaged Dr Olivieri's reputation.(2)

Third, in January 1999, the HSC removed Dr Olivieri from the directorship of the hemoglobinopathy program and issued directives that she and her supporters were not to discuss their concerns publicly.(1: 232) After Drs David Nathan and David Weatherall (two internationally renowned experts in the field) and others made representations to the University, these moves were rescinded by an agreement mediated by University President Robert Prichard.(1: 234)

The On-going Relationship between the University of Toronto, the Hospital for Sick Children, and Apotex

In 1991, discussions began between the University of Toronto and Apotex about a major donation that could also benefit the University's teaching hospitals, including HSC. Agreement in principle on the donation was reached in the spring of 1998. Discussions on this donation were suspended after the controversy involving Apotex and Dr Olivieri became public later in 1998. However, in 1999, the University and Apotex had further discussions on the donation. Apotex also requested assistance from University President Prichard in lobbying the Government of Canada not to make proposed changes to drug patent regulations that would adversely affect the company's revenues. President Prichard wrote to the Prime Minister saying that the proposed government action could jeopardize the building of the University's new medical sciences centre, because 'the adverse effect of the new regulations would make it impossible for Apotex to make its commitment to us'.(1: 103) After a Toronto newspaper obtained a copy of President Prichard's letter and published excerpts, he apologized to the University community for this action, saying that he had acted inappropriately. The lobbying efforts were unsuccessful, and later in 1999 Apotex withdrew from its 1998 agreement in principle.(1: 104) However, In late 2000, it was announced that Apotex had made a smaller ($5-10 million) donation to the University.(1: 104) In late 2001, it was announced that Apotex had made a further multi-million dollar donation to the University.(3)

Throughout all of this, Apotex's Vice-President of Scientific Affairs, Dr Michael Spino, held (and continues to hold) the status of professor in the University's Faculty of Pharmacy and, until the summer of 1998, continued to use laboratory facilities in the Hospital for Sick Children.(1: 99-100, 261) In addition, even after the trials were terminated in 1996, Apotex continued very substantial research funding for Dr Koren.(1: 159) Unknown to Dr Olivieri until after the fact, Dr Koren subsequently reanalyzed data from the terminated trials and published findings that the drug was effective and safe. Dr Koren's publications did not disclose Apotex's financial support for his research, made no reference to the risks of the drug that Dr Olivieri had identified (and published), and did not acknowledge her contributions to generating the data he used. The company used Dr Koren's statements and post-trial publications in communications with Health Canada to counter Dr Olivieri's adverse findings on its drug.(1: 169, 176) In 1999, the website of the Faculty of Medicine listed a research grant for Dr Koren of $250,000 for use in 1996-1997 but, contrary to standard practice for the listing, neither the source nor purpose of this large sum was specified. After repeated inquiry, it was ascertained from the University that the source was Apotex. The purpose remains undisclosed.(1: 159)

Summary Reflections on the Facts

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

the hospital and university. Thus, at issue was the right of participants in a clinical trial to be informed of a risk that an investigator had identified during the course of the trial and the obligation of the investigator to inform participants (both her own and those of other investigators). Also at issue was the obligation of institutions to protect and promote the well-being of research participants as well as academic freedom and research integrity, the obligations of research sponsors to inform participants, research regulators, and others about unforeseen risks, and the obligations of research regulators to ensure that participants are informed of unforeseen risks and to otherwise protect and promote research integrity.

Additionally, the Olivieri case raised issues concerning due process and grievance procedures. There were other examples of serious academic and professional misconduct, and there were serious lapses of institutional responsibility. These associated issues are fully described, and recommendations made in The Olivieri Report: The complete text of the report of the independent inquiry commissioned by the Canadian Association of University Teachers(1) and in the Supplement to the Report of the Committee of Inquiry on the Case Involving Dr Nancy Olivieri, the Hospital for Sick Children, the University of Toronto, and Apotex Inc, issued 30 January 2002.(4) In addition, the grievance procedures issue has also recently been dealt with in a report by the CAUT Task Force on Academic Freedom for Faculty at University-Affiliated Health Care Institutions 'Defending Medicine: Clinical faculty and academic freedom'.(5)

Part Two – Application of the Olivieri Case to New Zealand and Australia

Background Contexts

There are many similarities in the national contexts between Canada, New Zealand, and Australia. As in Canada, universities in New Zealand and Australia have faced significant cuts in their budgets. In New Zealand, it has been reported that government funding has fallen in real terms by 23% over the last decade.(6) In Australia, it has been reported that Commonwealth funding to universities fell from 60% to 40% of total funding between 1994 and 2002.(7)

At the same time, universities are under increasing pressure (both from fiscal necessity and explicit government direction) to increase their partnerships with industry. For example, the Performance Based Research Fund of New Zealand directly links government funding to 'external research income' (15%).(8: 51) In Australia, over the past decade an increasing proportion of the performance based funding formula used to distribute Commonwealth operating funds to Universities has been used to reward those Universities that can attract research funding from public and industry sources.

Governments are also providing significant incentives to the public research sector for partnering with industry. In New Zealand, 42% of the funds in Vote: Research, Science, and Technology are directed toward an 'Economic Goal'. Significant proportions of these funds are directed towards promoting partnerships between the public research and private commercial sectors through, for example, research consortia, 'Technology for Industry' fellowships, and Crown Research Institutes.(9) Similarly, the Australian government recently committed an additional $AUD65 million to support Collaborative Research Centres (these are research partnerships between the public and private sectors) and the latest funding policies include measures to 'encourage market-driven linkages between business partners as well as business and public sector research bodies'.(10)

The direct effects of these incentives are evident. For example, the proportion of private (industry and other) research funding in Australian Universities has increased from less than 25% of all research funding in 1992 to 33% of all research funding in 2003.(11) A further effect of the increasing push to maximize research income and potential for commercialization of university research is the growth of consulting companies attached to universities that seek to translate basic research into marketable products (patents, licences, consultancy services, etc). Bodies like the University of Auckland's UniServices Ltd., the University of Queensland's UniQuest, and Melbourne University's Bio21 have been established by universities to exploit the commercial potential of public research. Universities have increasingly appointed managers for the commercialization of research and lawyers specializing in contract research and intellectual property to protect and enhance their research investments.

As in Canada, however, institutional policy development in New Zealand and Australia has not kept pace with the changes in external funding for research to manage the consequential increase in conflicts of interest. Insofar as

policy changes have occurred, they have tended in the direction of facilitating commercialization of research and privately-funded research activities, rather than protection of academic freedom and management of conflicts of interest. There is a clear need for revisions and updating of policies and practices given the changed context that now exists.

It can be concluded that the national contexts in New Zealand and Australia make an 'Olivieri case' possible, if not likely, unless active steps are taken to prevent it. We would suggest that these steps take place in relation to two main issues: ongoing disclosure of risks and content of confidentiality clauses; and REC review of contracts and investigator agreements.

On-going Disclosure of Risks and Content of Confidentiality Clauses

New Zealand Rules

There are a number of potential sources of rules in relation to ongoing disclosure of risks to research participants and other relevant individuals and institutions, and the content of confidentiality clauses. These include: legislation; the New Zealand Regulatory Guidelines for Medicine; the Operational Standard for Ethics Committees; the national application form for ethical approval for research involving humans and the guidelines for completion of this form; contract law; and institutional policies. Consider each in turn.

There do not appear to be any statutes explicitly prohibiting the inclusion of confidentiality clauses limiting the ongoing disclosure of risks in research contracts or investigator agreements. However, the *Health and Disability Commissioner Act* 1994 states in section 20(1) that 'A Code of Health and Disability Services Consumers' Rights prescribed by regulations made under section 74(1) of this Act shall contain provisions relating to the following matters: (a) The principle that, except where any enactment or any provision of the Code otherwise provides, no health care procedure shall be carried out without informed consent'. 'Health care procedure' is defined as 'any health treatment, health examination, health teaching, or health research administered to or carried out on or in respect of any person by any health care provide; and includes any provision of health services to any person by any health care provider.' 'Informed consent' is defined as 'consent to that procedure where that consent – (a) Is freely given, by the health consumer or, where applicable, by any person who is entitled to consent on that health consumer's behalf; and (b) Is obtained in accordance with such requirements as are prescribed by the Code.' But is consent an on-going process under the Act? The Code of Health and Disability Services Consumers' Rights(12) which gives content to the Act in relation to these matters at first glance suggests that consent is not an ongoing process. Rights 6 and 7 (the right to be fully informed and the right to make an informed choice and give informed consent) appear to deal with a singular event (extended to research through Right 9). However, it is possible to read the Code as going further. The Regulatory Guidelines for Medicines interpret the consent right as including the right to information that becomes available during the course of a trial (rather than simply the right to information available at the time of the original consent upon enrollment in the trial).(13: 9) Similarly, the Operational Standard for Ethics Committees adopts an interpretation of consent as requiring ongoing disclosure of risks. These guidelines/standards would arguably shape the reading of the Code as, under Right 4, s.2, 'Every consumer has the right to have services provided that comply with legal, professional, ethical, and other relevant standards'.(14: 95) Thus, under legislation, it is not clear but it is probable that confidentiality clauses limiting the ongoing disclosure of risks in research contracts or investigator agreements would be prohibited.

The New Zealand Regulatory Guidelines for Medicines contain some additional relevant content:

> If new information of concern about the investigational product becomes available after commencement of the study it is the responsibility of the principal investigator to provide the ethics committee with a copy of this information. Significant new information may result in the ethics committee reconsidering the risk:benefit aspects of the study. In keeping with the requirements of the HDSC Code of Rights this information should be passed on to the participants in the study as it affects the basis of the participants' original informed consent.(13: 5-6)

Furthermore, the Guidelines explicitly require as part of a valid informed consent that the potential participants be told 'that new information relevant to the welfare of the participant which becomes available during the study will be passed on to the participant'.(13: 10)

The Guidelines require that the principal investigator inform the sponsor of any serious or unexpected adverse event. The sponsor, in turn, is required to report 'all serious adverse events which result in breaking of the study code to the regulatory authority within 72 hours of being informed of the adverse event' and 'all other serious adverse events which do not result in breaking the study code and which are not specified as study end points, should be recorded and presented to the ethics committees and/or the regulatory authority as part of the regular reporting requirements of these bodies'.(13: 40)

It is important to note, however, that these Guidelines apply only to clinical trials of investigational products and only to research 'conducted by the pharmaceutical industry intended for regulatory submission'.(13: 4)

The 'Operational Standard for Ethics Committees' in turn states clearly that:

> It is important that consumers, research participants or legal representatives continue to be informed throughout the duration of their participation in the research or innovative practice. This includes being kept apprised of any developments that could potentially impact on them and being informed of the results of the innovative practice or research.(14: 8)

In the National Application Form(15), in the section on Validity of Research, researchers are asked 'will any restriction be placed on publication of results?' and 'If yes, please supply details'. In the section on Privacy and Confidentiality, there is a requirement that the researcher 'Describe any arrangements to make results available to participants, including whether they will be offered their audio tapes or videos'. However, the Application Form, the detailed Pro Forma for Consent Form and the detailed Guidelines for the Preparation of Information Sheets do not include content on the ongoing rights and obligations with respect to the disclosure by researchers to participants about unforeseen risks discovered through the course of the trial.(15) Given the level of detail about other issues, this gap is significant. It is likely that researchers and RECs/HDECs/IECs will fail to turn their minds to the issue and that researchers will not realize that they have these obligations and that RECs/HDECs/IECs will not ensure that the participants' rights with respect to ongoing disclosure are not in jeopardy.

Looking to a different source of rules, it could be argued that a clause that limited a researcher's freedom to disclose risks discovered during the conduct of a trial would be found to be void as against public policy by a court should the researcher disclose and the sponsor sue the researcher for breach of contract.(1: 496-498) This, however, is a very weak protection as it requires a researcher to stand up to threats of legal action by a sponsor and it provides a defence to the researcher to the suit but imposes no obligation upon the researcher to disclose risks to research participants. Research participants would be much better protected through a proactive proscription on confidentiality clauses that limit a researcher's freedom to disclose risks.

Finally, looking to institutional policy, some research institutions have introduced policies that deal with confidentiality clauses but only in a limited fashion. For example, the University of Otago has a policy relating to confidentiality clauses.(16: 40) However, the Otago policy only deals with publication of results and clearly does not anticipate the issue of disclosure of unforeseen risks to participants. While the publication of results is critically important, it is not all there is to the confidentiality clause issue. Through a review of New Zealand University policies posted on the web, we could not find any institutional policies that explicitly deal with this issue.

Suggested Changes for New Zealand

Researchers in New Zealand clearly have an obligation to disclose risks to research participants whether those risks are known at the outset or become known during the course of a trial. That said, an Olivieri case could still happen in New Zealand. In Canada, research participants also had a right to ongoing disclosure of risks and the researchers had an obligation to disclose those risks. Unfortunately, the research sponsor and research institutions involved in the Olivieri case failed to recognize this and respectively threatened and failed to protect Dr Olivieri. What needs to happen in New Zealand is a concerted effort to explicitly incorporate the rules into the National Application Form for Ethical Approval of a Research Project and institutional policies and to educate researchers and research administrators about the rules. This should be done by taking the following five steps:

1. Inserting the following into the National Application Form for Ethical Approval of a Research Project:

Part 2: Ethical Principles
E. Informed consent
...
No agreements or contracts between researchers and sponsors that limit the right and responsibility of the researchers to disclose relevant information about unforeseen risks that become known in the course of the research, to participants in the study, members of the research group, other physicians administering the treatment, research ethics committees, regulatory agencies, and the scientific community, may be entered into by the researchers.
...

2. Inserting the following into the Pro Forma for Consent Form under the list of required information/phrases point 3 'The points covered by the following phrases should be included in language able to be understood by the participants':
   I understand that throughout the research process, I will be given any new information that might affect my decision to participate in the research. In particular, I will be told of any unforeseen risks that may be identified.
3. Inserting the following into the Guidelines for preparation of information sheets under 7. Participation:
   3. '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.'
4. Inserting the following into the Guidelines for completion of the National Application Form for Ethical Approval of a Research Project under E. Informed Consent:
   No agreements or contracts between researchers and sponsors that limit the right and responsibility of the researchers to disclose relevant information about unforeseen risks that become known in the course of the research, to participants in the study, members of the research group, other physicians administering the treatment, research ethics committees, regulatory agencies, and the scientific community, may be entered into by the researchers.
5. Ensuring that universities and hospitals and any of their affiliated research offices or companies strengthen their research policies on the issue of publication delays by including the following:
   No agreements or contracts between researcher/university/hospital and sponsor that limit the right and responsibility of the researcher to disclose relevant information about unforeseen risks that become known in the course of the research, to participants in the study, members of the research group, other physicians administering the treatment, research ethics committees, regulatory agencies, and the scientific community, may be entered into by the researcher/university/hospital.

Australian Rules

As in New Zealand, there are multiple potential sources of rules in relation to on-going disclosure of risks and the content of confidentiality clauses. These include: legislation; official annotations of the international Good Clinical Practice Guidelines; *the National Statement on Ethical Conduct in Research Involving Humans (National Statement)*; and the common law on consent. Consider each in turn.

As in New Zealand, there do not appear to be any Australian statutes explicitly prohibiting the inclusion of confidentiality clauses limiting the ongoing disclosure of risks in research contracts or investigator agreements. The legislation governing clinical trials of therapeutic goods in Australia, the *Therapeutic Goods Act* (1989), provides the national regulatory structure for controlling the quality, safety, efficacy and availability of therapeutic goods in Australia. That Act established the Therapeutic Goods Administration (TGA) as the body with responsibility for oversight of therapeutic goods and the process for approval for new drugs to be included on the Australian Register of Therapeutic Goods (ARTG). The TGA has established regulations allowing patients to access unapproved drugs as part of their participation in clinical trials. These regulations require that researchers apply for approval from both a Human Research Ethics Committee (HREC) (or multiple HRECs) and the TGA to conduct a clinical trial on an unregistered drug. The clinical trial can be conducted under either the Clinical Trials Notification Scheme (CTN) or the Clinical Trials Exemption Scheme (CTX). The chief difference between the CTN and CTX schemes is whether the TGA is involved in assessing the scientific validity of the trial design and safety and efficacy of the drug or the therapeutic good. Under both schemes, the researcher and sponsor have an obligation to provide the information

required for the assessment of the safety of the trial.

> Under the CTN scheme, all material relating to the proposed trial, including the trial protocol is submitted directly to the HREC by the researcher at the request of the sponsor. The TGA does not review any data relating to the clinical trial and the HREC is responsible to ensure that there is an assessment of the scientific validity of the trial design and the safety and efficacy of the medicine or device as well as the ethical acceptability of the trial process.(17)

Under the CTX scheme, the sponsor or researcher provides the TGA with 'summary information about the product, including the overseas status of the drug, proposed guidelines for the use of the product in the trial (called the Proposed Usage Guidelines), a pharmaceutical data sheet, and a summary of the preclinical data and a clinical summary.'(17) The TGA does not review the clinical trial protocol or study design. HRECs have responsibility under both schemes for reviewing the validity of the trial, and its ethical acceptability.

Under both the CTN and CTX schemes, sponsors are obliged to report any serious adverse events or safety concerns relating to a trial or trial drug to the TGA and to the relevant HREC.

> The TGA does require that sponsors report any significant safety concerns or actions taken as a result of the analysis of adverse reaction reports within Australia and overseas, including action by overseas regulatory agencies. The TGA will ensure that any such advice has been reported to the Australian investigators and the HREC.(17)

In addition to the *Therapeutic Goods Act* and regulations, the TGA has issued its interpretation of the internationally recognized Note for Guidance on Good Clinical Practice.(18) That document states:

> 4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IECs approval/ favourable opinion in advance of use. The subject or subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.(18: 18)

Thus, while the therapeutic goods legislation does not require disclosure, researchers are *prima facie* bound by good clinical practice to provide revised information to participants, whenever such new information arises.

However, given that Section 7.22 of the Note for Guidance on Good Clinical Practice Guidelines (7.22) also allows that sponsors may require researchers to be bound by confidentiality provisions regarding their product, researchers may face a conflict between their obligation to disclose new information to participants and their obligation to respect confidentiality agreements.

It must also be noted here that advice about serious adverse events or other safety concerns allows the TGA to assess whether to recommend discontinuation of the trial and it allows HRECs to consider whether to discontinue the trial in accordance with the *National Statement*, sections 2.44, 2.45, and 12.10.

> 2.44 Where an HREC is satisfied that circumstances have arisen such that a research project is not being or cannot be conducted in accordance with the approved protocol and that, as a result, the welfare and rights of participants are not or will not be protected, the HREC may withdraw approval, inform the researcher(s) and the institution(s) or organisation(s) of such withdrawal, and recommend to the institution(s) or organisation(s) that the research project be discontinued, suspended, or that other necessary steps be taken.
>
> 2.45 A researcher must not continue the research if ethical approval has been withdrawn and must comply with any special conditions required by the HREC.
>
> 12.10 It may be unethical for a researcher to continue a trial if:
>
> (a) there are or have been substantial deviations from the trial protocol;

(b) side effects of unexpected type, severity, or frequency are encountered; or
(c) as the trial progresses, one of several treatments or procedures being compared proves to be so much better, or worse, than other(s) that continuation of the trial would disadvantage some of the participants.(19)

Although an HREC may use the information provided to withdraw HREC approval for a trial or to require that 'other necessary steps be taken', there is nothing in the *National Statement* or the *Therapeutic Goods Act* that requires researchers or sponsors to disclose risks that emerge during the course of a clinical trial. The monitoring requirements for clinical trials in 12.8 of the *National Statement* (12.8) do reinforce the TGA requirement that researchers must:

(d) inform the HREC and the TGA of all serious or unexpected adverse events that occur during the trial and may affect the conduct of the trial or the safety of the participants or their willingness to continue participation in the trial ...(19)

However, it is left open to HRECs to interpret that requirement with respect to requiring disclosure to participants, depending on the nature of the information provided.

Further, neither the TGA regulations nor the *National Statement* address the problem that contracts between researchers and commercial sponsors may prevent researchers from disclosing unforeseen risks to participants. Indeed, HRECs may feel bound to support confidentiality clauses that prevent researchers from disclosing risk to participants, given 12.11 (b) of the *National Statement*:

12.11 In a clinical trial, data must be accurately recorded in a durable and appropriately referenced form and:
...
(b) if data are of a confidential nature, confidentiality must be observed;
...(19)

Turning now to the issue of the information that must be disclosed by a practitioner prior to obtaining consent, the Australian test is found in the High Court case of *Rogers v. Whitaker*.(20) The judgment stated:

The law should recognise that a doctor has a duty to warn a patient of a material risk inherent in the proposed treatment; a risk is material if, in the circumstances of the particular case, a reasonable person in the patient's position, if warned of the risk, would be likely to attach significance to it ...(20: 490)

In applying this disclosure standard to consent to participation in research, it is assumed that participants in research may view more risks as "material":

In determining what is a 'material' risk for the purpose of the test in *Rogers v. Whitaker*, a court would almost certainly require a higher standard of disclosure for research than that needed for therapeutic procedures. The reason is that a reasonable person would be more likely to attach significance to risks if the procedure is not being undertaken for that person's own benefit, but, rather, to benefit someone else.(21)

However, consent is not invalidated if a participant knows the general nature of the treatment and risks and agrees to participate.

Thus, the current *National Statement* and the *Rogers v. Whitaker* standard of disclosure appear to treat consent to participation in research as a singular event that occurs prior to participation, and not as a process that may require periodic renewal or review in light of new information. To a degree, the *National Statement* acknowledges that changed circumstances may mean that participants would wish to withdraw their consent or that HRECs should require researchers to discontinue research. However, the *National Statement* is missing an acknowledgement that respect for the autonomy and welfare of participants may mean that consent in light of new information should be re-negotiated as an alternative to continuing research without disclosing the new risks to participants or discontinuing the trial altogether.

Suggested Changes for Australia

As in New Zealand, there are gaps in the rules regarding ongoing disclosure of risks and confidentiality clause content such that an Olivieri case could happen in Australia. To close these gaps, the following steps should be taken:

1. Inserting the following into the TGA interpretation of Good Clinical Practice Guidelines to the effect that:
   No agreements or contracts between researchers and sponsors that limit the right and responsibility of the researchers to disclose relevant information about unforeseen risks that become known in the course of the research, to participants in the study, members of the research group, other physicians administering the treatment, research ethics committees, regulatory agencies, and the scientific community, may be entered into by the researchers.

2. Inserting the following into the *National Statement* in 2.7.16:
   The researcher must 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 committees, regulatory agencies, and the scientific community.

It must be noted here that the *National Statement* is under review and the *Review of the National Statement on Ethical Conduct in Research Involving Humans: First Consultation Draft (Consultation Draft)* (22) has been released for comment. Unfortunately, the *Consultation Draft* does not adequately address the concerns raised by the Olivieri case concerning disclosure and confidentiality agreements. On the matter of confidentiality clauses within investigator agreements or other contracts with sponsors, the *Consultation Draft* is silent (although it does note the effects of contracts, as is discussed below). In regard to consent in clinical trials and the need for disclosure of risks that arise in the course of research, the *Consultation Draft* provides general requirements for consent and those relating to clinical trials:

> 1.2.2 Each potential participant should normally be provided with information, at his or her level of comprehension, about the purpose, methods, demands, risks, inconveniences, discomforts, any relevant declarations of interest, including financial interests, and possible outcomes of the research (including the likelihood and form of publication of research results).
>
> 2.7.12 Due to the potential complexity of information to be provided to participants in seeking consent, the requirements of paragraph 1.2.2 must be carefully considered and followed. Researchers should pay particular attention to providing information at the level of comprehension of the participant and a clear description of what is involved in the proposed intervention or observation to be conducted, particularly the nature of any tests and full details of the collection and all intended uses of samples of human tissue.

Neither of the proposed sections address either the need to understand consent as a process that may be renegotiated during the course of a clinical trial, nor do they specifically require that participants be given information about risks that become evident during the course of a clinical trial.

In the sections of the *Consultation Draft* regarding monitoring of research, a significant change is proposed, in that HRECs must require researchers to inform participants (as well as the HREC and institution) of the reasons for discontinuation of trials. The *Consultation Draft* also acknowledges that new information (including unpublished studies) may affect the continued acceptability of a trial and may necessitate amendments. Nonetheless, the proposed sections do not yet specify that researchers are obliged to disclose new information about risks to participants if they believe those risks may be relevant to participants' continued consent.(22)

The *National Statement* should therefore be revised so as to include the statement for 2.7.16 set out above.

REC Review of Contracts and Investigator Agreements

New Zealand Rules

Under the New Zealand Interim Good Clinical Research Practice Guideline,

> A budget in the form of a written contract should be established and documented in the investigator's information package for each study, prior to its commencement. The budget should be developed through discussion between the sponsor and principal investigator and should be available for review by the relevant ethics committee(s). The information should clearly define how the expenditures are to be distributed, for example payment of volunteers, refunding expenses of participants, payment for special tests, etc.(13: 15)

However, there does not appear to be any requirement for the investigator to make the contract or investigator agreement available to the RECs/HDECs/IECs for review. Similarly, the Operational Standard for Ethics Committees does not establish a requirement for RECs/HDECs/IECs to review contracts and investigator agreements. Neither the National Application Form for Ethical Approval of a Research Project nor the Guidelines for Completion of the National Application Form for Ethical Approval of a Research Project include a requirement that contracts and investigator agreements be submitted.

Therefore, as happened in the Olivieri case, there could be objectionable confidentiality clauses that the REC/HDEC/IEC never sees and therefore can never remove. Consider the following examples of confidentiality clauses drawn from actual research proposal materials:

> All data generated from this study are the property of the X [the sponsor] and shall be held in strict confidence along with all information furnished by X and Y. Independent analysis and/or publication of these data by the investigator or any member of his/her staff is not permitted without prior written consent of X. Written permission to the investigator will be contingent on the review by X of the statistical analysis and manuscript and will provide for nondisclosure of X's confidential or proprietary information.

> 'Confidential Information' ... means information disclosed to, acquired by or otherwise known by B [the investigator], as a consequence of evaluation of documentation, or otherwise, by B for C [the sponsor], including all information gathered or developed by B ... B acknowledges and agrees that all Confidential Information is and shall be the sole and exclusive property of C and, as permitted hereunder, shall be held in the strictest confidence by B at all times. B shall only use the Confidential Information for the purpose of professional consultation in the context of this Agreement and shall not, directly or indirectly, use, disseminate, dispose, communicate, divulge, reveal, publish ... any Confidential Information. B shall only disclose the Confidential Information on a 'need to know' basis and only with the express written consent of C. Further, B shall provide to C and maintain a current list of all individuals who have been permitted access to the Confidential Information. B acknowledges that damages may be an inadequate remedy for breach of this Agreement and B hereby consents to C seeking and obtaining injunctive or other equitable relief in respect of the provisions thereof.... This Agreement shall ensure to the benefit of and be binding upon the respective heirs, executors, administrators, successors and assigns of each of B and C.

Under the current rules, the REC/HDEC/IEC may never see (and thereby be in a position to prevent) these glaring threats to the safety of the research participants.

Suggested Changes for New Zealand

This problem could be solved relatively easily – the National Application Form for Ethical Approval of a Research Project should be revised to require that contracts and investigator agreements be submitted to the REC/HDEC/IEC for review prior to approval. While waiting for this revision to the National Form, REC/HDEC/IECs should require investigators to submit contracts and investigator agreements for REC/HDEC/IEC review. REC/HDEC/IECs should then refuse to grant approval for any studies involving a restriction on the investigators' ability to inform participants of risks discovered during the course of the study. They should require the following text be a part of all contracts and investigator agreements:

> 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 committees, regulatory agencies, and the scientific community.

It should be noted here that the task of reviewing contracts at some universities in New Zealand appears to have been, to a certain extent, externalized. That is, distinct entities have been established with responsibility to managing contract research (for example, Auckland UniServices Ltd. and Victoria Link Ltd.) It is clear that contracts are being reviewed by these companies. However, it is not at all clear that they are being reviewed to ensure that there are no ethically unacceptable confidentiality

clauses of the sort described above. The focus of these companies appears to be on publication delays or bans rather than disclosure to participants. It also appears to be on intellectual property and commercialization. It should also be noted that these companies have a clear mandate to increase externally-funded research for the university. Thus, although there are some bodies that do appear to be reviewing contracts in New Zealand, it can be concluded that they are not the appropriate bodies (they do not have the required ethics mandate and orientation) nor do they appear to be conducting the reviews or providing advice such that the confidentiality clause issue will be adequately dealt with in the public interest, and with due regard to the protection of research participants. This drives us, then, back to the recommendations made above in relation to the National Application Form and the activities of RECs/HDECs/IECs being revised such that RECs/HDECs/IECs review contracts and investigator agreements and require statements of the sort suggested above.

Australian Rules

As in New Zealand, although researchers are required to provide Investigator Brochures and copies of budgets covering clinical trials to HRECs, the HRECs are not required to review the wording of clinical trial contracts and investigator agreements (beyond budgets (12.6)). Generally, the existing *National Statement* treats investigator agreements as outside the sphere of HREC concern. Therefore, as happened in the Olivieri case, there could be objectionable confidentiality clauses that the HREC never sees and therefore can never remove. In some Australian research institutions, review of such contracts is conducted by 'contracts lawyers' or 'business risk' lawyers, whose internally conflicted role it is to both secure contracts that bring external funding to the institutions and to minimize risk to the institution. As was noted in the case of New Zealand, there is reason to question whether this process adequately addresses the ethical implications of these contracts for researchers and research participants.

Suggested Changes for Australia

The *Consultation Draft* on revisions to the *National Statement,* does not require HRECs to review investigator agreements or other contractual relationships pertaining to trials, although it does acknowledge the potential for contractual relations to affect the ethical acceptability of research. Unfortunately, it does not give HRECs clear guidance:

> Australian common law obligations arise from the relationships between institutions, researchers and participants, while contractual arrangements may impose obligations on research funders and institutions. This Statement of ethical principles and considerations assumes, but does not address, this legal context. ...
>
> It is the responsibility of institutions and researchers to conform to both general and specific legal obligations, wherever relevant. HRECs need to be satisfied that the conduct foreshadowed in the research proposals they approve is lawful.(22)

It is likely that some HRECs would interpret the contractual obligations that sponsors and researchers enter into as imposing legal obligations that the HREC ought not to challenge, for example by requiring researchers to disclose risks that arise during a research trial. We would therefore recommend two inclusions in the revised *National Statement.* First, in discussing ethics and law in research in the Introduction, the *National Statement* should state:

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

Secondly, in Section 2.7 on Research Merit and Integrity in Clinical Trials, there should be a requirement that:

> HRECs must examine investigator agreements, research contracts or other contractual arrangements to ensure that no agreements or contracts between researchers and sponsors limit the right and responsibility of the researchers to disclose relevant information about unforeseen risks that become known in the course of the research, to participants in the study, members of the research group, other physicians administering the

treatment, research ethics committees, regulatory agencies, and the scientific community.

Conclusion

The Olivieri case brought to light significant gaps in the protection of the public with regard to clinical trials in Canada. Looking at the governance of research in New Zealand and Australia through an Olivieri case lens, we can see that there are similar gaps in Australasia. Unfortunately, there remains an urgent need in Australasia as well as Canada and elsewhere to protect the public interest by putting into place corrective measures. The promise of highly profitable developments in pharmaceutical, biotechnology, and genomics research in conjunction with the tighter fiscal realities of universities and hospitals makes appropriate and transparent resolution of conflicts of interest very important. No matter what our roles – as researchers, health law experts, ethicists, policy makers, health care providers, regulators, or health care consumers – we must take steps to ensure that we will not have more 'Olivieri cases'. We must all take steps to ensure that the issues raised in this paper are addressed right around the world. The integrity of contemporary health research and the safety of the public rests on our doing so.

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Notes

i The first part of this paper is adapted (with permission of the Health Law Journal) from Downie J , Baird P, Thompson J. Industry and the Academy: Conflicts of Interest in Contemporary Health Research. Health L J. 2002; 10:103-122. This paper was in turn based upon Thompson J, Baird P, Downie J. The Olivieri Report: The complete text of the report of the independent inquiry commissioned by the Canadian Association of University Teachers. Toronto: Lorimer; 2001. [Online], Available: http://www.dal.ca/committeeofinquiry [25.7.05].

ii REB's are known by various names and acronyms in various jurisdictions. In Australia, they are known as Human Research Ethics Committees (HRECs) while in New Zealand they are known as Regional Ethics Committees (RECs), Health and Disability Ethics Committees (HDECs), and Institutional Ethics Committees (IECs). For the purposes of this paper, we will use Research Ethics Committee, REC, as a generic label for a committee tasked with the conduct of ethics review of research involving humans and REB, REC/HDEC/IEC, or HREC when referring specifically to one jurisdiction.

iii This is a program through which patients can gain access to drugs that are not yet approved for sale in Canada. This is equivalent to the 'exemption for medicine required by medical practitioner', s.29 of the New Zealand Medicines Act 1981 and the Special Access Scheme under the therapeutic goods legislation in Australia.

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