23 April 2019
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Mr. Brian Porter,
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Dear Dr. Smith and Mr. Porter:

We write further to our letter of 9 April 2019, which we believe that Dr. Baker has shared with Dr. Smith. That letter was written to follow up on communications about the Inquiry coordinated by Dr. Baker about patient safety in the Thalassemia Program at UHN. We write this letter to emphasize again that Dr. Baker's Inquiry into patient care, while critical, is not sufficient. We write to urge the implementation of a parallel Inquiry, to investigate potential violations of ethical and legal standards in the Thalassemia Program at the UHN. Unlicensed deferiprone was prescribed over six years in more than 40% of locally-transfused patients at UHN while those in administrative authority were fully informed and took no effective action. Arising from this fact, there are a number of serious and potentially ongoing legal and ethical considerations, many of which we outline below:

1. Under what authority was deferiprone prescribed as an unlicensed drug for six years at UHN?

Drs. Richard Ward and Kevin Kuo reported in *Blood,*[1] the Journal of the American Society of Hematology, that deferiprone was administered under a program of research "approved by the REB of the UHN." The same year,[2] Drs. Ward and Erik Yeo made an identical claim in a submission to the US Food and Drug Administration. Supporting this claim, as you are now aware, is the testimony of Mr. Ronald Ward (Manager of Privacy Operations and Freedom of Information Coordinator, UHN) who in response to FOI applications dating back to 2016, testified to the Privacy Commissioner that Drs. Ward, Kuo, Yeo, and others were conducting "research" in deferiprone at UHN and, therefore, that the information requested was sheltered from scrutiny under FOI. Contradicting this claim is the failure of UHN to provide the clinical trial registration number corresponding to the alleged research study (as required by law, and despite our repeated requests) as well as the evidence identified in the patient EMRs which indicate (and in some cases, explicitly state) that deferiprone was prescribed at UHN under Health Canada's "Special Access Program (SAP)".[3] Which was it? Why have UHN physicians and staff said that it was provided through a research program yet the only available evidence indicates that deferiprone was provided through the SAP? Why have the former Head of the UHN REB (Dr. F.J. Holland), Mr. Ward, Dr Bradley Wouters and several others in authority repeatedly declined to clarify the issue of authority and refused to supply evidence in support of their clarification? If deferiprone was prescribed through a research program, there should be REB applications and approvals and renewals as well as adverse event reports etc. If it was prescribed through SAP, there should be Form A's for every patient for every time a request was made for the drug and for every renewal as well as reports on all adverse events.

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[1] Miscevic F, Kuo K, Ward R. Single centre, North American experience with compassionate use of deferiprone in patients with beta-thalassemia major. Blood. 2011; 118:3185a

[2] Ward R, Yeo E. Letter to FDA in support of Ferriprox®, New Drug Application 021825 http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM271676.pdf2011.

[3] The SAP is a program under which the treating physician must confirm "*conventional therapies have failed, or are unsuitable or unavailable*", which provides access to a drug which should "*be limited in duration and quantity to meet emergency needs only.*"

3. Were patients fully informed when switched from licensed therapies to deferiprone? And what were they told about unforeseen risks that became apparent during the years of patients being on deferiprone and about any ways in which they themselves were harmed?

Many of the UHN patients switched from first line therapy to deferiprone suffered serious harms.

Did the patients switched to deferiprone understand that they were being switched from treatment (deferiprone and deferasirox) whose safety and efficacy had been established and licensed by regulators, including Health Canada, to an unlicensed drug (deferiprone)? How were the medical outcomes (sustained elevations in liver iron concentration to levels associated with premature death, new diabetes mellitus, liver dysfunction) explained to patients and families treated with deferiprone? How was the death of a young mother (*a patient who had expressed a desire to continue standard licensed therapy, but who was prescribed deferiprone instead*) explained to her family and children? What did these patients understand about the literature (*discussed in PLoS 2019*) about the published effectiveness of reduction of liver or heart iron during deferiprone monotherapy? Were patients informed in particular that all regulatory agencies mandate weekly monitoring for deferiprone-induced agranulocytosis and that less monitoring has led to many deaths? Was the patient repeatedly exposed to deferiprone after developing life-threatening agranulocytosis informed that such re-exposure is contra-indicated?

4. What safety monitoring was done (as required by TCPS is being prescribed under a research program)?

If deferiprone was prescribed under a research program, the researchers had an obligation to monitor the safety of the research participants. Was this done consistent with the TCPS?

5. Were findings of the results (including but not limited to adverse events) experienced by UHN patients during deferiprone exposure reported to regulatory agencies, as required by law?

a) Health Canada licensing

Deferiprone was licensed "primarily on the basis of the Canadian data package" comprising the results of deferiprone exposure of UHN patients from 2009 to 2015 and submitted to Health Canada by Drs. Ward and other UHN physicians who, with Apotex, had switched these patients to deferiprone over those six years. Since 2015, we have requested this "Canadian data package" and UHN has declined to provide it. This is despite the requirement, under Health Canada's Special Access Program, that a "practitioner" (in this case, Drs. Ward, Yeo, Kuo and others) is required to maintain all records for a period of 25 years "in a manner that permits rapid retrieval if necessary." That such retrieval is indeed necessary cannot now be disputed. We identified a high frequency of severe adverse events which do not appear to have been reported to Health Canada, either at the time of observation, or at all: Health Canada's website reveals that up to 2016, exactly 19 severe adverse events (SAES) were reported (two were reported in the remote past, prior to 2009) in patients receiving deferiprone. Of the 17 SAEs reported in the relevant period (that is, after 2009), 15 were reported <u>*after*</u> the licensing of deferiprone in February 2015. As you may know, it is the responsibility of any prescribing physician(s) to confirm that all relevant information (including effectiveness, adverse events and deaths) is truthfully submitted before market approval.

b) US FDA

(i) Drs. Richard Ward and Erik Yeo wrote to the US FDA wherein they stated they "…cannot state how strongly we support [the approval of deferiprone] at the FDA" [footnote 2] and in which included a report of findings in UHN patients that appears to be substantially different from the data we obtained in the UHN EMRs, including with respect to: deferiprone dosing, CBC monitoring, frequency of MRI monitoring, and adverse effects developing during deferiprone exposure. In particular, in their letter to the FDA, Drs. Ward and Yeo reported that:

(ii) "50% of the UHN patients were treated with a dose of 75 mg/kg/day, the remainder with up to 100 mg/kg/day."[4] Our study identified doses exceeding 100 mg/kg/day (mean 113±1.2 [101-127] mg/kg/day) in 54% of deferiprone treatment intervals. The deferiprone doses prescribed by Drs. Ward and Yeo are the highest we could identify in the published literature; we could identify no other study in which doses > 105 mg/kg/day were prescribed for extended periods.

(iii) "[UHN] patients complied with CBCs every 5-10 days."[5] However, our study identified that CBCs in 34% of UHN patients had been monitored at approximately five week-intervals, a practice acknowledged (not by Drs. Yeo or Ward) in one patient's record as a failure of "critically important monitoring investigations". In many other records, no record of frequency and no CBC results could be documented.

(iv) "all [patients] have MRIs every 3-6 months". We were unable to confirm this frequency of MRI monitoring. Many patients underwent MRI monitoring (of critical liver as well as heart iron) at more than 12-month intervals, and in several others, MRI monitoring of liver or heart was obtained at more than 24-month intervals.

(v) "four patients had an asymptomatic transient increase in ALT, which settled spontaneously, or with transient interruption of deferiprone." However, our study identified ALT elevations in 26 / 40 evaluable (65%) patients with mean peak elevations (8.4-fold) recorded after 15 months (these increases, therefore, were not "transient"). Although the FDA monograph states that practitioners should "consider interruption of therapy if there is a persistent increase in the serum transaminase levels," deferiprone was continued in 21 of the 26 patients in whom ALT increased; in 16 of the 21, serum ALT, after 49±6 months of exposure, remained elevated at 5-fold over baseline. In 10 patients, challenge, de-challenge, and re-challenge with deferiprone confirmed the relationship of ALT elevation to the drug.

c) Health Canada Special Access Program

If deferiprone was being prescribed under the authority of the Special Access Program (as indicated in many of the EMRs), the prescribing physicians have significant obligations re: reporting to Health Canada. As noted above, we identified a high frequency of severe adverse events which do not appear to have been reported to Health Canada, either at the time of observation, or at all: Health Canada's website reveals that up to 2016, of the 17 SAEs reported in the relevant period (that is, after 2009), 15 were reported after the licensing of deferiprone in 2015. Practitioners providing drugs through the SAP must make attestations, one of which includes the agreement to provide "a report on the results of the use of the drug including information on Adverse Drug Reactions." If prescribed under SAP, were these reporting obligations met?

d) UHN REB

If deferiprone was being prescribed under a research program, the researchers have significant reporting obligations to the REB. The adverse events noted above would have had to be reported to the REB. If prescribed under a research program, was that done?

6. How was the practice of switching patients from licensed therapies to unlicensed deferiprone at UHN permitted to develop?

[4] All international guidelines recommend deferiprone doses do not exceed 100 mg/kg/day.

[5] in compliance with all international guidelines including the FDA monograph and the professional product label stating that absolute neutrophil counts must be monitored weekly.

a) Background of deferiprone in Toronto

As outlined previously, Olivieri and coworkers reported in 1996 that liver iron concentration, the only parameter correlated with body iron burden, was inadequately controlled in nearly 40% of deferiprone-exposed patients; Apotex abruptly and prematurely terminated the trials threatening "all legal remedies" against Dr. Olivieri and against publication. The ensuing ethical controversy generated great public interest.

b) Removal of expert care from UHN thalassemia patients in 2009

In 2009, Dr. Olivieri was informed that "corporate UHN thinks you're trouble." Dr. Malcolm Moore (Former Director, Medical Oncology & Hematology) removed her as Program Director (offering her inducement of money to accept this dismissal which Dr. Olivieri refused). Dr. Olivieri was then embroiled in ongoing -- ultimately, successful -- lawsuits against Apotex and Random House, and could not afford to continue to fight dismissal by UHN. Contemporaneously, in 2009, "The Alexandra Yeo Chair in Benign Hematology" was established at UHN; Dr. Erik Yeo (Alexandra's widower) was appointed UHN's Director of Benign Hematology. Canadian-trained physicians applied for the position of clinic physician. Dr. Yeo hired Dr. Richard Ward over these applicants. Dr. Richard Ward was a UK citizen and in 2009, a trainee, who had previously worked under UK physicians supportive of deferiprone. Lacking Canadian training or a Canadian fellowship, Dr. Ward was awarded by UHN a "special license" to practice in Canada.[6] Beginning in 2009, an effective program of intimidation and marginalization of Dr. Olivieri and her research team was well documented. There are documented examples of coercion of patients, include threats of withdrawal of care if patients chose to enrol in Dr. Olivieri's research studies. The bullying, discrimination and harassment culminated in Dr. Olivieri's long employed Clinical Research Officer quitting abruptly in 2010. This situation was known and reported to the responsible authorities at UHN. No actions were taken.

c) Notification of UHN administrators and lawyers about deferiprone use at UHN

Ten years prior to our paper reaching the press, in 2009 the UHN Administration commissioned a "Report" from Dr. Anne Yardumian a former UK colleague of Dr. Ward. Dr. Yardumian had trained, worked and published with Apotex' key opinion leaders, and publicly defended Apotex' actions against Dr. Olivieri. Dr. Yardumian approved the use of deferiprone at UHN. The Yardumian Report, which was relied upon in subsequent communications to Dr. Olivieri,[7] became central to the continuing use of deferiprone at UHN over the next five years.

d) Formal inspection of Dr. Olivieri's UHN data (July 2009) by the US FDA Division of Scientific Investigations' leads to FDA's cancellation of deferiprone approval (September 2009)

UHN was informed in late 2009 that the FDA had cancelled Apotex' application for market approval of deferiprone after a formal inspection by its Division of Scientific Investigations (DSI) of Dr. Olivieri's data (arising from the original trials in patients at UHN and The Hospital for Sick Children) which was sparked by Apotex' incorrect allegations about Dr. Olivieri. In July 2009, DSI identified inconsistencies between data in Dr. Olivieri's original case report forms, and the data which Apotex had submitted to the FDA in UHN patients. In

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[6] This was identical to the same license provided by The Hospital for Sick Children in the 1980s to Dr. Gideon Koren; see: https://www.thestar.com/news/investigations/2019/02/26/study-co-authored-by-gideon-koren-retracted-as-journals-continue-review-of-disgraced-doctors-published-works.html

[7] For example, Dr. Charles Chan (Vice-President, Medical Affairs & Quality Care at UHN) wrote (*inter alia*) to Dr. Olivieri in 2012: "*the appropriateness of the clinical use of deferiprone at UHN has been exhaustively reviewed in the relatively recent past and has been completely validated*." Dr. Chan has since "retired" from UHN.

September 2009, FDA cancelled the scheduled meeting to review Apotex' submission for licensing of deferiprone "because of the significant concerns raised by the inspection," including these key observations:

(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, Apotex's data set excluded in their entirety 23 of 63 treated subjects treated subjects."

(iii) "The rationale for exclusion of 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.

As noted by the most prominent Health Research organization in the USA, "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."[8]

Despite the public availability of these documents, prescribing of deferiprone continued to escalate at UHN up to 2015, as our PLoS 2019 paper indicates.

7. How were conflicts of interest for UHN, Dr. Ward and Dr. Yeo managed by UHN?

While launching new lawsuits against Dr. Olivieri from 2008, Apotex was in 2010 providing substantial funding to the thalassemia program at UHN. In addition, a donation of between "$1 million and $5 million" by Barry Sherman (the now-deceased CEO of Apotex) to UHN is recorded. Funding from Apotex to UHN included unrestricted educational grants (*although name brand firms are now prevented from providing these grants, as a generic company, Apotex had no such restrictions*). Although then-UHN Director of Research Dr. Christopher Paige denied the provision of Apotex funding in December 2011, this has since been confirmed in documents obtained through Freedom of Information, which also revealed correspondence between Apotex and Dr. Ward about obtaining market approval of deferiprone at Health Canada, as well as requests to Apotex from Dr. Ward for increasing amounts of funding.[9]

8. When will the UHN stop the ongoing obstructions to thalassemia research at UHN ?

An REB-approved study by Drs. John Dick and Nancy Olivieri, which builds on 30 years of fetal hemoglobin research, has been prevented from going forward because Dr. Ward does not want it to go forward. Dr. Ward has

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[8] Wolfe S, Carome M. Public Citizen Letter to FDA Opposing Approval of Deferiprone 2011. (Health Research Publication #1973). https://wwwcitizenorg/hrg1973.

[9] The Royal College of Physicians of Canada notes that such conflicts of interest are problematic: "Institutions may receive industry funding for an important part of their activities. They may be financially dependent on these sponsors for funding some aspects of the health care they provide, social activities for patients and staff, academic chairs and/or research or educational activities. Decisions about which drugs to prescribe, research priorities, allocation of research space, assigning research mandates, promoting specific research agendas, and providing priority access to patients within a health care institution, could be (or could be perceived to be) influenced by these financial interests. An institutional COI can also exist when a company or individual donates a significant amount of money to an institution, and when research or decisions within the institution may affect the financial interests of that company or individual. The concern would be that the institution has an interest in keeping the donor satisfied and happy."

tried to prevent it by stating that Dr. Olivieri is not in the "circle of care." As the TCPS emphasizes, individuals 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, including Dr. Wouters and Dr. Oza, have failed to resolve this problem. Important REB approved research continues to be blocked. The academic freedom of Drs. Olivieri and Dick continues to be violated.

9. Conclusion

As we stated in our recent article on this situation "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."

For the reasons set out above, we ask that you commission an independent expert review of the legal and ethical aspects of the situation brought to light most recently and publicly in our paper. Dr. Baker's review is necessary but not sufficient as it is focused on the clinical aspects of this situation. The legal and ethical review must be independent, because of the apparent conflicts of interest at the institutional level, and because some of the legal and ethical concerns relate to steps taken (or not) by the very people you appear to have named to the internal review committee. It must be expert, because significant legal and ethical concerns have been raised, and experts in health law and research ethics are needed to assess what happened and make recommendations about how to respond. We believe that it is essential to meet the UHN's legal and ethical responsibilities to the patients who were switched to deferiprone, the patients who are being prescribed it now and may be provided with it in the future, UHN patients more generally, UHN physicians and staff, Health Canada, and the public.

We also understand that it is essential to restore confidence in the UHN leadership by demonstrating a commitment to transparency and accountability in the interests of those we serve.

Yours sincerely,

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