2 December 2019
Dr. Kevin Smith
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Dear Dr. Hodges and Dr. Smith

Re: **The Odame Review**: "Review of chelation therapy practice in the red cell disorders program at UHN")

We reply to your email of November 18, 2019 (**attached** as a PDF). We raised several issues including in our letters 23 October 2019 and 11 November 2019 related to **The Odame Review** which you sent us September 30, 2019.

1. You wrote:

"Dr. Michael Baker, with your support, led the review, in collaboration with Dr. Isaac Odame, who has the necessary credentials and expertise in the treatment of hematological disorders including thalassemia to serve as a reviewer."

This is incorrect. Stating that Michael Baker *"was supported by us"* does not acknowledge that at the January 2019 meeting before the February 2019 publication of our PLoS paper, Dr. Smith assured us that a Review to address the switching of UHN patients from first-line treatment to unlicensed deferiprone between 2009 and 2015,which led to harms published in PLoS, would be conducted by at least one, possibly two, *additional external experts* who would support Dr. Michael Baker.

Dr. Baker is a self-admitted non-expert in thalassemia. At the January 2019 meeting, Dr. Baker requested an external expert be appointed to assist in this Review. Dr. Smith agreed and added that the additional reviewer(s) would objectively be determined to have no conflicts of interest, adequate expertise in the treatment of thalassemia and iron-chelating therapy, and be ***approved by both parties***; that is (i) the physicians responsible for exposing UHN patients to unlicensed deferiprone over six years including Dr. Richard Ward and others; and (ii) Drs Gallie and Olivieri, who uncovered this unlicensed exposure and published its outcomes in PLoS.

"Nothing will be done without mutual consent" was how Dr. Smith phrased his promise.

Subsequent written correspondence was exchanged to select individual(s) without personal or professional conflicts of interest. Dr. Ward suggested several Apotex consultants to review his conduct, including a physician whose US clinic had hired a full-time Apotex employee to advise on patient care and a longstanding Apotex consultant who holds a patent for the (unproven) "cardiac protective effect" of deferiprone (this conflict of interest was undisclosed by Dr. Ward). The individuals suggested by Dr. Ward would be unsuitable to participate in an unbiased review according to Dr. Smith's stated terms, since they had financial conflicts of interest, lack of experience and knowledge, personal allegiances to Dr. Ward, and/or personal and professional alliances with Apotex. Our suggestion of two non-

conflicted, expert individuals external to Toronto (one from UK, one from US) were rejected by Dr. Ward; UHN executives agreed to their elimination.[1] See our letter to you (**Olivieri/Gallie to Baker Reviewers March 5 2019)**.

Without our knowledge, UHN unilaterally and secretly selected Dr. Isaac Odame to "assist" Dr. Baker. It would be difficult to identify an individual with more conflicts of interest in this matter than Dr. Odame. Dr. Odame has close personal and professional relationships with Dr. Ward, although information about their relationships was expunged in the version of Dr. Odame's CV provided as the "official" one to accompany his Review. Other versions of his CV document show that *inter alia*, Dr. Odame is Dr. Richard Ward's supervisor and mentor, "meets regularly with" Dr. Ward, regularly "provides career advice" to Dr. Ward, supervised Dr. Ward's research dissertation, and co-authored a publication with Dr. Ward months before undertaking the Review under discussion. Dr. Odame has also accepted funding from Apotex.

Neither Dr. Odame nor Dr. Baker are experts in iron-chelating therapy (your claim that Dr. Odame "has the necessary credentials and expertise in the treatment of hematological disorders including thalassemia to serve as a reviewer" is incorrect, by objective criteria including Dr Odame's own CV.[2]

Finally, Dr. Odame and Dr. Baker are both internal reviewers, not external as promised January 2019 by Dr. Smith.

Some of this information was conveyed to you in the letter **Olivieri/Gallie to Baker 20 August 2019.**

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[1] Dr. Ward raised at least two objections against one of our suggested reviewers: i) the proposed reviewer is a pediatrician. Dr. Isaac Odame is a pediatrician. Why was our suggested reviewer (with no allegiance to Dr. Ward) rejected because he is a pediatrician, while Dr. Odame (a pediatrician with allegiances to Dr. Ward) was acceptable as a reviewer?

2 A second objection raised by Dr. Ward regarding our suggested reviewer is that "[he] does not work in the thalassemia field" along with the insight that "sickle cell is a very different disease from thalassemia." But there is no evidence that Dr. Odame "works in the thalassemia field." Dr. Odame's CV reveals exactly two publications relevant to thalassemia: one published seven years ago (in which Dr. Odame was fourth author of ten), and a second published six years ago (in which Dr. Odame was ninth author of 13). Dr. Odame's expertise is in sickle cell disease. If UHN sought a non-conflicted opinion, why was Dr. Ward empowered to choose who would review his management of the patients?

2. You wrote:

"The conclusion of the quality of care review has been that the prescribing practices and documentation on behalf of patients receiving *compassionate use* of deferiprone from 2009-2015 were justified; with respect to present prescribing practice, the conclusion of the review is that such practices in place at UHN today meet the standard of care."

This statement contradicts information that was previously provided by Dr. Ward, other UHN physicians, and UHN Administrators. Drs. Ward and Kevin Kuo reported in *Blood*[3] (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, Drs. Ward and Erik Yeo made a similar claim in a submission to the US Food and Drug Administration.[4] Furthermore, in response to Freedom of Information (FOI) applications, Mr. Ronald Ward (Manager of Privacy Operations and Freedom of Information Coordinator at UHN) testified to the Privacy Commissioner that Dr. Ward and others had been conducting "research" on deferiprone at UHN and, therefore, all information requested was sheltered from scrutiny under FOI.

Yet now, you indicate that deferiprone was provided under "compassionate use." Why then had UHN informed the Privacy Commissioner that deferiprone was supplied to patients at UHN within a research study? That this unlicensed drug was provided to 71 UHN patients under Special Access -- a program under which the treating physician must confirm "*conventional therapies have failed, or are unsuitable or unavailable",* to provide access which should "*be limited in duration and quantity to meet emergency needs only"* -- raises the concern as to whether Health Canada was fully informed as to the legitimacy of 71 applications. Further, if deferiprone was supplied as "compassionate use." Dr Ward's submissions to an international scientific meeting and to the FDA may have been incorrect.[5] Binding *et al* published in August 2019, also confirmed that deferiprone was supplied under compassionate use.

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[3]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

4 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.

5 The CPSO declares as an act of professional misconduct (clause 51 (1) (c) of the Health Professions Procedural Code: "Signing or issuing, in the member's professional capacity, a document that the member knows or ought to know is false or misleading."

3. You wrote:

"The Hospital has ensured safe and effective care was and is in place and our review is now complete."

The Hospital has done nothing to ensure "safe and effective care" for these patients. "Safe and effective care" ***informs patients each of whom has a right to autonomy in care*.** Many of the UHN patients switched from first line therapy to deferiprone suffered serious harms, published in our PLos paper. We ask:

How was Dr. Odame able to determine that the 71 patients switched to deferiprone understood that they were being switched from treatment(s) whose safety and efficacy had been established, licensed as first line therapy by Health Canada, to an *unlicensed* drug?

How did Dr. Odame determine how the unfavorable medical outcomes (sustained elevations in liver iron concentration to levels associated with premature death, new diabetes mellitus, liver dysfunction) that developed during deferiprone were explained to these patients?

How did Dr. Odame determine how the death of a young mother (a patient whose UHN EMR documents that she had expressed a desire to continue standard licensed therapy, but was instead prescribed deferiprone) was explained to her family and children?

How did Dr. Odame determine what these patients were told about the effectiveness of deferiprone *monotherapy*?

How did Dr. Odame determine that patients were informed that (all) regulatory agencies mandate *weekly* monitoring for deferiprone-induced agranulocytosis, and that the less frequent monitoring practiced regularly at UHN placed them at heightened risk?

Why did Dr. Odame determine that re-exposure to deferiprone in a patient who had developed life-threatening agranulocytosis after the first and second exposures -- re-exposure that is contra-indicated -- represented "safe and effective" care?

How did Dr. Odame determine whether safety monitoring of patients exposed to unlicensed deferiprone was consistent with the TCPS?

How did Dr. Odame determine whether, and when, the results including but not limited to severe adverse events experienced during deferiprone were reported to regulatory agencies as required by law?[6]

How did Dr. Odame determine that in all 71 patients – under the program of "compassionate use" you

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[6] We identified a high frequency of severe adverse events which were not 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 after 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. The CPSO declares the following as an act of professional misconduct for the purposes of clause 51 (1) (c) of the Health Professions Procedural Code: "Making a misrepresentation respecting a remedy, treatment or device."

now acknowledge as the mechanism through which deferiprone was provided at UHN from 2009-2015 – "conventional therapies have failed, or are unsuitable or unavailable"?[7]

Although UHN patients' records indicate that deferiprone was released under Special Access, in this group of patients we "could identify no explanation for a proposed switch to deferiprone that was supported by evidence of failure of licensed therapy prescribed as recommended[8]; indeed, many patients appear to have been switched to deferiprone despite optimal responses, or improvements during treatment with first-line therapies: We could was no evidence that the UHN patients switched to deferiprone met Health Canada's eligibility criteria under its Special Access Program. Deferiprone is licensed only as a "last resort" therapy. Its use in 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.[9]

How could Dr. Odame have identified the robustness of Health Canada's eligibility criteria of each patient switched to deferoxamine under the Special Access Program in the short period in which Dr. Odame was allegedly to have examined 71 EMRs? In years of searching the same EMRs, we were unable to identify confirmation of these eligibility criteria.

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] which included a report of findings in UHN patients. Their report is substantially different from the data we obtained in the UHN EMRs, with respect to: deferiprone dosing, CBC monitoring, frequency of MRI monitoring, and adverse effects developing during deferiprone exposure. These are the SAME patients which the PLoS paper reported.[10]

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[7] Under the rules of the SAP, the treating physician must confirm to Health Canada that "conventional therapies have failed, or are unsuitable or unavailable". Deferiprone was prescribed to 41 study patients between 2009 and 2015. We could identify in the EMR 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 six 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. The CPSO declares the following as an act of professional misconduct for the purposes of clause 51 (1) (c) of the Health Professions Procedural Code: "Signing or issuing, in the member's professional capacity, a document that the member knows or ought to know is false or misleading." "

8 PLoS P. 12

9 The CPSO declares as an act of professional misconduct (clause 51 (1) (c) of the Health Professions Procedural Code: "Making a misrepresentation respecting a remedy, treatment or device."

10The CPSO states that for the purposes of clause 51 (1) (c) of the Health Professions Procedural Code: "Making a misrepresentation respecting a remedy, treatment or device" is an act of professional misconduct

How were these incongruities resolved by Dr. Odame?

Over the six years (2009-2015) that deferiprone was prescribed to half of locally-transfused UHN patients, it was unlicensed. Practitioners are not free to supply *unlicensed* drugs without informed consent. From the UHN EMR notes that we examined, many patients did not appear to understand that deferiprone was not a licensed drug.[11]

"Safe and effective care" must be *free from conflicts of interest*. You are aware that while Barry Sherman was launching new lawsuits against Dr. Olivieri from 2008 to 2010, he was providing substantial funding to UHN's thalassemia program. Funding from Sherman to UHN included unrestricted educational grants; *although name brand firms are now prevented from providing these grants, as a generic company, Sherman had no such restrictions*. A direct donation of between "$1 million and $5 million" to UHN from Sherman is also recorded. Although then-UHN Director of Research Dr. Christopher Paige denied in 2011 that UHN was supplied with money from Apotex, the Apotex funding was confirmed through a Freedom of Information search which also revealed correspondence between Apotex and Dr. Ward about obtaining market approval of deferiprone at Health Canada and requests to Apotex from Dr. Ward for increasing funding.[12] How did Dr Odame determine that conflicts of interest for UHN, Dr. Ward and Dr. Yeo were appropriately managed by UHN?[13]

4. You wrote:

"With respect to findings flowing from the review and how they differ from your own research, you will recall that the purpose of this review was to assure that safe and high quality care for patients was and is being delivered. We have confirmed that is the case and have now completed and closed this important process."

Our 2019 PLoS paper was not a prospective study but a retrospective review of all data contained in 41 charts of patients exposed to unlicensed deferiprone from 2009 to 2015. We reviewed the UHN EMR data over six years. Dr. Odame was charged with reviewing these in a day. How can his conclusions

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[11] The CPSO states that for the purposes of clause 51 (1) (c) of the Health Professions Procedural Code: "Making a misrepresentation respecting a remedy, treatment or device" is an act of professional misconduct."

[12] 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."

[13] The CPSO states that for the purposes of clause 51 (1) (c) of the Health Professions Procedural Code: *"Having a conflict of interest"* is an act of professional misconduct.

arise from the same data? On 10 June 2019 we provided documents that were important for the Review as proposed by Dr. Smith January 2019, with details of the 41 patients who consented to our study of their EMR, who from 2009 to 2015 had been switched by Dr. Ward, et al. from licensed therapies to then-unlicensed deferiprone, including:

- Summaries of relevant medical histories and laboratory testing;
- A separate folder titled "Liver Enzyme Changes on Deferiprone";
- A binder containing the files: "CBC monitoring during deferiprone"; "Non-liver complications during deferiprone" and "Transfusion alterations during deferiprone";
- A summary sheet of all the data contained in our PLoS paper.

Did Dr. Odame and Dr. Baker examine these data?

These detailed values on 41 patients clearly point to significant harms to patients under the care of Dr. Ward. All these data reported in PLoS was collected long before the conflicted review was initiated. The files examined by Dr. Odame in his secret review would have been the data reported in PLoS data (unless these data were altered in some way) which we extracted directly from the UHN EMR from 2009 to 2015.

5. You wrote:

"We understand you have separately raised issues of academic integrity and these will be addressed by another well designed process, of which we will fully participate."

For the purposes of CPSO referrals of doctors involved in this matter, or a complaint of research misconduct to the University or other bodies, participation of the UHN will be demanded by the investigating bodies, not by us.

6. You wrote:

"We hope you'll appreciate that with respect to the remainder of your questions that pertain to the process of the review and/or conclusions reached, including your request for the names of all patients whose records were examined, as well as rough and formal notes recorded by Drs. Odame and Baker during their investigation, that such information is either confidential patient health information, or is subject to quality assurance privilege, or both and as such we are unable to share that with you".

We appreciate the importance of confidential patient information. We hope that you'll recall that previously considerable efforts were exerted by you, Mr. Topping and others to induce us to provide you with the names of our 41 consented patients to examine their records claiming there was "no legal impediment" to doing so. On what basis do you now refuse us access to this information in these same 41 patients? To be clear, we are not asking for their records (which we can access under our REB-approved study). We are requesting the notes recorded by Drs. Odame and Baker during their purported investigation. It is not clear on what basis you are claiming that these data are protected under "confidential patient health information."

Finally, we ask:

1. What was the role of Dr. Baker in the Review process?
2. Were there other files provided to Dr Odame that were not in the EMR? If so who/what provided these files and how was their authenticity confirmed?

It is dismaying is that you continue to refuse to provide us with any details of this Review.

We can only assume, as we describe here, that an adequate Review has not taken place.

The UHN has not yet acted consistent with its responsibilities to oversee the safety of patients.

Yours sincerely,

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