Appendix A

(1) Schafer letter of inquiry to Drs. Kevin Smith and Brian Hodge

July 4, 2019

Dr. Kevin Smith

President & CEO, University Health Network

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Dr. Brian D. Hodges

EVP and Chief Medical Officer

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Dear Drs. Smith and Hodges:

I am doing research on some of the ethical issues arising from the PloS One paper published this past February by Drs. Nancy Olivieri, Amir Sabouhanian and Brenda Gallie. You will doubtless be familiar with the troubling health outcomes identified in this paper since the reported findings deal with patients treated in the UHN thalassemia programme.

I write to clarify some points arising out of this publication (which details the exposure of 41 UHN patients to then-unlicensed deferiprone after they were switched from first line drugs). According to PloS, a lack of long term

effectiveness was observed with several patients sustaining complications and one death.[1]

As you know, from 2009-2015 two licensed drugs were available for the treatment of iron overload, while deferiprone remained unlicensed in Canada. In the jurisdictions in which deferiprone has been licensed, I understand that it has been licensed only as "last-resort" therapy (to be prescribed only when first line therapies have failed). PloS states (and I confirmed after perusing the Health Canada website) that in February 2015, deferiprone was also licensed only as "last-resort" therapy based primarily upon "the Canadian data package" (presumably derived from Canada's largest thalassemia clinic, viz., the UHN clinic.)

My questions for you are related to the above general background. I will be grateful for answers and guidance:

I. Under what mechanism was deferiprone prescribed as an unlicensed drug for six years at UHN? According to the PloS paper, from 2009 to 2015 "40% of locally-transfused" UHN patients were switched from (licensed first line) therapies to (unlicensed) deferiprone. But (as with all drugs unlicensed in Canada) deferiprone would have had to be provided either (i) through Health Canada's "Special Access Program" or (ii) in a REB-approved clinical trial. (In Canada patients cannot simultaneously be treated through both). Under the Special Access Program, the treating physician must confirm to Health Canada that "*conventional therapies have failed, or are unsuitable or unavailable".* But the authors the PLoS paper state 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."* The authors outline (in Supporting information to the PLoS paper) and they have confirmed to me, that several patients were switched to deferiprone despite improvements, including optimal responses, during treatment with licensed therapies.

[1] I note that according to a more recent publication, not one but four deaths in UHN patients are acknowledged (during this period of unlicensed deferiprone).

With respect to the *alternate* consideration that deferiprone was provided within a UHN REB-approved clinical trial, in 2011 a published abstract stated that deferiprone was provided under a study "approved by the REB of the UHN."[2] The same year, two physicians Drs. Richard Ward and Erik Yeo, made an identical claim to the US FDA in a publicly available letter.[3]

Drs. Olivieri and Gallie informed me that in attempts to sort out this confusion, in 2016 they began applications under *Freedom of Information* laws. The Freedom of Information Coordinator at UHN testified that UHN had provided deferiprone within a clinical trial (*the data of a clinical trial are protected from scrutiny, under Freedom of Information laws*), and not under the Special Access Program (*the data arising from use in the Special Access Program Special Access Program are not protected from scrutiny under Freedom of Information*). Yet, I understand from Drs. Olivieri and Gallie that many patients' records indicate (and in some cases, explicitly state) that deferiprone was prescribed under Health Canada's "Special Access Program (SAP)".[4] A Hospital REB-approved clinical trial would have required both pre-trial registration[5] and a Data and Safety Monitoring Board to be

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[2] Miscevic F, Kuo K, Ward R. Blood 2011; 118 Abstract 3185

[3] 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.

[4] 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." My understanding is that Health Canada's Special Access Program is not intended to be a mechanism to promote or encourage the early use of drugs, to conduct research, or to circumvent the clinical trial or drug review process.

[5] In Canada, all clinical trials that are part of a new drug application, i.e., an application to have a new drug approved in Canada, must be registered. Trials are registered by the sponsor: an individual, corporate body, institution or organization that conducts a clinical trial. This includes individuals, companies, institutions or organizations that take responsibility for the initiation, management and/or financing of a clinical trial. Individual physicians can be identified as being the sponsor.

established *(ab initio*) and annual REB updates disclosing deaths and other serious adverse events. I was unable to identify any information about trial registration for such a trial. Also if deferiprone was prescribed through a research program, there should be REB applications, approvals, and renewals as well as adverse event reports. **Could you kindly confirm that these were submitted and if possible could you provide me with copies?** If deferiprone was prescribed through SAP, there should be Form As for every patient for every time a request was made for the drug, and for every renewal and especially reports on all adverse events. **Could you kindly advise me with confirmation that these requirements were complied with?**

I am also informed by Drs. Olivieri and Gallie, that since 2015, they have directly questioned (in writing) UHN Administration about this matter - including whether a trial was approved by the UHN REB, and if so whether it was registered – but that they have not yet been provided answers from UHN. I also understand that Drs. Olivieri and Gallie pursued these issues, unsuccessfully, with UHN Administration and members of the REB in further efforts to obtain clarity.

It would assist my ethics research if you could clarity for me under what mechanism deferiprone was prescribed as an unlicensed drug for six years at UHN.

II. Could you confirm whether the switching to deferiprone placed UHN patients at increased risk? Could you also indicate if UHN has investigated the findings of Drs. Olivieri and Gallie in their PLoS paper, in an effort to understand how and why the health of UHN thalassemia patients was adversely affected by the decision to switch them from licensed to unlicensed therapy?

Here is my (non-expert) take on the PLoS manuscript findings. In 41 patients, among other findings:

(a) Liver enzymes (ALT) rose and elevations persisted in many over years in 65% exposed patients and were confirmed by “challenge and re-challenge”.

(b) New diabetes was diagnosed in 6 patients continued on deferiprone despite elevations of liver iron.

(c) Mean liver iron increased to > 15 mg/g and levels > 15 mg/g were observed in 50% of patients.

(d) Improvements in "cardiac iron" were not observed in patients in whom liver iron remained high.

(e) Deferiprone was introduced as first line therapy in most patients and also frequently combined with low doses of first line agents.

III. Has the UHN determined the indications which had originally governed the switching to deferiprone from licensed therapies in the 41 patients reported in PLoS? I refer to the published Supporting information in PLoS, "*S1 text discussing indications*". Although toxicity and/or poor iron control on other drugs was claimed as a reason to switch to deferiprone, S1 appears to rule out this explanation, particularly on page 3 where the circumstances in 41 patients suggest that none of them had required a switch to third line drugs.

IV. I seek help from you to discover how relevant findings, particularly toxicity, arising in UHN patients during exposure to deferiprone were reported to regulatory agencies. This is a two-part question related first to reporting to the US FDA, and second to the Canadian regulator, Health Canada.

Drs. Olivieri and Gallie indicate to me that since 2015, their requests to the UHN Administration for information regarding the "Canadian data package" (comprising the findings of UHN patients' exposure to deferiprone) have been refused. Nevertheless, Drs. Olivieri and Gallie report that they have identified some (publicly-available) information about reporting by UHN to the FDA and Health Canada. I was hoping that you, as senior UHN Administrators, could help me with two documents.

The first publicly available document is a **2011 letter from** two UHN doctors **to the United States FDA** in support of the US market approval of deferiprone)[6] in which these physicians report, that they *"care for 80% of Canada's Hemoglobinopathy patients"* and that they *"…cannot state how strongly we support [the market approval of deferiprone at the FDA]".* Drs. Olivieri and Gallie have informed me that this letter contains substantial differences from the data they recorded from the UHN patient records, published in PLoS. My questions about this letter also stem from personal communications with Drs. Olivieri and Gallie, indicating that the UHN patient records indicate prescribed doses of (unlicensed) deferiprone, frequency of monitoring during deferiprone exposure over years, and side effects sustained during deferiprone exposure, differ significantly from the information which UHN doctors provided to the FDA in support of the licensing of deferiprone. **Has the UHN confirmed whether the information provided to this federal agency was accurate?**

A second, related question; It has been pointed out to me by Drs. Olivieri and Gallie that the Health Canada website reveals **19 entries up to the end of 2016** reporting serious adverse events (SAES) in patients receiving deferiprone. Two of these SAEs were reported prior to 2009. Of the 17 other SAEs, 15 were reported *following* the licensing of deferiprone in February 2015. This suggests that only two SAEs in patients receiving deferiprone were reported from 2009 to 2015 by UHN physicians. But the PLoS paper identified several SAEs in patients receiving deferiprone between 2009 and 2015. **My question is: Could you please provide confirmation that the requirements to report toxicity arising from deferiprone exposure at UHN from 2009 to 2015 were fulfilled?**

V. What were UHN thalassemia patients informed when they were switched from licensed therapies to deferiprone? I understand from Drs. Olivieri and Gallie that many patients switched from first line therapy to deferiprone suffered serious harms as a result of the switch. Did the patients switched to deferiprone understand that they were being switched from treatment whose safety and efficacy

[6] Although this letter by Drs. Ward and Yeo is posted on the FDA website, that this might have been a draft version is suggested by the note on page 3: "APOTEX ARE CHECKING THIS DATE AND WILL GET BACK TO US."

had been established and licensed by regulators, including Health Canada, to an unlicensed drug (deferiprone)? How were the adverse medical outcomes explained to patients and families treated with deferiprone? How were the deaths explained to families? Were UHN patients given enough information so that they could adequately comprehend the literature pertaining to the effectiveness of deferiprone?

VII. Were conflicts of interest disclosed by UHN and the physicians involved?
I understand from Drs. Olivieri and Gallie that their FOI searches reveal that Apotex was providing substantial funding to the thalassemia program at UHN. Further, a donation of between "$1 million and $5 million" from Barry Sherman, now-deceased CEO of Apotex, to UHN is recorded in the UHN Atrium. I understand from Drs. Olivieri and Gallie as per the FOI documents obtained in 2013, that funding from Apotex to UHN included unrestricted educational grants. Freedom of Information documents also reveal 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 additional of funding. The Royal College of Physicians of Canada notes that such conflicts of interest are problematic[7]. **I have written extensively about the ways in which conflicts of interest are relevant to research ethics and I would appreciate learning from you whether and how UHN discloses such conflicts to patients and research subjects and whether UHN acknowledges that the core values of research integrity and patient safety both require that conflicts of interest be eliminated.**

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[7] "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

Thank you for your assistance in answering my queries. A response as soon as possible but in any event no later than the end of July would be much appreciated.

Yours sincerely,

Professor Arthur Schafer

Founding Director

Centre for Professional and Applied Ethics

University of Manitoba

(2) Schafer letter of inquiry to Drs. Richard Ward and Kevin Kuo

22 July 2019

Dr. Richard Ward
Dr. Kevin Kuo
Division of Hematology/Oncology
University Health Network

By Email:
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Kevin.Kuo@uhn.ca

Dear Drs. Kuo and Ward:

I am preparing an analysis of the ethical issues arising from the PloS One paper published this past February by Drs. Nancy Olivieri, Amir Sabouhanian, and Brenda

Gallie. I write to clarify some points arising out of this publication which details the switching of 41 UHN patients to then-unlicensed deferiprone from first line drugs. (I understand from your more recent publication that another 30 patients, totaling 71 patients manage at UHN in total, were treated with unlicensed deferiprone from 2009 to 2015).[8] I also understand that in all jurisdictions in which deferiprone has been licensed, worldwide, it has been licensed as "last-resort" therapy (to be prescribed only when first line therapies have failed). The PloS paper states (as I confirmed from review of the Health Canada website) that in February 2015 deferiprone was licensed in Canada (again only as "last-resort" therapy) "based primarily upon the Canadian data package" -- presumably derived from Canada's largest thalassemia clinic, viz., the UHN clinic.

My questions for you are related to the above general background. I will be grateful for answers and guidance:

Under what mechanism was deferiprone prescribed as an unlicensed drug for six years at UHN? According to the PloS paper, from 2009 to 2015, a proportion of locally-transfused UHN patients were switched from (licensed, first-line) therapies to (unlicensed) deferiprone. As with all drugs unlicensed in Canada, deferiprone would have had to be provided either through (i) Health Canada's "Special Access Program" or (ii) a REB-approved clinical trial. (In Canada, patients cannot simultaneously be treated through both). Under the Special Access Program, the treating physician must confirm to Health Canada that "*conventional therapies have failed, or are unsuitable or unavailable".* The authors the PLoS paper state 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."* The authors also outline (in *Supporting information* in the PLoS paper: "*S1 text discussing indications*") that several patients were switched to deferiprone despite ongoing improvements, including optimal responses, during treatment with licensed therapies. As well, I understand that although toxicity and/or poor iron control on other drugs was claimed as a reason to switch to deferiprone, the *S1 text discussing indications* appears to rule out this explanation, particularly on page 3, where the circumstances in 41 patients suggest that none had required a switch to third line drugs.

[8] Binding A, Ward R, Tomlinson G, Kuo K. Deferiprone exerts a dose dependent reduction of liver iron in adults with iron overload. https://onlinelibrary.wiley.com/doi/abs/10.1111/ejh.13244

I would be grateful if you could please provide comment on my above understanding.

With respect to the *alternate* consideration, that is, that deferiprone was provided within a UHN REB-approved clinical trial, in 2011 you published an abstract that stated that deferiprone was provided under a study "approved by the REB of the UHN."[9] Drs. Ward and a Dr. Erik Yeo also made an identical claim, in a publicly-available letter, to the US FDA.[10]

Drs. Olivieri and Gallie informed me that in attempts to sort out these contradictory facts, they launched, in 2016, applications under Canadian *Freedom of Information* law. The Freedom of Information Coordinator at UHN later attested that UHN had provided deferiprone within a clinical trial (*as you may know, data of a clinical trial are protected from scrutiny under Freedom of Information laws*), and not under the Special Access Program (*the data arising from which are not protected from scrutiny under Freedom of Information laws*). Yet, I understand that many patients' records indicate (and some explicitly state) that deferiprone was prescribed under Health Canada's "Special Access Program (SAP)".[11] As you know, a UHN REB-approved clinical trial would have required both pre-trial registration[12] and a Data and Safety Monitoring Board to be established *(ab initio*), as well as REB applications, annual approvals, renewals and adverse event reports disclosing deaths and other adverse events. I was unable to identify any information about trial registration for such a trial. **Could you kindly confirm that these were submitted? If possible, could you please provide me with (anonymized) copies?** Alternatively, if deferiprone *was* prescribed through the SAP, there should be Form As for every patient for every time a request was made for the drug and for every renewal, especially reports on any adverse events. **Could you kindly advise me whether these requirements were complied with?**

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[9] Miscevic F, Kuo K, Ward R. Blood 2011; 118 Abstract 3185

[10]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.

[11] 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." My understanding is that Health Canada's Special Access Program is not intended to be a mechanism to promote or encourage the early use of drugs, to conduct research, or to circumvent the clinical trial or drug review process.

[12] In Canada, all clinical trials that are part of a new drug application, i.e., an application to have a new drug approved in Canada, must be registered. Trials are registered by the sponsor: an individual, corporate body, institution or organization that conducts a clinical trial. This includes individuals, companies, institutions or organizations that take responsibility for the initiation, management and/or financing of a clinical trial. Individual physicians can be identified as being the sponsor.

In summary, it would assist my research if you could clarity for me under what mechanism deferiprone was prescribed as an unlicensed drug for six years at UHN.

The following is my (non-expert) take on the PLoS manuscript findings. In 41 patients, among other findings:

(a) Liver enzymes (ALT) rose and elevations persisted in many patients over years, in total in 65% exposed patients and in many this relationship was confirmed by "challenge" and "re-challenge".
(b) New diabetes was diagnosed in six patients continued on deferiprone and most had over year sustained unacceptable elevations of liver iron.
(c) Mean liver iron concentration increased; levels > 15 mg/g were observed in 50% of patients.
(d) Improvements in "cardiac iron" were not observed in patients in whom liver iron concentration remained high.
(e) Deferiprone was introduced as first-line therapy, most often as monotherapy and also frequently combined with low doses of first line agents.

I seek help from you to discover how these findings, particularly the toxicity arising in UHN patients during deferiprone exposure were reported to regulatory agencies. Drs. Olivieri and Gallie indicate to me that although since 2015, their requests to the UHN Administration for information regarding the "Canadian data package" have been refused, there is publicly-available information about the reporting by UHN to FDA and Health Canada, including two documents about which I have questions. The first publicly available document is a 2011 letter to the United States FDA in support of the US market approval of deferiprone)[13] in which Dr. Ward (with Dr. Erik Yeo) reported that the UHN program *"care[d] for 80% of Canada's Hemoglobinopathy patients"* and that [Dr Ward] could not *"…state how strongly [he] support[s] [the market approval of deferiprone at the FDA".*

Drs. Olivieri and Gallie have informed me that this letter contains substantial differences from the data they recorded from the UHN patient records, and published in PLoS, in particular with respect to the doses of (unlicensed) deferiprone prescribed, the frequency of monitoring during deferiprone exposure, and the side effects observed during deferiprone exposure. **Was this information you provided to the FDA different from that in the patient records?**

A second question: My review of the Health Canada website reveals 19 entries up to the end of 2016 which disclose serious adverse events (SAEs) in patients receiving deferiprone. Two of these SAEs were reported prior to 2009. Of the 17 other SAEs,

[13] Although this letter by you and Dr. Yeo is posted on the FDA website, that this might have been a draft version is suggested by the note on page 3: "APOTEX ARE CHECKING THIS DATE AND WILL GET BACK TO US."

15 were reported *following* the licensing of deferiprone in February 2015; hence, only two SAEs in patients receiving deferiprone were reported from 2009 to 2015. But the PLoS paper (and your paper does as well) identified several SAEs in patients receiving deferiprone between 2009 and 2015. **Could you possibly please confirm that all requirements to report to Health Canada including reports of all SAEs arising from deferiprone exposure at UHN from 2009 to 2015 were fulfilled?**

What were UHN thalassemia patients informed when they were switched from licensed therapies to deferiprone? It seems that many patients switched from first line therapy to deferiprone suffered serious harms. Did the patients switched to deferiprone understand that they were being switched from drugs whose safety and efficacy had been established and which were licensed as first line therapy by regulators, including Health Canada, to an unlicensed drug (deferiprone)? How were the adverse medical outcomes explained to patients and families treated with deferiprone? How were deaths explained to families? Were UHN patients given enough information so that they could adequately comprehend the literature pertaining to the effectiveness of deferiprone?

Were your personal and financial conflicts of interest disclosed? I understand that FOI searches reveal that Apotex provided substantial funding to the thalassemia program at UHN from at latest, 2010. As well, a donation between "$1 million and $5 million" from the now-deceased CEO of Apotex is recorded in the UHN Atrium. Finally, I understand that FOI documents indicate that Apotex supplied funding to UHN in the form of unrestricted educational grants to the Thalassemia Program, that correspondence over years between Apotex and Dr. Ward focused upon obtaining market approval of deferiprone in Canada, and that requests from Dr. Ward for funding were issued to (and fulfilled by) Apotex. I have written extensively about the ways in which conflicts of interest are relevant to research ethics. It would be important to me to learn from you whether, and how, you disclosed these conflicts to patients (and/or research subjects if this was a research study)?

Thank you for your assistance in answering my queries.

A response as soon as possible would be greatly appreciated.

Yours sincerely,

Professor Arthur Schafer

Founding Director, Centre for Professional and Applied Ethics
University of Manitoba

Appendix B: Health Canada's Guidance Document for Industry and Practitioners – Special Access Programme for Drugs. 2008

Following are some of the passage (all emphases added) from the 2008 Health Canada Guidance Document for the Special Access Programme for Drugs. These passages support the view that access to deferiprone could have been via an SAP or it could have been via a clinical trial **but not both**:

> Prior to market authorization of a drug access is usually limited to clinical trials sponsored by a manufacturer or research organization, and authorized by Health Canada through a clinical trial application. *On those occasions when a drug is not available through enrollment in a clinical trial,* Health Canada may allow an exemption from the Food and Drugs Act and its Regulations to permit the sale of an unauthorized drug for a medical emergency.
>
> Special access by Canadian health practitioners to unauthorized drugs is intended for serious or life-threatening conditions where conventional therapies have failed, are unsuitable, or are unavailable either as marketed products *or through enrollment in clinical trials.*
>
> Emergency access should be exceptional and where possible, open label or compassionate access trials should be incorporated into drug development plans to meet the needs of patients *not eligible for enrollment in other pivotal trials*.