Institutional conflict of interest: attempting to crack the deferiprone mystery

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ABSTRACT

A recent study by Olivieri *et al*, published in *PLOS ONE*, reports that between 2009 and 2015 a third of patients with thalassaemia in Canada's largest hospital were switched from first-line licensed drugs to regimens of deferiprone, an unlicensed drug of unproven safety and efficacy. Based on retrospective data from patient records, the PLOS Study reports that patients treated with deferiprone, either as monotherapy or in combination with first-line drugs, suffered serious (and often irreversible) adverse effects. The data reported by Olivieri *et al* give rise to a number of ethical issues. These ethical issues are identified, placed in historical context and analysed. For purposes of this analysis, reliance is placed on two core principles of research ethics, harm minimisation and informed consent, and also on the hospital's mission statement. Then a mystery is explored: How and why did it happen that Toronto's University Health Network treated large numbers of patients with an unlicensed drug over a period of many years? 'Institutional conflict of interest' is considered as a possible explanatory hypothesis.

INTRODUCTION

Thalassaemia is an inherited anaemia that exerts an enormous disease burden worldwide.[1] Along with sickle cell disease, it is one of the two most common single gene disorders. Indeed, 'the alpha and beta thalassaemias are the most common inherited single-gene disorders in the world…'[2]

A newly published study by Olivieri, Sabouhanian and Gallie[3] analyses and assesses the comparative efficacy and safety profile of two drugs: deferiprone (Ferriprox; Apotex) and deferasirox (Exfade; Novartis). Both of these 'iron-chelating' drugs remove ('chelate') iron deposited, as a result of transfusions, in the tissues of patients with thalassaemia.

The present-day first-line chelator, deferasirox, was licensed by the US FDA in 2005. The evidence for its safety and effectiveness was judged to be substantial and, accordingly, the FDA licensed it as a first-line agent. The prime advantage of deferasirox, in comparison to deferoxamine, an older drug that was formerly the gold standard of iron-chelating therapy for thalassaemia, is that deferasirox is orally active (that is, taken in pill form), while deferoxamine is more burdensome for patients because it has to be taken parenterally (that is, via injection). Deferiprone, like deferasirox, is taken orally but has not been licensed anywhere as first-line treatment. The FDA withheld market approval for deferiprone because there were/are no controlled trials demonstrating direct treatment benefit. Although the FDA did eventually approve deferiprone, in 2011, it gave approval only as a last-resort treatment for those patients in whom other chelators had been tried unsuccessfully.[i]

The data presented by Olivieri *et al* in their *PLOS ONE* paper indicate that the drugs differ significantly with respect to their effectiveness and safety. This commentary explores some of the ethical issues raised by the PLOS data.

HISTORICAL CONTEXT

In order to understand properly the significance of the *PLOS ONE* Study some historical context will be helpful. What follows is a brief sketch of that context.[ii]

In 1993 Dr Nancy Olivieri, a specialist in blood diseases at Toronto's Hospital for Sick Children (HSC or 'Sick Kids') and Professor of Pediatrics and Medicine at the University of Toronto (U of T), signed a contract with Apotex, a generic drug company, to continue studies of deferiprone, the early promise of which she had already reported in the literature. Olivieri's thalassaemia research was initially supported by the Medical Research Council of Canada, but now she sought additional funding to extend her clinical trials. Apotex contributed this additional funding, thereby obtaining worldwide patents on the still-experimental drug.

Despite early promise, by 1996 Olivieri's research began to indicate that deferiprone might be inadequately effective in many patients, posing risks of potentially serious harm. Olivieri communicated to Apotex her intention to inform patients of this unexpected risk and she proposed also to amend the study's consent forms. She wished to continue amended studies of the drug, and to publish her findings.

Apotex responded to Olivieri that they disagreed with her interpretation of the data and the company's CEO threatened her with 'all legal remedies' should she inform patients or publish her findings. In issuing these threats, Apotex relied on a

[i]The FDA refused first-line approval of deferiprone because of Apotex's 'failure to provide answers to [FDA's] questions on efficacy and safety'. See reference 4.[23] But the FDA approved it as a 'last-resort' therapy. The FDA's drug monograph confirms that 'no controlled trials of deferiprone demonstrate a direct treatment benefit'.[24]

[ii]For a fuller account of the historical context, see reference 7.[4] The authors of the CAUT report spent 2 years doing a detailed analysis of hundreds of primary documents. They were thus able to produce an authoritative account of this complex case. In what follows I have relied extensively on their analysis. For a fuller account of the ethics of the original Apotex-Olivieri scandal, see reference 6.[13]

confidentiality clause in a legal contract Olivieri had signed with Apotex in 1993. This contract prohibited disclosure 'to any third party' without the express permission of Apotex.[iii]

Despite the objections raised by Apotex, Olivieri saw it as her professional duty to disclose her findings. The Research Ethics Board (REB) of Sick Kids Hospital reached the same conclusion. In compliance with instructions from the Hospital's REB, Olivieri duly informed both her patients and the regulatory authorities.

When Olivieri later identified a second risk—that liver damage progressed during deferiprone exposure—Apotex issued additional legal warnings. Olivieri nevertheless proceeded to inform her patients of this additional risk and published her findings.

Since patient safety, research integrity and academic freedom were all at stake in this dispute, Olivieri appealed for assistance, repeatedly, to senior officials at both the U of T and Sick Kids Hospital. Neither the University nor the Hospital provided the support she requested. In the words of the *Report of the Committee of Inquiry on the Case Involving Dr Nancy Olivieri, the HSC, the U of T, and Apotex Inc*[4]:

> The HSC and the U of T 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.

Instead, both the University and the Hospital 'took actions that were harmful to Dr. Olivieri's interests and professional reputation and disrupted her work'.[4] The harmful actions included firing Olivieri from her position as Director of the Hemoglobinopathy Program at Sick Kids Hospital and referring her for discipline to the College of Physicians and Surgeons of Ontario (CPSO).

Only later did it emerge that, during this period of conflict, the U of T was negotiating with Apotex for a major donation towards building the University's proposed new molecular medicine building. Some speculated that the University's failure to support Olivieri may not have been unconnected from its desire to appease a wealthy corporate donor. This speculation was reinforced when it was discovered that the then President of the University, Robert Prichard, had secretly lobbied the government of Canada for changes in drug patent law, changes that would favour Apotex.[iv]

Apotex proceeded to sue Olivieri for defaming both the company and their drug; she sued the company for defaming her.

The Canadian Association of University Teachers (CAUT) and the U of T Faculty Association (UTFA), to whom Olivieri appealed for assistance after being rebuffed by the U of T and HSC, viewed the underlying issue as one of academic freedom. Both CAUT and UTFA provided support, including legal advice, to Olivieri.

Thus began what is widely acknowledged to be the greatest scandal in Canadian academic history. Commissions of inquiry, books and articles (both scholarly and popular) proliferated, not to mention newspaper and television stories. John le Carré's novel *The Constant Gardener* and the Hollywood movie based on the book both appeared to draw heavily on the Olivieri-Apotex scandal. An inquiry into the dispute commissioned by Sick Kids Hospital (the Naimark Inquiry)[v] absolved Apotex of wrongdoing but suggested that Olivieri was seriously at fault.[5] She was charged with research misconduct and failures of patient care and was referred first to the Hospital's Medical Advisory Council and subsequently to the disciplinary committee of the CPSO. Unsurprisingly, these widely publicised referrals were prejudicial to Olivieri's reputation.

The CAUT then commissioned an independent inquiry.[vi] The 540-page CAUT report on the Olivieri/Apotex affair[4] gave a markedly different account of the scandal from that offered by the hospital-commissioned Naimark Report. A few excerpts from the CAUT report will convey its central findings:

> Apotex issued more legal warnings to deter Dr. Olivieri from communicating this second unexpected risk of L1 (deferiprone) 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.
>
> Apotex acted against the public interest in issuing legal warnings to Dr. Olivieri to deter her from communicating about risks of L1.
>
> Apotex's legal warnings violated Dr. Olivieri's academic freedom.[vii]

Shortly after the CAUT report absolved Olivieri of misconduct, the CPSO published the findings of its inquiry. The CPSO report exonerated Olivieri of all misconduct charges. Indeed, their report concluded that her conduct had been 'commendable'.[6] This favourable verdict did not, however, bring an end to litigation.

In 2004, 8 years after the first legal threats had been issued, Apotex signed a mediated settlement with Olivieri. Nevertheless, litigation continued for another 10 years. Those unfamiliar with the workings of the law may wonder how it is possible for litigation to continue for such a long period after a mediated settlement. Litigation continued because Apotex alleged that Olivieri had violated their agreement. Olivieri insisted that she was in compliance with the terms of the settlement. Court decisions were appealed by both parties. A final settlement was not reached between Olivieri and Apotex until 2014.[viii] Shades of *Jarndyce v. Jarndyce* in Charles Dicken's novel *Bleak House*.

The HSC settled its dispute with Olivieri in 2006 and, although her research programme at the Hospital continued, she ceased to provide clinical care to HSC patients. From 1997 to 2009, Olivieri served as Director of the University Health Network (UHN) Hemoglobinopathy Program. She continued, as she had since 1997, to assist in the clinical care of UHN patients with thalassaemia and to enrol them in her research studies. In March 2009, however, Olivieri was dismissed by UHN from

[iii] It should be noted, however, that the CAUT report on the Olivieri-Apotex scandal, discussed below, concludes that the confidentiality clause did not in fact cover the disputed clinical trial. See pages 25 and 26 of reference 7[4] at points 12, 14 and 22.

[iv] The private letter President Prichard wrote to the Canadian prime minister explained that he was concerned about a decrease in Apotex revenues because he was hopeful of receiving a substantial donation from the company towards the university's new molecular medicine research centre. See reference 7,[4] page 13.

[v] The hospital's appointed reviewers were Arnold Naimark, Fred Lowy and Bartha Knoppers.

[vi] The three reviewers for the CAUT inquiry were: Jon Thompson, Patricia Baird and Jocelyn Downie.

[vii] All quoted passages taken from page 29 of reference 7.[4]

[viii] For further information on these multiple and seemingly never-ending legal proceedings between Apotex and Olivieri, see references 10 and 11.[25 26]

her position as Director. No reason was given for her dismissal (Personal communication. Olivieri, 2019).

The *PLOS ONE* Study data[3] show that, after Olivieri's dismissal from her position as Director, the UHN thalassaemia Clinic began almost immediately to switch patients to (unlicensed) deferiprone. Olivieri has described how her UHN research work, from this time forward, was marginalised (https://inthepatientsinterest.org/wp-content/uploads/2019/12/2018-12-20-GallieOlivieri-to-SmithHodges.pdf).

Meanwhile, Freedom of Information (FOI) requests filed by Olivieri after her dismissal revealed that Apotex was supplying unrestricted educational grants to UHN's thalassaemia programme as well as providing research support. The FOI requests filed by Olivieri also revealed that Apotex was strategising with the programme's new director about how best to obtain licensing for deferiprone from the regulator (Health Canada).[ix] With this dramatic background as historical context, we commence our discussion of the ethical implications of the *PLOS ONE* paper.

FINDINGS OF THE *PLOS ONE* PAPER

In their 2019 *PLOS ONE* study Olivieri *et al* conclude, based on a retrospective review of patient data at Toronto's UHN, that deferiprone is inadequately effective and associated with serious toxicity. Their review also confirms that, by contrast, deferasirox is effective and associated with relatively few adverse effects.[3]

Olivieri *et al* report that '[b]etween 2009 and 2015, a third of patients transfused and managed in Canada's largest transfusion programme were switched from first-line, licensed drugs to regimens of unlicensed deferiprone'.[3] This finding raises the ethically troubling question: How and why were so many locally transfused patients at UHN treated over such a long time period with an unlicensed drug of unproven safety and efficacy? This ethical concern is followed immediately by another related concern: Why did the UHN thalassaemia programme continue to treat large numbers of its patients with deferiprone—despite ongoing evidence of inadequate effectiveness and serious (and often irreversible) adverse effects?[3]

To recapitulate: the *PLOS ONE* paper demonstrates that a substantial proportion of UHN patients with thalassaemia was switched, between the years 2009 and 2015, from first-line licensed therapies (deferasirox or deferoxamine) to deferiprone. During this entire period, deferiprone was unlicensed in Canada. To this day in every jurisdiction in which deferiprone has been licensed it has been licensed only as 'last resort' therapy. The ethical concern is to explain and to explore possible justifications for how and why so many patients at one particular thalassaemia treatment centre were prescribed a drug whose safety and efficacy were unproven in face of availability of licensed effective drugs. The urgency of the concern derives partly from the paper's finding that those patients who were switched to deferiprone displayed evidence of increases in body iron and experienced the harms associated with body iron increase.[3] This finding raises a second troubling ethical question: Why were patients not switched back to a first-line licensed therapy after they began to experience serious adverse effects from treatment with unlicensed deferiprone?

How and why?

In a sustained effort to discover answers to these questions, Olivieri and Gallie have been in communication since 2015, by email and in personal meetings, with senior officials at UHN. Olivieri and Gallie report, however, that no definitive answers have yet been provided to any of their questions. FOI requests were filed but they, too, failed to produce definitive answers. (Olivieri and Gallie to Smith & Porter, 2019, https://inthepatientsinterest.org/wp-content/uploads/2019/12/2019-04-23-OlivieriGallie-to-SmithPorter.pdf).[x] I, too, wrote to the CEO/President of UHN and to the Chief of Medical Staff, in an attempt to discover answers to a number of the ethical questions posed in this commentary. The hospital, however, has not responded to any of my questions.[xi]

Olivieri and Gallie have recently posted documentation of their correspondence with senior UHN administrators (https://inthepatientsinterest.org/). In September 2019 the UHN administration responded to the *PLOS ONE* paper by revealing that it had conducted a 'Review of chelation practice in the red blood cell disorders program at UHN'. However, as Olivieri and Gallie document on the web, the hospital's 'Review' does not address any of the safety concerns flagged in the *PLOS ONE* paper (https://inthepatientsinterest.org/wp-content/uploads/2019/12/Letter-to-Smith-and-Hodges-2-12-19.pdf). Nor does the 'Review' address any of the ethical concerns raised here.

Despite UHN's apparent reluctance to provide the information requested, here's what we know or can reasonably infer. Deferiprone was unlicensed in Canada during the relevant period, that is, from 2009 to 2015. 'Unlicensed' is different from 'off-label', the latter referring to a drug that has been licensed but is being provided for an indication other than that for which it is approved. Prescription of any unlicensed drug to Canadian patients can be accomplished only in one of two mutually exclusive ways: either through Health Canada's 'Special Access Program (SAP)' or via an REB approved clinical trial. It has to be one or the other since, as Health Canada's Guidance Document[7] makes clear, patients cannot be simultaneously treated through SAP and in a research trial.[xii] Under the SAP, the treating physician must confirm to Health Canada that 'conventional therapies have failed, or are unsuitable or unavailable'. Although some of the UHN patients' records indicate that deferiprone was released under the SAP, Olivieri *et al* report that they 'could identify no explanation for a proposed switch to deferiprone that was supported by evidence of failure of licensed therapy prescribed as recommended'[3]; indeed, the authors write that many patients appear to have been switched to deferiprone despite optimal responses, or improvements during treatment with first-line therapies. Here's the relevant paragraph from their *PLOS ONE* article:

[ix] See https://inthepatientsinterest.org/wp-content/uploads/2019/12/Jan-May-2011-FOI-UHN-APO.pdf and https://inthepatientsinterest.org/wp-content/uploads/2019/12/June-Aug-2011-FOI-UHN-APO.pdf.

[x] For example, Olivieri and Gallie inquired about the authority under which deferiprone was prescribed to UHN patients as an unlicensed drug for 6 years. They asked why the former head of the UHN REB and others in authority repeatedly declined to clarify the issue of authority and repeatedly declined to supply evidence on this point. If deferiprone was prescribed through a research programme, there should be REB applications and approvals and renewals, as well as adverse event reports.

[xi] The letter I sent to the President/CEO of UHN and the Chief Medical Officer, and the letter I sent to the two UHN physicians responsible for the thalassaemia clinic, seeking answers, are in online sup[plementary appendix A. No replies has been received.

[xii] See online supplementary appendix B for passages from Health Canada's SAP Guidance Document supporting the view that these two approaches are mutually exclusive.

> Deferiprone was prescribed to 41 study patients between 2009 and 2015. We could identify in the electronic medical records no explanation for a proposed switch to deferiprone that was supported by evidence of failure of licensed therapy prescribed as recommended. There was no indication that any patient switched to deferiprone over these 6 years had 'failed' therapy with either deferoxamine or deferasirox. Many patients were recorded as tolerant of at least one and (in most), both licensed first-line chelating agents; some had sustained minor adverse events during deferasirox that had resolved by the time deferiprone was prescribed.[3]

In other words, according to the data found in UHN patient records, there is no evidence that the patients with thalassaemia who were switched to deferiprone met Health Canada's eligibility criteria under SAP. Since deferiprone is licensed only as a 'last resort' therapy, its employment to treat patients who can tolerate either of the first-line therapies might improperly expose those patients to risks of serious medical harms, up to and including death.

On the other hand, one should also consider the alternate possibility that, over the 6-year period studied by Olivieri *et al*, deferiprone was prescribed as part of a clinical trial. In favour of this hypothesis, one notes that the UHN physician primarily responsible for the widespread prescribing of deferiprone during the relevant time period claimed, in 2011, that deferiprone was provided to patients under a study approved by the REB of the UHN.[8] UHN physicians also made this identical claim in a publicly available letter to the US FDA.[9] Moreover, in response to an FOI application filed by Olivieri, UHN claimed that deferiprone was provided at UHN during a clinical trial (the data of which are protected from scrutiny under FOI laws), and not under SAP (the data of which are not protected from scrutiny under FOI). However, Olivieri *et al* have been unable to find any record of registration for such a trial, as required by Canadian Clinical Trial guidelines.[xiii] Requests to the UHN administration for confirmation that a clinical trial existed remain unanswered.[xiv] My own efforts to find some registration record for this putative clinical trial of deferiprone have been equally unsuccessful.[xv]

TWO CORE ETHICAL PRINCIPLES: HARM-MINIMISATION AND INFORMED CONSENT

If the deferiprone used to treat UHN patients with thalassaemia was obtained from Apotex as part of a randomised clinical trial, responsibility for approving the trial would fall to the UHN's REB. In Canada, both researchers and REBs are governed by the Tri-Council Policy Statement (TCPS) 'Ethical Conduct for Research Involving Humans'.[10] The 1998 version of this policy statement (TCPS1) and the subsequent 2010 version (TCPS2), both applicable to research trials during this period, stipulate that clinical trials must be designed so that harm to research subjects will be minimised.[xvi] For example, TCPS1 specifies, in section 1.5, that 'Research subjects must not be subjected to unnecessary risks of harm'. TCPS2, under the rubric 'Core Principles', requires similarly that clinical trials must 'ensure that participants are not exposed to unnecessary risks'.

Data presented by Olivieri *et al* in their *PLOS ONE* Study indicate that UHN patients exposed to unlicensed deferiprone, either as monotherapy or in combination with low dose of a first-line chelator ('combination therapy'), experienced significant harms as a result of poor iron control, but very few if any compensating benefits.

> We provide new evidence of inadequate reduction in hepatic iron, a 17% incidence of new diabetes and new liver dysfunction in 65% of patients, many who were challenged and rechallenged with deferiprone despite elevated liver enzymes developed during previous exposure. We identified no evidence of 'cardio-protective' effect during deferiprone therapy.[3]

In light of *PLOS ONE* Study data indicating serious adverse events (SAEs) for patients switched to deferiprone from first-line drugs one is led to question why the study protocol did not, in anticipation of such a contingency, provide for a resumption of licensed therapy for patients doing poorly on the unlicensed drug. Moreover, the investigators were obliged to report adverse events to the hospital's REB. Were the adverse events so reported? And if they were then why did the UHN REB not seek to protect patient safety by insisting that licensed therapy be resumed for deferiprone-harmed patients?

In an effort to establish whether the deferiprone 'clinical trial' satisfied the TCPS harm-minimisation principle, I made inquiries about how the adverse findings described by the *PLOS ONE* paper were reported to the hospital's REB and also how they were reported to the regulatory authorities, that is, Health Canada and the US FDA. But my queries, like those made previously by Olivieri and Gallie, have not succeeded in eliciting this ethically relevant information.[xvii] Neither UHN nor its thalassaemia clinic responded to my letters of inquiry. It is known, however, from a publicly available 2011 document, that physicians in the UHN thalassaemia clinic strongly supported the market approval of deferiprone by the FDA.[xviii] This support is difficult to reconcile with the toxicities recorded in UHN patient records. So, a final verdict on the issue of whether the UHN deferiprone 'clinical trial design' violated the TCPS harm-minimisation principle cannot be reached until those involved in conducting and monitoring clinical trials at UHN make available the relevant information. An independent public inquiry may be necessary to achieve the necessary degree of accountability.

Reference has been made, above, to the TCPS core ethical requirement of harm-minimisation, applicable in Canada both to researchers and to REBs. It is important to note, however, that

[xiii] Clinical trial guidelines were formalised in 2007 by the National Institutes of Health and were then adopted by a number of countries, including Canada. They applied throughout the period of any deferiprone trial at UHN. See also: TCPS2, 11.2, which declares that 'There are compelling ethical reasons for the registration of all clinical trials'.

[xiv] Private communication with the authors.

[xv] A search on the following link https://clinicaltrials.gov/ct2/results?cond=Thalassemia&term=deferiporone&cntry=&state=&city=&dist= confirms that 22 trials involving deferiprone are listed. But, none of the 22 is relevant to the assertion by the treating physicians that the administration of deferiprone at UHN, while deferiprone was unlicensed in Canada, was conducted under an approved registered trial. See also online supplementary appendix A, Schafer's letters to UHN Administrative officials and UHN thalassaemia doctors.

[xvi] The (2018) revised version of the second edition, TCPS2, is not applicable because it had not been promulgated during the period under study.

[xvii] See my letters to the UHN and to Drs Ward and Kuo in online supplementary appendix A.

[xviii] See reference 14.[9] This point will also become relevant when we consider whether UHN physicians fulfilled their ethical obligation, discussed below, to alert research subjects and the UHN Research Ethics Board to the presence of individual and institutional conflicts of interest.

TCPS2, like its predecessor, TCPS1 (and, indeed, like virtually every postwar code of research ethics) also stipulates as a second 'core principle' that 'Researchers shall provide to prospective participants, or authorised third parties, full disclosure of all information necessary for making an informed decision'.[xix] Moreover, as the then-current TCPS guidelines make clear, 'consent is an ongoing process'; so, assurance should be given to prospective participants that they 'will be given in a timely manner *throughout the course of the research project*, information that is relevant to their decision to continue or withdraw from participation'.[xx] (My emphasis). Finally, TCPS2 imposes on researchers the additional ethical requirement that they disclose to research subjects 'information concerning the possibility of commercialisation of research findings, and the presence of any real, potential or perceived conflicts of interest on the part of the researchers, their institutions or the research sponsors'.[xxi] There is also an expectation that conflicts of interest will be disclosed to the REB. Whether there was adequate disclosure of Apotex funding either to research subjects or to the UHN REB is still unknown.

Thus, in order to assess the ethical adequacy of the putative UHN thalassaemia clinical trial one must inquire whether UHN patients/subjects were given adequate risk information when they were first enrolled, subsequently, when they were switched from treatment with deferasirox or deferoxamine to treatment with deferiprone and then, finally, when they experienced SAEs. That is, in order to know whether the putative deferiprone clinical trial conformed to established principles of research ethics, one would need to know whether patients/research subjects understood that they were being switched from licensed first-line drugs of proven efficacy to an unlicensed and unproven third-line drug. One would also need to know whether the deferiprone 'research subjects' were informed about conflicts of interest arising from Apotex donations (A) to the UHN. (B) To the hospital's thalassaemia programme,[xxii] as well as the hoped-for commercialisation of deferiprone via Health Canada and FDA licensing.

If there was a failure to obtain ongoing informed consent and/or a failure to disclose conflicts of interest (to patients and to the REB) then this would constitute a violation of research ethics. Unfortunately, my attempts to elicit the clinical trial's consent to research information from the UHN and its thalassaemia clinic met with as little success as earlier attempts made by the *PLOS ONE* authors.[xxiii]

REB REVIEW: SAFETY MONITORING

Although every clinical trial requires safety monitoring, those trials which involve non-negligible risk of significant harm to patients/subjects require especially rigorous safety monitoring.[xxiv] Because the exposure of deferiprone to UHN patients posed risks of organ dysfunction and death, the need for safety monitoring was exigent. As the TCPS1 and TCPS2 both make clear, those who conduct research have an obligation to monitor and protect the safety of their research subjects.

Moreover, it is now widely recognised that individuals closely involved with the design and conduct of a trial may not be able to be fully objective in reviewing interim data for any emerging concerns.[xxv] Hence the importance of REBs, part of whose role is to provide safety monitoring initially and, for ongoing trials, over the entire period of the trial. In order to assess the adequacy of the safety monitoring for the UHN 'deferiprone trial' one would need to know whether the hospital's REB was provided with regular and accurate reports of SAEs and what actions this REB took in response to those reports.

It has become common practice in North America 'that for any controlled trial of any size that will compare rates of mortality or major morbidity', a data safety monitoring board (DSMB) will be established.[xxvi][11 12] A DSMB is constituted by a panel of independent (and otherwise unbiased) individuals with expertise pertinent to reviewing trial data on a regular ongoing basis. Its role is to advise the sponsors regarding the safety of trial subjects and to recommend early termination where indicated, for example, on grounds of patient safety.[xxvii]

Since there are no specifically Canadian requirements with respect to the establishment of DSMBs, Canadian REBs tend to follow FDA guidelines. Those guidelines recommend that a DSMB should be established when the study end point is such that a highly favourable or unfavourable result at an interim analysis might ethically require termination of the study. Advance information suggesting the possibility of serious toxicity with the study treatment is another a priori reason for safety concern that would justify the establishment of a DSMB.[12]

For reasons given above, the UHN deferiprone trial appears to have been a prime candidate for the establishment of a DSMB; but it is not known whether the study's research protocol, purportedly submitted for approval to the hospital's REB, included a DSMB; nor is it known whether a DSMB was established and reported regularly to the trial's sponsors. Data on the toxicity of deferiprone, provided by Olivieri *et al* from their retrospective study of UHN patient records, suggest that had a DSMB existed for this putative clinical trial the trial might, on grounds of patient safety, have been a candidate for premature cancellation. Lacunae in our knowledge of the safety monitoring provisions of the deferiprone 'clinical trial' make it difficult to reach any firm conclusion as to whether the 'trial' met prevailing safety monitoring requirements.

The apparent unwillingness of the UHN to answer questions relating to safety monitoring might mean that an inquiry is needed to fill in our knowledge gaps and thereby make ethical evaluation possible. For the findings of such an inquiry to be minimally credible it should be carried out by individuals who possess the requisite scientific/medical expertise and who are independent of the hospital and its thalassaemia clinic and who are demonstrably impartial. An inquiry carried out, for example, by someone whose research has been funded by Apotex and/or by an expert with close professional and personal ties to one or more of the physicians in the UHN thalassaemia clinic would not satisfy the hospital's duty of accountability for patient safety.

[xix] TCPS2, Article 3.2

[xx] TCPS, Article 3.2, (d)

[xxi] TCPS2, Article 3.2, (e)

[xxii] Discussed later under the heading 'Institutional Conflict of Interest'.

[xxiii] See online supplementary appendix A.

[xxiv] See TCPS2 Article 6.12, 'Risk and Proportionate Approach'.

[xxv] In the USA, DSMBs are referred to as Data Safety Committees (DSCs). See reference 16.[11]

[xxvi] Loco citato.

[xxvii] TCPS2, Article 11.6, 'Monitoring Safety and Reporting New Information', discusses the important role of a DSMB in protecting the safety of research subjects.

ETHICAL CONCERNS

A Recapitulation

The serious complications experienced by deferiprone-exposed UHN patients, as described by Olivieri *et al* in their *PLOS ONE* article, raise a number of ethically important questions. How could an unlicensed drug of unproven efficacy and safety—a drug that has been questioned by regulatory agencies such that it is licensed only as a "last resort" therapy—have been administered to so many patients over a period of so many years when two licensed drugs, both proven adequately safe and effective and licensed as first-line therapies, were available? How did UHN physicians gain access to deferiprone from Health Canada when there is little evidence in UHN patient records that the deferiprone-exposed patients satisfied Health Canada's criteria for Special Access? Why was a putative UHN REB-approved research study involving deferiprone not registered as a clinical trial? Did the trial design include a DSMB, to protect patient safety and, if not, why not? Were SAEs reported to the UHN REB and to regulators, as required? Were deferiprone-treated UHN patients with thalassaemia adequately informed of the unlicensed status, unproven efficacy and reported toxicities of deferiprone? Were deferiprone-exposed patients informed of harms they themselves had sustained during deferiprone from this exposure?[xxviii] Did the evidence of systematic treatment failure, as outlined in the *PLOS ONE* paper, raise red flags for thalassaemia clinic physicians and for the REB of UHN? And if serious problems were flagged what actions were taken to protect patient safety?

INSTITUTIONAL CONFLICT OF INTEREST

The literature on biomedical conflicts of interest tends to focus on the ways in which financial support of individual researchers by the pharmaceutical industry can adversely affect both research integrity and patient safety.[13–16] But similar ethical problems arise at the macro level when institutions, such as hospitals and clinics, depend on drug company funding to support patient care and clinical research.[13 15] Notable scandals associated with institutional conflicts of interest include the David Healy/Eli Lilly scandal at Toronto's Centre for Addictions and Mental Health (CAMH),[13] the Aubrey Blumsohn/Proctor and Gamble scandal at Sheffield University (UK)[17] and the Carl Elliott/Janssen Pharmaceuticals scandal at the University of Minnesota.[17] The underlying pattern in each of these scandals involves (A) a biomedical researcher who is concerned about patient safety coming into conflict with (B) a pharmaceutical company which funds both the researcher's hospital and university and (C) a failure by the institutions involved vigorously to defend patient safety and research integrity when doing so might offend a wealthy sponsor.

It should not be assumed that corporate influence on university medical centres is necessarily exerted by means of threats or other direct forms of intervention. The mere presence of corporate funding can be sufficient to produce a corporate-friendly result. This point is illustrated by a recent *STAT* article, a propos the financial support which Purdue Pharma provided to Massachusetts General Hospital. The very title of the article encapsulates the ethical problem of institutional conflict of interest: 'Purdue Pharma cemented ties with universities and hospitals to expand opioid sales, documents contend'.[18] Nor should it be supposed that the problem of institutional conflict of interest arises exclusively in the context of biomedical research. A recent *Guardian* article on the Mobil Oil Corporation describes how 'Oil giant Mobil sought to make tax-exempt donations to leading universities … to promote the company's interests and undermine environmental regulation, according to internal documents from the early 1990s obtained by the *Guardian*'.[19]

As mentioned above, deferiprone, whose safety and efficacy are the central concern of Olivieri *et al*'s *PLOS ONE* paper, is manufactured by Apotex. When we seek to understand why deferiprone was so frequently prescribed to UHN patients, from 2009 to 2016, despite its being unlicensed and despite evidence of poor patient outcomes,[3] it may be relevant to note that Apotex provided substantial funding to the UHN thalassaemia clinic.[xxix] Moreover, a publicly displayed UHN banner lists 'Apotex Inc – Barry and Honey Sherman' as having donated between $1 million and $5 million to the hospital itself.[xxx]

As every biomedical researcher understands, correlation is not causation. Nevertheless, the correlation between industry funding of hospitals, on the one hand, and industry-friendly decisions made by researchers and administrators at those hospitals, on the other, is worth pondering. Physicians and researchers who speak or write critically of drugs manufactured by wealthy donor companies may find that their careers are jeopardised. Nancy Olivieri's dismissal from two Apotex-funded teaching hospitals illustrates this phenomenon as does the termination of psychiatrist David Healy from Toronto's CAMH.[13] Healy's appointment as Head of the CAMH Mood Disorders Clinic was rescinded almost immediately after he gave a public lecture at the hospital—a lecture in which he called for further research into the potentially adverse effects of Eli Lilly's antidepressant drug, Prozac. Healy was particularly concerned about SSRI-induced suicidal ideation. After his lecture the hospital decided that he was not 'a good fit' with their programme and terminated his appointment. Shortly thereafter the hospital opened its Eli Lilly wing.[13]

UHN, like every other research and teaching hospital in Canada, receives most of its funding, directly or indirectly, from governments.[20] [xxxi] Nevertheless, UHN, again like other hospitals, faces ongoing pressure to find additional sources of revenue to support both patient care and clinical research.[xxxii] The pharmaceutical industry is a prime source of much-needed 'top-up' financial support for Canadian hospital research and clinical care.[21] Hospital administrators, researchers and clinicians are thereby placed, willy nilly, in a conflict-of-interest situation. Because of funding exigencies, hospitals and other healthcare institutions, like individual physicians and researchers, have a strong vested interest in pleasing corporate sponsors and encouraging their ongoing support. Moreover, institutional

[xxviii] The ethical obligation to disclose harms to patients is unambiguous. For example, reference 18[27] declares: 'The full and open disclosure of harms sustained by patients is an important aspect of patient centred health care … this lies at the heart of patient autonomy'. Other authorities concur, including reference 19.[28] Reference 20[29] insists that should harm occur 'it should be disclosed to patients',

[xxix] Revealed in FOI requests made by Olivieri and Gallie and described in a letter (15 May 2019) they sent to Dr Kevin Smith, UHN President and CEO and Mr Brian Porter, Chair, UHN Board of Trustees [https://inthepatientsinterest.org/wp-content/uploads/2019/12/2019-04-23-OlivieriGallie-to-SmithPorter.pdf]

[xxx] Loco citato.

[xxxi] Canada's healthcare system is predominantly public, with 70% of healthcare funding coming from the public sector and the remaining 30% from the private sector.[30]

[xxxii] As the Financial Accountability Office of Ontario reports, in its 2019 Health Sector Update, hospital spending growth is escalating so rapidly that, despite recent funding increases from government, the system is facing numerous challenges.[31]

administrators, not unlike individual researchers and clinicians, typically experience a need to express their gratitude to donors by returning kindness for kindness and benefit for benefit. Thus, both the need for ongoing corporate sponsorship and the need to reciprocate for past corporate generosity create for hospital administrators (as well as for researchers and clinicians who work within hospitals) a conflict-of-interest situation in which their decision making may be skewed, consciously or unconsciously, in favour of the benefactors' products.[13 15 16 21]

Here's an example of the manner in which an institutional conflict-of-interest situation can potentially bias the judgement of hospital administrators. Hospitals are required to exercise their disinterested judgement in the appointment of medical and scientific staff and in the ethical monitoring of research. This moral obligation follows directly from their fundamental commitment to promote and defend patient safety and research integrity. To illustrate: UHN's website, under the heading *Purpose, Values and Principles*, declares that '[o]ur Primary Value and above all else: the needs of patients come first'.[22] It would be difficult to find any hospital whose Mission Statement did not proclaim a similar commitment to the primacy of patient well-being. In a similar vein, the UHN website, under the heading *Information for Patients*, subheaded *Our Mission*, declares: 'We believe that health equity is achieved when each person is: Enabled to choose the best care and treatment based on the most current knowledge available'.

From this fundamental commitment, it follows that healthcare institutions are obliged rigorously to monitor the quality of care provided to their patients and research subjects. As an important element of protecting patient safety, hospitals are required to appoint the most qualified and competent candidates to clinical and research positions. But, as noted above, conflicts of interest are a risk factor for bias, conscious or unconscious, in personnel decisions.[22] So, when a research hospital depends on corporate donations there is a risk that physicians and researchers may be appointed to key positions because they are known to be sympathetic to the donors' product(s) rather than because they are the best qualified and the most competent. Contrariwise, physicians and researchers believed to be unsympathetic to the donors' products are at risk of losing their jobs or of not being hired in the first place. The cases of Olivieri, Healy and Blumsohn illustrate this point.[13 17]

As explained above, we know from the extensive literature on conflict of interest that when research and clinical care are funded by industry there is a marked tendency for both to favour the sponsors'/donors' products.[13 15 16 18] Significantly, the UHN itself explicitly recognises the danger to patient safety posed by systemic biases. Its *Mission Statement* commits the hospital to ensuring that every patient is '[m]ade aware of existing systemic biases to support the best possible health decisions'.[22] Unfortunately, it is not possible at present to ascertain whether UHN conformed to this ethical commitment in the case of its deferiprone research/treatment clinic. In order to make such an ethical determination we would need to know the mechanism by which the UHN thalassaemia clinic gained access to deferiprone and whether the clinic provided information about systemic bias to patients with thalassaemia and to the hospital's REB.

CONCLUSIONS

Hospitals worldwide proclaim that their primary commitment is to meet the needs of their patients. Institutional codes of ethics and mission statements insist that patient needs come first. Indeed, meeting 'patient needs' is agreed to be *the fundamental value* to which all other hospital goals should be subordinated. Toronto's UHN declares unequivocally that it shares this value: '[t]he needs of patients come first'.[22]

Although patients have many and various needs, the need for safety must be counted as the sine qua non. If the need for safety is not met then other needs become irrelevant.

The findings of Olivieri *et al* in their *PLOS ONE* paper raise many troubling questions about the safety of patients in UHN's thalassaemia clinic. One would expect that when top UHN officials became aware of the *PLOS ONE* data they would immediately have recognised the ethical red flags. Hospitals are ethically obliged both to investigate thoroughly possible safety failures and to rectify any problems identified.

Over a period of several years, both before and after the publication of their research findings, Drs Olivieri and Gallie communicated regularly with UHN officials (https://inthepatientsinterest.org/). Multiple safety concerns were brought to the hospital's attention. Numerous questions were asked by the *PLOS ONE* authors and specific concerns were raised. To date, the hospital has not definitively addressed these issues. I posed a series of ethically salient questions to these same hospital officials (see online supplementary appendix A). My queries were ignored; there was no response from UHN.

If a healthcare institution such as UHN claims that patient safety is its top priority then when safety issues are raised, it necessarily incurs an obligation of accountability. It would, for example, scarcely be adequate for a hospital, such as UHN, unilaterally to investigate alleged failures, declare that there has been no violation of patient care standards, and then to stonewall all further inquiries, whether those inquiries originate from its own medical staff, as was the case with Olivieri and Gallie, or from outside scholars, as was the case with me.

When an unlicensed drug is prescribed to hospital patients, over a period of years, as happened in the UHN thalassaemia programme, it is surely the hospital's obligation to answer questions about how and why this extraordinary practice occurred. When hospital records reveal that patients switched from licensed to unlicensed medication, have experienced serious harms, up to and including death, it is surely the hospital's obligation to answer in a conscientious and complete manner all the ethically troubling questions that have been identified. This obligation of accountability is owed both to patients and to staff. Thus far, UHN has not been willing to accept the implications of its own mission statement (https://www.uhn.ca/corporate/AboutUHN/Quality_Patient_Safety).

The *PLOS ONE* Study by Olivieri Sabouhanian and Gallie spurs us to inquire whether the benefits which accrue to society from corporate sponsorship of healthcare institutions may, on balance, be outweighed by the associated harms. Admittedly, for governments committed to constraining public expenditures, the transfer of substantial healthcare costs to private corporations represents a benefit for public finances. But, as we have seen, when one considers this financial benefit, one ought also to take into account the spectrum of negative consequences potentially generated by institutional conflicts of interest. The price for our continued acceptance of corporate funding of scientific research and clinical care may be the erosion of public trust. Arguably, it would be preferable if our research hospital were to aim instead for the complete elimination of systemic biases.

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