December 20, 2018

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Dear Dr. Smith and Dr. Hodges,

Thank you for agreeing to meet with us. Our intent is to acquaint you briefly with the relevant history that is essential background to understanding the full implications of our manuscript, now under final review. This may help you and the UHN to deal with the upcoming challenges likely to arise from data and circumstances around the UHN patients that we describe in that manuscript. While the challenges are unsettling, we have ideas on how the UHN might move forward in a constructive way.

Our manuscript reports findings of a UHN REB-approved study to examine treatment outcomes in iron-loaded patients at UHN, led by Principal Investigator Dr. Nancy Olivieri, ongoing since 2000. This study permits access to the electronic patient records (EPR)s of consented iron-loaded UHN patients. We compared toxicity and effectiveness of two iron chelators, deferiprone and deferasirox, in 96 UHN patients from 2009 to 2015. During this period, deferiprone was not licensed for sale in Canada.

These findings and our concern that they point to safety issues in UHN patients have been previously discussed with Drs. Peter Pisters, Charlie Chan, Brad Wouters, Mansour Husain, Brian Hodges (as well as Chris Paige), and others at UHN. Correspondence on this matter dates back to 2009. The issues of patient care, informed consent, and the protection of patient safety at UHN, that we now again bring forward, have not been addressed.

Relevant Past History

In 1996, two pivotal, investigator-initiated and federally funded clinical trials of deferiprone, led by Dr. Olivieri, were prematurely terminated by Apotex (which had been providing partial support for one trial, and supplying drug for the second trial). The ensuing ethical controversy involved SickKids and U of Toronto and generated great public interest. The definitive summary of the controversy, *The Olivieri Report*,[1] was published in 2001 and encouraged SickKids to pursue settlements with Dr. Olivieri in 2002 and in 2006. Apotex continued to launch lawsuits against Dr. Olivieri until a full settlement was reached between Dr. Olivieri and Apotex in 2014.

Prior to 2009, few UHN patients had been treated with deferiprone (two patients known to Dr. Olivieri to have continued to take deferiprone against her advice after the original trial terminations, died from hepatocellular cancer, a risk arising from fibrosis of the liver, a concern raised by Dr. Olivieri in the NEJM 1998[2]).

Between 2000 and 2009, the patients in the UHN Hemoglobinopathy Program were jointly supervised in productive collaboration of Drs. Nancy Olivieri (Hemoglobinopathy Program Director since 1997) and Ian Quirt. Dr. Quirt retired in 2009.

Dr. Olivieri was told in March 2009 by Medical Oncology Director Dr. Malcolm Moore: “Corporate UHN thinks you’re trouble.” Dr. Moore removed Dr. Olivieri as Program Director (offering in writing an inducement of money to accept this dismissal, which she refused). This dismissal provoked a three-year dispute involving legal representation on both sides. Because Dr. Olivieri was embroiled in legal issues with Apotex, she could not afford to continue to fight the dismissal from the clinical program by UHN.

In 2009, **"**The Alexandra Yeo Chair in Benign Hematology**"** was established at UHN. Dr. Eric Yeo, Alexandra's widower and a longstanding clinician at UHN, was appointed Director of Benign Hematology. Several Canadian-trainees and physicians applied for the position of primary clinic physician to work with the UHN thalassemia patients. Dr. Yeo hired Dr. Richard Ward, trained in the UK under hematology programs supportive of use of deferiprone, with a special license to practice in the UHN clinic.

Dr. Ward and Yeo renamed the program "The Red Cell Disorders Program" (RCDP). From March 2009 to January 2015 (70 months), 41 UHN regularly transfused patients were switched from one of two first-line licensed iron-chelating drugs (parenteral deferoxamine or oral deferasirox) to unlicensed deferiprone, as monotherapy or combined with licensed agents.

In 2009, deferiprone was licensed in Europe only as last-resort therapy after first-line chelating agents have failed (still its status of licensing in every world jurisdiction). Simply, deferiprone is not to be introduced unless both effective first line drugs have failed. The combination of deferiprone with a second iron-chelating drug represents "off-label prescribing", a non-approved practice.

That same year Dr. Olivieri and patients submitted written concerns about widespread "switching" of patients from licensed therapy to deferiprone to the attention of Director Malcolm Moore and other UHN administrators. The UHN responded by unilateral appointment of two UK colleagues of Dr. Ward to conduct a review of the practices of prescribing deferiprone within UHN. Dr. Anne Yardumian trained, worked, and published with Apotex's key opinion leaders and has publicly defended Apotex's actions against Dr. Olivieri. The second reviewer was research nurse in sickle cell disease in a UK center. The Yardumian Report in Dec 2010 concluded that deferiprone was being administered *"in accordance with practices in the UK."* Dr. Olivieri, UHN patients and others responded that the reviewers had conflicts of interest, possessed inadequate expertise, and had not interviewed all UHN patients/staff who had requested interviews. UHN administrators and Bella Martin (UHN lawyer) defended both the prescribing practices of deferiprone at UHN, and the Report, including the unilateral choice of reviewers.

Dr. Olivieri was informed that her views had no merit. UHN Vice-President, Medical Affairs & Quality Dr. Charles Chan wrote: "the appropriateness of the clinical use of deferiprone at UHN has been exhaustively reviewed in the relatively recent past, and *has been completely validated*." Our study of UHN EMR data shows very much the opposite. Dr. Olivieri's data and conclusions are deeply rooted in science and point-of-care evidence within the UHN EMR.

FDA 2009-2011 cancelled licensing after inspection of original UHN data

In July 2009 Apotex applied for first-line deferiprone therapy market approval in the US. The FDA commissioned a formal inspection in Toronto of the trials prematurely terminated in 1996 by Apotex after Dr. Olivieri raised concerns about patient safety. The FDA inspection report provided the following key observations:[3]

(i) Data submitted by Apotex to FDA compared to original data summaries "raised a number of questions regarding Apotex's criteria for inclusion and exclusion of data … with respect to hepatic iron concentration data" [the primary endpoint of the trial]

(ii) "Specifically, Aotex's data set excluded <u>in their entirety</u> 23 of 63 treated subjects treated subjects.

(iii) "The rationale for the exclusion of the data was inconsistently applied by Apotex.

(iv) "The inspection of Dr. Olivieri's site (1) revealed discrepancies in the hepatic iron concentrations between Apotex's data listings, and the documents at Dr. Olivieri's site, and where source documentation was available, Dr. Olivieri's data appeared to be reliable; (2) Data Apotex excluded from the 24-month completer analyses may not have been appropriate for exclusion, and (3) Dr. Olivieri had documents at her site that suggested increased hepatic iron and/or hepatic fibrosis with chronic deferiprone therapy, although FDA was not able to verify the source for these values.

(v) "A meeting of the ODAC was scheduled for October 2009, to review the NDA submission for deferiprone, but this meeting was cancelled, presumably because of the significant concerns raised by DSI's inspection of study LA01.

(vi) "Given the lack of data from adequate and well-controlled clinical trials demonstrating the safety and efficacy of deferiprone, as well as serious questions raised by the FDA inspection of the Toronto study, the FDA should reject approval of deferiprone. Approval based on such inadequate data would indeed set a recklessly dangerous precedent for drugs reviewed under an accelerated approval process in the future."

Despite this public document, released in October 2011, our research study of the EMR up to 2015 shows that the administration of deferiprone to UHN patients continued to escalate.

Submissions to the FDA from UHN 2010-2011

A Freedom of Information (FOI) request revealed that from at least 2010 Apotex was providing substantial funding to the RCDP at UHN. This included unrestricted educational grants (*although name brand firms are now prevented from providing these grants, as a generic company, Apotex had no such restrictions*) and studies to demonstrate the efficacy and safety of deferiprone. For example, FOI documents reveal correspondence dating from 2010 between Apotex, Dr. Ward, and Health Canada respecting market approval of deferiprone, and requests to ApoPharma from Dr. Ward for increasing amounts of funding in 2010 and 2011.

In 2011, Ward and Yeo wrote to the FDA that they "…cannot state how strongly we support [the market approval of deferiprone at the FDA]" and "since our change in chelation practice, a number of patients across Canada have now been prescribed deferiprone" such that "40 patients, 25% of our chelated population is treated with deferiprone … a proportion in line with the rest of the world, excluding USA."

The letter by Ward and Yeo to the FDA contains substantial differences to the data in our present study:

(i) They indicated to FDA *"50% of the UHN patients were treated with a dose of 75 mg/kg/day, the remainder with up to 100 mg/kg/day" (*all international guidelines recommend not exceeding 100 mg/kg/day). Our study of the UHN EMR identifies doses exceeding 100 mg/kg/day (mean 113±1.2[range 101-127] mg/kg/day; the highest doses identified in the literature), prescribed in 54% of deferiprone treatment intervals.

(ii) They reported to FDA *"[UHN] patients complied with CBCs every 5-10 days"* (in compliance with all international guidelines and the Ferriprox (Apotex deferiprone) professional product label stating that the absolute neutrophil count must be monitored weekly*)*. Our study showed that 34% of patients had CBCs at intervals of approximately five weeks, a practice acknowledged in one patient's record as a failure of "critically important monitoring investigations"; in many records, no record of frequency was documented.

(iii) They affirmed to FDA that *"all [patients] have MRIs every 3-6 months";* we were unable to confirm this frequency of MRI monitoring.

FDA Licensing of deferiprone as last resort therapy in 2011

The FDA finally licensed deferiprone as third-line (after failure of two licensed chelators) based on a *post-hoc*, retrospective analysis of a subset of subjects enrolled in 12 previously conducted clinical trials of deferiprone varying widely in study design. In 2011, the FDA confirmed there were *"no controlled trials demonstrating a direct treatment benefit such as improvement in symptoms, functioning, or increased survival"* and demanded additional studies because *"the clinical benefit of deferiprone [must be verified*]" [Subpart H--Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses Sec. 314.510].

Health Canada licensed of deferiprone for use after failure of licensed chelation therapy

In February 2015, Health Canada issued market approval for deferiprone "when current chelation therapy is inadequate", "based primarily on a critical assessment of the Canadian data package."

Since the UHN is the largest chelation clinic in Canada, we asked UHN to compare our results to the "Canadian data package". We received no information. Although in Canada deferiprone "can be dispensed only to patients who … meet all conditions [including failure of current chelation therapy]," following market approval many additional patients were removed from first-line chelation therapy and prescribed deferiprone.

Our study revealed widespread prescribing of deferiprone at UHN

From our study of the EMR over 70 months (March 2009 to January 2015), deferiprone was prescribed to 41 patients with thalassemia major, representing 43% of locally transfused patients. Regimens were frequently altered in response to toxicities and/or ineffectiveness, so in order to avoid erroneous attribution of effectiveness we examined *intervals of chelating therapy* with one drug or drug combination bracketed by initial and final liver iron concentrations, cardiac T2* (estimate of cardiac iron) or both. We identified 70 intervals of deferiprone monotherapy in 41 patients and 62 intervals of deferasirox monotherapy in 56 patients (manuscript under review).

In 2017 we approached CEO Pisters, Dr. Chan and Dr. Wouters about our concerns that our study of the UHN EMR suggested patients were at risk:

(a) Liver enzymes rose in 65% deferiprone exposed patients, persisting in many over years. Mean elevation of ALT over baseline was 8 fold [range 2–24]. Often therapy was not altered in response to this toxicity. Many patients were continued for years on deferiprone despite large ALT elevations. Elevations were often confirmed by challenge and re-challenge with deferiprone.

(b) New diabetes developed after years of liver iron elevation in 6/36 (17%) originally non-diabetic patients. Several of these were continued on deferiprone despite elevations of liver iron exceeding 40 mg/g over years. In the modern era of chelation with effective drugs, the incidence of new diabetes in thalassemia is reported between 0.8–3%.

(c) Mean liver iron rose to >15 mg/g, the threshold for cardiac disease and early death; elevations >15 mg/g were observed in 50% of patients.

(d) No improvements were noted in estimates of cardiac iron in patients in whom liver iron remained high.

Six years of prescription of an unlicensed drug to one-third of patients in UHN, while serious sustained toxicities were recorded without resumption of licensed therapy, suggests a need for review of standards of clinical practice, protection of patient safety, processes of patient consent, and other ethical and administrative issues at the UHN Canada's largest research institute.

UHN refuses access to the Deferiprone "Data Package" provided to Health Canada

In 2015 deferiprone was licensed (last resort) at Health Canada "on the basis of the Canadian Data Package." Dr. Olivieri requested this package through Freedom of Information (FOI) in 2015 from Health Canada and UHN. Based on *Doshi vs Health Canada* 2018, legal means may be required. The most recent reply to Dr. Olivieri's FOI application to the UHN was that the six years of exposure to deferiprone was under the auspices of a clinical trial (clinical trial data are protected from scrutiny under the FOI laws). This response falls directly to the Research Ethics Board area of management and responsibility. Some EMR records indicate deferiprone was released under the Special Access Program (SAP) of Health Canada; patients cannot be simultaneously treated through SAP and on a research study or clinical trial. We cannot find any deferiprone trial registration, as required by Canadian law.

Obstruction of ongoing thalassemia research at UHN

The UHN REB approved in 2017 a study by Drs. John Dick and Nancy Olivieri that builds on 30 years of fetal hemoglobin research, largely from clinical observations of Sir David Weatherall, Dr. Olivieri and others. Dr. Richard Ward has prevented this from going forward, indicating that Dr. Olivieri is not in the "circle of care." However, those in the circle

of care are in fact *less* well placed to consent patients than are those outside the circle of care. Meetings of Drs. Dick, Olivieri and Gallie with UHN administrators have failed to resolve this problem and important high-level REB approved research continues to be blocked.

A pattern of intimidation and marginalization of Dr. Olivieri and her research team began in 2009 after the establishment of the UHN Red Cell Disorders Program. Negative aspersions about the research conducted by Dr. Olivieri and her character are well documented. There are examples of coercion of patients including threats of withdrawal of care if they enrolled in Dr. Olivieri's research studies. This culminated with Olivieri's long-employed Clinical Research Officer quitting abruptly in 2010. All this is extensively documented and can be independently corroborated. The UHN past administrators have addressed none of these concerns, which have all been brought to their attention.

The disregard and dismissal of Dr. Olivieri's expertise and deep knowledge of iron chelation and Thalassemia by the previous UHN administrators is sadly misplaced and harmful to the patients who rely on the UHN stated values "Our Primary Value and above all else, the needs of patients come first; Values are Safety, Compassion, Teamwork, Integrity, Stewardship".

Thank you for reviewing these issues. We provide details to facilitate a productive discussion of "What next?" We hope that you agree that there are multiple complex issues that will have a major impact on UHN and indeed the world, when they are public.

We offer to discuss how we can help the UHN manage these circumstances in the best way to achieve the UHN patient safety, quality care and research rigor, for which we would all like to be proud. We have constructive ideas that could mitigate the inevitable negative outcomes identified by our excellent UHN research into patient safety.

Sincerely yours,

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1 Thompson, J., Baird, P. & Downie, J. The Olivieri Report: the complete text of the report of the committee of inquiry commissioned by the Canadian Association of University Teachers., (James Lorimer & Co., 2001).

2 Olivieri, N. F. *et al.* Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. *N Engl J Med* **339**, 417-423 (1998).

3 Carome, M. & Wolfe, S. M. *Letter to FDA Opposing Approval of Deferiprone*, <https://www.citizen.org/our-work/health-and-safety/letter-fda-opposing-approval-deferiprone> (2011).