TORONTO STAR

A controversial blood drug. Funding from Apotex. Accusations of a whitewash. Why this scientist has spent decades fighting Toronto hospitals

UHN stands by its decision to use the drug deferiprone to treat thalassemia. Hospital officials reject allegations that money from Apotex influenced patient care.

By Rachel Mendleson Staff Reporter
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Dr. Nancy Olivieri was in the lobby of Toronto General Hospital, waiting in line at Starbucks, when one of her former patients approached her to tell her that they were now taking deferiprone.

Olivieri was taken aback. Decades earlier, when she was just starting her career at a major nearby hospital, she had been one of the first scientists to test the drug on patients with thalassemia, a hereditary blood disease that can be life-threatening.

The trial came crashing down in the mid-'90s when Olivieri's research led her to doubt the efficacy and safety of the medication. She went public with her concerns. The drugmaker, Apotex, tried to muzzle her. The hospital where she worked at the time demoted her and referred unfounded concerns about her to Ontario's medical watchdog. She was pushed to the margins and ostracized.

In 2009, when she encountered the patient, the scientific debate over deferiprone remained unsettled. The drug wasn't yet licensed in Canada or the U.S.

Until recently, Olivieri had been clinical director of the thalassemia program at Toronto General. She recalled the patient had been doing well on approved drugs. Standing in the coffee line, she

felt powerless to protect this patient, who was now taking an experimental medication she believed carried serious risks.

“I felt heartsick,” she said.

Other former patients soon began approaching her with similar stories.

Olivieri didn’t back down in her first fight over deferiprone, and she wasn’t going to back down now.

She brought her concerns to officials at University Health Network (UHN), a collection of Toronto hospitals that includes Toronto General. They did not stop the use of the unlicensed drug. So, Olivieri went to the patients’ medical records.

What she found alarmed her. In some cases, she said, patients were kept on deferiprone despite clear warning signs or documented past problems with the medication. With her longtime colleague and ally Dr. Brenda Gallie, she found most of the 41 patients whose records she had approval to examine suffered “significant toxicity,” including diabetes and liver dysfunction. A woman in her 30s died in 2013, “presumably of cardiac failure,” 13 months after being placed on the drug in combination with a low dose of an approved medication.

For 14 years, Olivieri has continued digging. She uncovered that the hospital clinic giving the unlicensed drug to patients was receiving money from Apotex. She also found that an internal UHN review of the care thalassemia patients received – which concluded the clinic’s use of the unlicensed drug was “justified” – overlooked what she considered to be important evidence and had discomforting ties to the drug’s maker.

Like she did decades ago, Olivieri has once again sparked a controversy that has divided doctors and raised uncomfortable questions about the influence of funding from Big Pharma inside trusted Toronto health institutions.

The Star has interviewed key players in the dispute and reviewed hundreds of pages of records, including internal hospital emails and correspondence from Apotex, obtained through Freedom-of-Information legislation (FOI). The investigation’s findings leave Olivieri and Gallie concerned about a possible whitewash.

UHN is standing by the review’s finding that the clinic’s patients were “receiving appropriate and safe care.” In interviews for this story before the pandemic, and in written responses to recent questions, officials rejected allegations that funding from Apotex influenced the treatment of its patients or its handling of the review.

But Carl Elliott, a professor of bioethics at the University of Minnesota, said he’s “baffled by how bad it looks.”

“It just seems like stunningly bad judgment, unless you were trying to rig the result,” he said of UHN’s review. “If your aim was to rig the result, this is exactly what you would do.”

Olivieri's deferiprone trial

Olivieri believed deferiprone could be a gamechanger.

In 1989, when she started her first trial at the Hospital for Sick Children (SickKids), the standard treatment for severe thalassemia – a blood disorder that prevents the body from making enough hemoglobin – was grueling, especially for kids. The life-threatening form of the disease requires frequent blood transfusions. The transfusions lead to another dangerous problem – excess iron, which, if allowed to build up, can cause organ damage or even death.

At the time, the only approved therapy to remove excess iron had to be administered under the skin; most often, the drug was infused overnight, through a pump. Though it was effective, it was also onerous and sometimes painful around the injection site.

Deferiprone could be taken orally, in the form of a white pill.

Apotex provided funding to help Olivieri continue her trials in 1993. When she began to express concerns about the drug, the company abruptly shut down the testing and threatened Olivieri with legal action, alleging she'd violated a confidentiality agreement.

SickKids did not defend Olivieri. Instead, the hospital took action against Olivieri amid escalating attacks from Apotex and Olivieri's notorious partner on the trial, someone who, while continuing to receive funding from the drug company, wrote anonymous "poison pen" letters, disparaging Olivieri and her small band of supporters, including Gallie, who was her supervisor.

The University of Toronto (U of T), which shares responsibility for the research conducted by doctors in its affiliated hospitals, stepped in to mediate the dispute between Olivieri and SickKids.

Dr. David Nathan, a world-leading blood researcher and Harvard University professor, came to Toronto to defend Olivieri. He said he was "stunned" by the "stone wall" he hit in his meetings with university officials.

"It was clear that they saw her just the way the French saw Joan of Arc," he said, referring to the patron saint of France, who was burned at the stake in the 1400s for heresy after challenging the will of the establishment. "They just couldn't stand listening to her, and I think it's terrible."

Nathan, who holds emeritus positions at Boston Children's Hospital and the Dana-Farber Cancer Institute, understood why Olivieri's relentlessness rankled Toronto's medical elite. But he also knew that she was bright, curious and "a completely patient-oriented investigator."

"She can scratch at your skin … but you have to ignore all that," he said. "The issue is, what's the best way to treat patients with thalassemia? That's all we should be focusing on."

As Olivieri sees it, dispensing with "social superficiality" is a small act of rebellion against those who hold power in a system that has betrayed her trust.

Once she realized the system tends to punish whistleblowers and cover-up misconduct, she said, "I never saw the point of being polite."

Olivieri and SickKids reached an agreement, brokered by U of T, which saw her compensated for some of her legal expenses and reinstated as head of the hemoglobinopathy program, in 1999. She moved her office down the street, to UHN's Toronto General, where she was also running a thalassemia program for adult patients.

The controversy unfolded as U of T was negotiating with Apotex for a $30-million donation to the university and its affiliated research hospitals. Arthur Schafer, the founding director of the Centre for Professional and Applied Ethics at the University of Manitoba, has said that Olivieri "was seen as standing in the way" of the hospital's desire to make SickKids "world class."

The case generated international headlines and underscored the dangers of institutional conflicts-of-interest.

Schafer said he thought it would have left an indelible impression on UHN, which, like SickKids, is affiliated with U of T and relies, in part, on corporate donations.

"The lesson they should have learned is that they've got to be extremely careful about institutional conflicts of interest," said Schafer, who has published a paper about the controversy over the use of unlicensed deferiprone at UHN.

"Whatever I expected," he said, "it didn't happen."

Olivieri's ouster

In 2009, a few months before the run-in with the patient in the Starbucks line, Olivieri says UHN removed her from her position as clinical director of the thalassemia program. Dr. Richard Ward – who had come to Canada from the U.K. – would be made director.

The Canadian Association of University Teachers (CAUT), which had defended Olivieri during the dispute at SickKids, alleged at the time that she had been edged out of the clinic at UHN, in part, because of the safety concerns she'd already flagged related to deferiprone.

The drug was approved in Europe for use in "exceptional circumstances," but it wasn't licensed in Canada when Ward took over the clinic.

And around that time, there was a desire to test deferiprone at UHN. Someone submitted an application in 2008 to run a clinical trial at the hospital. The trial never started, though it's not clear why, and a hospital spokesperson refused to identify who the researcher or sponsor was.

A senior hospital official did not answer a question from the Star about Olivieri's charge that she was removed.

Olivieri, who remained a senior scientist at UHN, knew the hospital's thalassemia patients and their medical histories well. She had cared for some of them for decades, beginning when they were children at SickKids. In interviews for this story, two patients said they continued to seek out her expertise after Ward took over because she had always been a fierce advocate for their interests. They said her meticulous attention to detail and uncanny ability to recall precise lab findings from years earlier made her well-suited to troubleshoot treatments for their complex needs.

By 2009, many thalassemia patients no longer relied on nightly injections to remove excess iron. A few years earlier, the Swiss company Novartis got approval for deferasirox, a tablet that could be dissolved in water and taken orally. It had become standard therapy – a safe and effective first-line treatment. Although it can cause stomach upset, Olivieri said that with some trial-and-error around dosing, most patients can tolerate the drug.

Longtime UHN patient Alexa Virani, 49, said she was taken aback when, shortly after the leadership shakeup in the thalassemia clinic, in around 2010, Ward asked her if she wanted to switch from the approved oral treatment to deferiprone.

Virani had participated in Olivieri's deferiprone trials at SickKids in the 1990s. Initially, she seemed the poster-child for the medication; Virani raved in media interviews about the drug that had freed her from nightly injections.

However, by 1997, Virani said, she was back on the old treatment. Liver biopsies had revealed scarring that Olivieri predicted could become irreversible if Virani continued taking deferiprone. Virani chose to go back to injections until deferasirox was approved.

Ward's suggestion that Virani try deferiprone left her with the impression that he had "zero regard" for her personal medical history, she said.

It seemed that Ward wasn't familiar with her file, which felt "a little irresponsible." Ward, she said, didn't comprehensively advise her of the risks or make clear that deferiprone wasn't approved in Canada.

"Patients weren't being adequately informed of what the risks were or what other patients had gone through on that drug," she said.

Virani is still a patient at UHN, but moved her transfusions to another hospital, in part, she said, because of this episode.

Neither Ward nor UHN directly addressed Virani's claims about her experience.

In 2011, Apotex gave an $80,000 unrestricted grant to UHN's thalassemia clinic, according to internal records Olivieri obtained through FOI, and shared with the Star. Ward agreed to share patient data with the company and report on his centre's experience, the documents show.

Ward declined an interview request, and did not answer detailed questions for this story. In an email, he said the Star is raising matters that "have been thoroughly investigated by UHN and the University of Toronto on several occasions, with validation of our actions."

"As an academic clinician I take my ethical, academic, and regulatory responsibilities seriously," he said. "Myself and clinical colleagues in the (Red Blood Cell Disorders) program at UHN have acted, and will continue to act, in the best interests of patients, and to prioritize those interests over the interests of external parties, such as the pharmaceutical industry."

Apotex has always rejected concerns about the safety and efficacy of deferiprone and defended its funding of research.

"(All) research funded by Apotex is undertaken with the strictest of policies and guidelines and any decisions regarding disclosure of funding resides with a researcher," Apotex spokesperson Jordan Berman said.

The hospital told the Star that patients who received deferiprone before it was licensed did so through Health Canada's Special Access Program – a compassionate-use protocol for patients who can't access conventional medications or for whom those medications are unsuitable or don't work.

"(Patients) were not given deferiprone as part of a clinical trial, but rather through a process that considered the appropriateness of their treatment as part of standard clinical care," UHN spokesperson Gillian Howard said, adding that all patients who got the drug did so "following discussion regarding the risks and benefits" and permission from Health Canada.

By the end of 2010, roughly one-quarter of the hospital's thalassemia patients receiving regular transfusions were relying on the unlicensed drug to remove excess iron, according to an earlier review of the program UHN commissioned.

The review found that the use of the drug was in line with how doctors were giving it to patients in the U.K., where the medication was approved.

The change in leadership within UHN's Red Blood Cell Disorders Clinic, as it is now known, occurred as Apotex was trying to get deferiprone approved in the U.S. In the summer of 2009, an inspector from the U.S. Food and Drug Administration (FDA) spent several days in Olivieri's Toronto office, combing through source data from one of the trials she ran at SickKids in the '90s.

Apotex had sought to downplay the importance of the trial in its licensing application, alleging Olivieri's trial fell short of the FDA's standards. However, the FDA found the trial to be "in general compliance" with its standards, and suggested in its correspondence with the company that Olivieri's trial was the most scientifically significant investigation into the drug conducted to date. Unlike another trial Apotex cited as "pivotal," Olivieri had measured outcomes through liver-iron levels, which the FDA had recognized as the most precise marker to assess efficacy.

The inspection revealed significant "inconsistencies" between the source data and Apotex's application; the company had completely excluded the findings from more than 35 per cent of subjects. The FDA concluded that there was "insufficient information about the drug to determine whether the product is safe for use." Approval didn't go ahead at that time.

A few years later, in 2011, Ward touted the benefits of deferiprone to the FDA, before the medication was approved in the U.S. as a second-line treatment. The following year, as Apotex was preparing to submit its application to Health Canada, the company invited Ward to attend a meeting with the federal regulator in Ottawa, documents Olivieri obtained through FOI show.

Health Canada approved deferiprone – marketed as Ferriprox by Apotex – for thalassemia patients whose current treatment is inadequate – in 2015.

Italian drug firm Chiesi Group now owns the medication's patent.

The data on deferiprone

Gallie is not an expert in blood diseases. But what she saw in late 2013, when she examined the raw data that Olivieri had been collecting, stopped her cold.

The link between exposure to high levels of the drug and adverse effects in individual patients was "absolutely scientifically clear," said Gallie, a specialist in data analysis who does pioneering research at UHN in retinoblastoma, a rare form of eye cancer in young children, and treats patients at SickKids. "It was like turning the light switch on in your bathroom."

Her support for Olivieri during the dispute at SickKids had carried consequences. In 1998, Gallie stepped down from her supervisory role at the hospital after her boss issued an ultimatum, telling her she could not continue to publicly "denigrate" the institution and remain part of its leadership. She kept seeing patients at SickKids but moved her lab to UHN.

Once again, Gallie said she felt she could not stay silent. She joined Olivieri, helping to organize and distill the raw data Olivieri had collected, so that "any citizen" could see the "devastating" impacts of the drug on individual patients, she said.

Seventeen per cent of the UHN patients who took deferiprone developed diabetes, "a recognized consequence of inadequate iron control," compared to two per cent of those who took the approved tablet deferasirox, their study found. The woman in her 30s who died in 2013 was taking deferiprone in combination with a low dose of deferasirox.

Over several years, Gallie and Olivieri had repeatedly alerted officials at UHN to their findings, but the hospital hadn't taken action. They met again with executives in January 2019, about a month before their study was published. Dr. Brian Hodges, UHN's chief medical officer, told them that plans were underway to review the care the clinic's patients had received – a pledge the hospital reiterated publicly when the paper came out.

The hospital asked Dr. Michael Baker, a UHN hematologist and its former physician-in-chief, to lead the review. He had supported Olivieri during the dispute at SickKids, and was well aware of the controversy at UHN.

The first step in the review process, the hospital said, would be to secure an "external" expert to assist.

Baker told Olivieri and Gallie in an email that hospital executives were "surveying the field world wide" and would ensure the expert has "no relationship to Apotex whatsoever at any time."

The institution's relationship with Apotex was tangled. The company and its founder, the late Barry Sherman and his wife Honey, donated more than $3 million to UHN's foundations since 1985, according to the hospital, and more than $12 million to the UHN-affiliated U of T.

Questions about conflict of interest

Olivieri and Gallie didn't learn Dr. Isaac Odame had been tagged as the external expert until the review was already well underway.

In a letter to Baker and hospital executives, they said, "it would be difficult to identify an individual with more conflicts of interest in this matter than Dr. Odame."

Odame was the head of hematology at SickKids and U of T.

He also had participated in clinical trials funded by Apotex. While this conflict would be noted in UHN's report on his review's findings, the report would not mention that Odame had also received consulting fees from the company – roughly $4,000 in about 2012, he told the Star. The report also would not disclose his ties to Ward, the head of the program whose conduct Odame was now, in part, reviewing.

Odame supervised Ward's research dissertation for a Masters degree in the U.K., according to Odame's resume, and continued to "provide career advice" to Ward, who played a leadership role in a professional organization that Odame founded.

When questioned by the Star, Odame said, "I wasn't made aware that this was UHN's attempt to have (someone) external," he said.

Odame said that because of his leadership position at U of T, where all the physicians involved hold cross-appointments, his inquiry should be regarded as "a purely internal" process.

He acknowledged that questions about his possible bias are "valid," but said his ties to key players did not cloud his objectivity.

“I’m a strong advocate for patients. And I tell you, if I found any hint that somehow patients were being given a raw deal I would point it out, and I (would) do so in the public domain,” he said.

Any assertion that he is “somehow in the pocket” of Apotex is “absolutely nonsensical,” he said, noting that he has received far more research support from the company’s competitor, Novartis.

“You couldn’t work in this field and not work with manufacturers of drugs that are life-saving for these patients,” he said, “but ... I have no interest in any company that would want to take advantage of patients. That’s not me.”

Hodges, UHN’s chief medical officer, told the Star in 2020 that a number of other candidates for the reviewer position were “unwilling” to wade into the charged debate over thalassemia treatments, and all had some potential for bias. UHN said that Olivieri and Gallie refused to accept several suggested candidates; internal emails show that Olivieri put forward another name that Ward rejected.

As the hospital was anxious to get on with the review in light of possible patient safety concerns it chose Odame, who had the necessary expertise and “did not have a significant conflict of interest that we thought would interfere with his ability to judge the adequacy of care,” Hodges said.

Baker has told the Star Odame is a “distinguished, highly respected leader in his field and there was no room (for) anything except giving me expert content opinion on the numbers that we saw.”

Olivieri and Gallie had expected the review would dig into their findings on patient harms, including death. They believed the reviewers should examine their analyses of the hospital records alongside the justification that doctors provided to Health Canada to access unlicensed deferiprone.

Those things didn’t happen.

Over several weeks, reviewers met for a total of 2.5 days and did not review the materials the two researchers left for them.

“I never opened the box. I gave them the box back because I didn’t think I would have the time or the expertise to review an entire five-year study of patients,” Baker told the Star, adding that it “would have been moot” because they looked at “the original documents of far more than the patients they (Olivieri and Gallie) studied.”

Gallie disagrees. “I can’t understand how they can consider this a review ... They did not examine the evidence we have published in our unchallenged paper that there was serious patient harm,” she said.

She describes UHN’s review as “a farce.”

“The institution knows perfectly well that there has been a conflict of interest in their relationship with the drug company, so they are doing everything they can to avoid that coming out,” Gallie said.

UHN officials said in a statement that the hospital “wholly rejects any accusations that a conflict of interest has influenced in any way the care of patients in the (Red Blood Cell Disorders Clinic) or in our assessment of the quality of care in this clinic ... UHN takes its integrity most seriously and works to continuously ensure that conflicts of interest, real or perceived, do not impact decision-making at any level.”

The hospital’s review looked at the records of 72 patients – 41 of whom were part of the study by Olivieri and Gallie, the hospital said.

Odame said the review was not intended to “rebut” or “validate what had been published.”

His inquiry focused on the decision-making process in the clinic. He said he “wanted to be sure” that Ward and his team were not engaging in a “concocted plan” to switch patients from (the approved oral treatment) deferasirox to unlicensed deferiprone “without any … reason for it,” he said.

“I didn’t see anything nefarious,” he said. “I didn’t see anything to suggest there was any penchant to perpetuate a medication at all costs.”

Before UHN’s review was finalized, hospital officials invited Gallie and Olivieri to meet with the reviewers, but they declined.

Olivieri said she refused because she felt Odame was too conflicted to fairly review. She believed “UHN was preparing to whitewash our patient safety concerns.”

The hospital’s review found four deaths of patients being treated with deferiprone from 2009 to 2015, only one of which was linked to deferiprone, and no connection between the use of the drug and diabetes.

Olivieri and Gallie say the generalized summaries contained in the 11-page report do not include enough detail to compare its findings to their analyses or even see how the reviewers arrived at their conclusions.

They say it is “impossible” that the review looked at the same patient data as their study – which examined every page of the medical record over the course of 10 years – and reached such startlingly different conclusions.

UHN officials responded that an analysis of medical charts, such as the one conducted by Olivieri and Gallie, can’t assess the quality of care patients received. These studies, they said, “have access to a limited set of information” and “do not consider all the factors” used to make treatment decisions. The officials did not address questions about specific discrepancies.

Odame acknowledged that his review didn't "speak to the same issues" as the study by Olivieri and Gallie and was "nowhere close to what they did, in terms of looking at more granular data in every detail."

"I agree with them that it's like comparing apples to oranges," he said.

Deferiprone: A matter of debate or a matter of harm?

Both UHN and U of T, which shares responsibility for research conducted by physicians in its affiliated hospitals, have characterized the controversy as a dispute between duelling experts.

"These types of disagreements are part of the scientific endeavour," a spokesperson for U of T said.

Hodges, UHN's chief medical officer, said the paper by Olivieri and Gallie was "excellent" – "a welcome addition to the science."

But Jim Turk, the former head of CAUT, who has supported Olivieri since the '90s, said it is "outrageous" for the university and hospital "to obfuscate this as an academic debate."

"It's not a matter of debate," he said. "It's a matter of harm, where these harms are reported. What did you do about the reports?"

The decades-long battle over deferiprone has taken a toll on Olivieri. Although she has continued her research on thalassemia, and her work overseas, where a charity she founded supports the treatment of patients with the disease, at home, she said she feels she has been exiled from the mainstream medical community. Her once promising career as a clinician scientist, pursuing new therapies to improve the lives of patients, has stalled out.

Yet she is determined to press on.

"If I hadn't fought I would have been letting my patients down," she said. "They needed honesty and this fight in their defence, even if they still don't know it."

In June 2021, Gallie reached out to Baker, the UHN physician who led the review. She indicated that she and Olivieri wanted to challenge the hospital's response to their concerns.

Gallie was unsure how Baker would respond, given the findings of his review, in part, that they were now challenging. A year earlier, on the eve of the pandemic, Baker told the Star he would "personally back up" the conclusion that "patients were treated (with) a proper standard of care."

But now his tone seemed to shift.

Baker thanked Gallie for the "magnum opus" she'd attached to her note – a detailed timeline chronicling the alleged cover-up by UHN.

“With that amount of careful documentation you will probably trigger a truly ‘independent’ review of the whole issue organized by U of T,” he wrote. “Go for it.”

Rachel Mendleson is a Toronto-based investigative reporter for the Star. Follow her on Twitter: @rachelmendleson