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Short Communication

Ethical Problems for Canada's Largest Research Hospital and the Dangers of Institutional Conflict of Interest

Arthur Schafer*

Department of Philosophy, University of Manitoba, Manitoba, Canada

ABOUT THE STUDY

Much like hospitals in the USA and the UK, Canadian research hospitals depend upon donations from Big Pharma. Unfortunately, the bigger the donation, the bigger the ethical problems it creates.

The University Health Network [UHN] in Toronto, Canada's largest health sciences research and education hospital, received major financial support between one and five million dollars from Apotex, a drug company, and its late CEO, Barry Sherman. Moreover, Freedom of Information [FOI] requests filed by Dr. Nancy Olivieri reveal that UHN's Thalassemia programme received unrestricted educational grants from Apotex as well as research support. FOI requests also reveal that Apotex strategized with the programme's director, Dr. Richard Ward, about how best to obtain licensing from the regulator, Health Canada, for its iron chelation drug, deferiprone.

Now, both the Hospital, and its Thalassemia Programme are embroiled in a major ethical controversy. This controversy provides an illuminating case study for every hospital, indeed, for every major public institution in North America and Western Europe [1].

A recently published study by Olivieri, Sabouhanian and Gallie in the journal PLOS One [2] finds that large numbers of UHN patients with thalassemia, a common blood disorder, were switched, between 2009 to 2015, from two licensed chelating drugs, both proven safe and effective, to an unlicensed drug, deferiprone (Ferriprox®; Apotex), for which there is no evidence demonstrating direct treatment benefit.

Based on retrospective data from patient records, the PLOS study by Olivieri and colleagues reports that patients treated with deferiprone, either as monotherapy or in combination with first-line drugs, suffered serious (and often irreversible) adverse effects.

Shortly after the PLOS One study was published, The Toronto Star gave the story prominent coverage [3] but, when there was no follow-up from investigative journalists, the story faded from public awareness.

Some historical background. Dr. Olivieri was Director of UHN's Thalassemia programme up until 2009. That year she was dismissed as Director, with no reasons provided. But, as the PLOS One data show, her replacement as programme director, Dr. Richard Ward, immediately began to switch the Clinic's patients from first-line licensed drugs to unlicensed deferiprone. Olivieri has described how her UHN research work was subsequently marginalized [4]. For a fuller account of background to the controversy see [1].

How it came about that UHN patients were switched to unlicensed deferiprone is still something of a mystery. Clearly, there are ethically important questions that need to be answered. A sample of such questions: Why was an unlicensed, often ineffective, drug administered to many patients over many years? Did the patients who were switched to deferiprone know that it was unlicensed and of unproven efficacy and safety? Did they understand the risks to which they were being exposed? Did they understand that both UHN and its Thalassemia Programme were contemporaneously receiving funding from Apotex?

From the PLOS One study we discover that patients appear to have been switched to unlicensed deferiprone even though they were responding well to one of the two first-line licensed drugs. Olivieri and Gallie could identify no medical rationale for this switch and found no indication in patient records that the patients switched to deferiprone were intolerant of first-line drugs. So: What was the medical rationale for switching their medication?

The records of patients who were switched to deferiprone show that many experienced significant harms. One patient died, several developed new diabetes and many experienced signs of liver problems. Despite this evidence of harm, many UHN patients were continued for years on unlicensed deferiprone.

Correspondence to: Arthur Schafer, Department of Philosophy, University of Manitoba, Manitoba, Canada, E-mail: Arthur.schafer@umanitoba.ca

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The poor results for UHN patients exposed to deferiprone contrasted markedly with the beneficial outcomes for UHN patients who remained on licensed therapy. So: Why were these patients not switched back?

Another puzzle: Under what authority was deferiprone prescribed to UHN patients? UHN officials have repeatedly declined to answer this question. But here's what we know.

Prescription of an unlicensed drug to Canadian patients can be accomplished only in one of two mutually exclusive ways: either through Health Canada's Special Access Programme (SAP) or via an approved registered clinical trial [1].

Unlicensed drugs can be obtained under the SAP programme only if "conventional therapies have failed, or are unsuitable or unavailable"; but Olivieri and colleagues found "no evidence of failure of licensed therapy prescribed as recommended". Moreover, under the SAP "access to any drug should be limited in duration and quantity to meet emergency needs only". Yet, as reported in PLOS One, deferiprone was administered for six or more years to many UHN patients.

Alternatively, perhaps deferiprone was prescribed as part of a clinical trial. Repeatedly UHN officials and physicians have made this claim, including in scientific papers, and to the US FDA. But there appears to be no record that such a trial was ever registered, as required by Canadian clinical trial guidelines.

Over a period of several years, Olivieri and Gallie pressed UHN officials for answers to the questions flagged above, without success. I, too, wrote to UHN's CEO and to the physicians in charge of its Thalassemia Clinic, seeking answers to a number of ethically troubling questions.The Ethical concerns raised by my letters, similarly, received no reply. Unwillingness to answer ethical questions violates both the hospital's duty of public accountability and its commitment to protect patient safety.

Last September, UHN conducted a "Review of chelation practice" [at UHN]. A disinterested review of the Hospital's chelation programme was certainly needed. But the "thalassemia expert" appointed by UHN administrators, Dr. Isaac Odame, had himself received financial support from Apotex. Moreover, Odame is closely connected, personally and professionally, to Dr. Richard Ward, the physician responsible for switching most patients to deferiprone. Not surprisingly, therefore, the Hospital's Review delivered no answers to the safety concerns flagged by the PLOS One paper [5] nor did it deliver answers to any of the ethical issues flagged in my letters to Hospital officials. An external independent expert inquiry is needed.

There is now an extensive body of literature demonstrating that when research and clinical care are funded by industry there is a marked tendency to favour the donors' products [6].

CONCLUSION

The UHN's Mission Statement commits the Hospital to ensuring that every patient is "made aware of existing systemic biases to support the best possible health decisions." But has UHN lived up to its commitment? And isn't it about time that institutional conflicts of interest were eliminated altogether from every hospital, in Canada and abroad?

Professor Arthur Schafer is Founding Director of the Centre for Professional and Applied Ethics at the University of Manitoba. For a fuller discussion of these issues see his recently published article in the Journal of Medical Ethics, "Institutional Conflict of Interest: Cracking the deferiprone mystery".

COMPETING INTERESTS

The author served as (unpaid) ethics consultant to Dr. Nancy Olivieri during her conflict with Apotex, the Hospital for Sick Children and the University of Toronto. He appeared at three press conferences with Nancy Olivieri in the autumn of 1998 and the winter of 1999, at which his role was to analyse and evaluate the ethical issues arising from the conflict.

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