Drug-testing rules broken by Canadian researchers

Top Canadian doctors running clinical trials have risked patient safety, failed to report serious side-effects suffered by their human test subjects and botched the scientific research of the drugs.

The late Dr. Atilla Turgay, former chief of medical staff of the Scarborough Hospital, did not report several side-effects suffered by child subjects participating in his clinical trial.

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Top Canadian doctors running clinical drug trials failed to report serious side-effects suffered by their human test subjects.

The doctors, some of them esteemed researchers from Canada's most prestigious hospitals and academic institutions, have also routinely broken rules designed to protect participants and botched research of new treatments.

Using records obtained through U.S. freedom of information legislation, a Star investigation has found the following problems in the system designed to ensure new drugs are safe and effective:

- In 2012, a top Toronto cancer researcher failed to report a respiratory tract infection, severe vomiting and other adverse events.
- A clinical trial run by an Alberta doctor reported that patients responded more favourably to the treatment than they actually did.
- A Toronto hospital's chief of medical staff ran a clinical trial of autistic children on a powerful antipsychotic, and he did not report side-effects suffered by four of the children.
- And numerous doctors across the country failed to tell participants that one of the goals of the clinical trial was to test the safety of the drug they were taking.

Health Canada inspects a small number of the 4,000 drug trials running at any one time across the country. The inspection results are kept secret.

But the Star was able to learn about problems with some of the trials through records from the U.S. Food and Drug Administration.

This is because the experiments, run by Canadian doctors and involving Canadian test subjects, were used to see if a drug was safe for the U.S. market and were therefore open to inspection by the FDA. Many of the drugs have also been approved in Canada.

The FDA makes inspection dates and results available to the public on its website. When the Star sought additional details of the violations American inspectors found in Canada, the FDA provided the records with little delay.

The FDA inspection reports on Canadian trials show shoddy and sometimes risky work performed by Canadian doctors, some of whom have accepted money from the same drug companies sponsoring the trials.

The U.S. inspectors' findings suggest pervasive problems in Canadian clinical trials: The FDA found objectionable conditions in more than 60 per cent of the 192 study sites they have visited since 1981.

At least eight Canadian doctors are repeat offenders, including an Alberta cancer researcher, Dr. Alexander Paterson, whose work has been flagged for problems in three separate FDA inspections.

Clinical trials are experiments using volunteer subjects to determine whether a drug is safe and effective, as well as what side-effects it may cause. Participants may experience side-effects, which the doctors leading the trials must report.

STEPHANIE LAKE

Dr. Sunil Verma of Toronto's Sunnybrook Hospital was cited by a U.S. health inspector for failing to report adverse reactions suffered by five patients in a drug trial. Verma said it was due to an oversight by his nurse.

“That data is going to support whether a new drug is safe,” said Tamika Cathey, a former FDA agent whose tasks included inspecting clinical trials. “If there are additional adverse events, and the clinical investigator does not document and notify the (drug company), it could in the end put the patient at risk if the product is submitted and cleared for approval. That’s the bottom line. That’s why it’s critical.”

The Star found at least 18 Canadian doctors did not report all adverse events suffered during their clinical trials.

In late October 2012, a U.S. agent arrived at Toronto’s Sunnybrook Health Sciences Centre to inspect a clinical trial run by Dr. Sunil Verma, chair of breast medical oncology at Sunnybrook’s Odette Cancer Centre.

A Swiss drug company that funded the experiment was using the study to get the U.S. regulator to approve the drug, T-DM1, which had shown success in targeting cancer cells and a lower rate of severe side-effects compared to other treatments.

The inspector found problems with Verma’s study: He failed to report to the sponsoring drug company adverse reactions suffered by five patients, including a respiratory tract infection and severe vomiting that lasted two weeks.

Doctors running the clinical trials are obligated to report side-effects to the experiment’s sponsor, often drug companies, who must include the information in their application to regulators for drug approval.

In an interview with the Star, Verma said all the adverse events were recorded during the trial, but “a very small proportion of it” was not input into an electronic database supposed to hold all the side-effect data. He said it was a staff member’s fault.

“This was purely a clerical issue. This was clearly an oversight on the part of the nurse,” Verma said.

The FDA inspector also found the clinical trial staff discarded original medical observation notes after the information was transcribed elsewhere, which made it impossible “to verify the validity and integrity of data captured at your site.”

Verma said all the problems were fixed during the inspection.The FDA later sent a letter acknowledging Verma’s assurancesthat measures were put in place to ensure similar “objectionable conditions” do not occur in future trials.

“We are very proud of the great clinical research we do here,” Verma said. “At no point did the patients’ care get affected, at no point did the overall conduct of the trial get affected and at no point was there an intentional purpose by our clinical trial staff to purposely not enter information.”

Verma conducted the trial for the company, Hoffmann-La Roche. The doctor said he was not paid by the company for his work on the trial, something that he said would be unethical, but that he is on the firm’s advisory board.

When asked about this type of work, he said that from time to time he gets paid to give an “educational presentation” on breast cancer — a day’s work that brings him around $1,500. A Hoffman-La Roche spokesperson said the company’s work with doctors running clinical trials “is not dictated by any speaking engagements the . . . physicians may undertake.”

The FDA approved the drug, branded Kadcyla, in February 2013, and Health Canada followed with its approval later that year.

Health Canada said it did not inspect this trial but provided few other details of its inspection program.

Health Canada only began its trial inspection program in 2002, and the data the regulator makes available shows it has not met its goal of inspecting 2 per cent of the country's trials each year. A 2011 auditor general report found when the regulator does find problems, it takes as many as 142 days to inform the study leaders of the deficiencies.

Health Canada reports on inspection findings that have been published but, unlike FDA records, they do not identify the drugs, the doctors running the trials, or the name of the drug companies. Health Canada told the Star that "confidential and/or proprietary information is removed" from the summary reports.

Over the past 12 years, Health Canada found at least 33 clinical trials had critical problems and were "non-compliant." In July, the Star asked for details of these and other inspections, and last week Health Canada refused, saying that providing records "would require an exhaustive manual paper file review."

The regulator also said the release of these clinical trial inspection reports could only come after consultation with third parties, typically the doctors and drug companies.

The Canadian regulator refused to say how many clinical trials it has shut down or stopped, if any.

At Toronto's Scarborough Hospital in the early 2000s, Dr. Atilla Turgay was studying the use of an antipsychotic called risperidone to treat children with autism. Some of the trial subjects were as young as five.

Turgay, then the hospital's chief of medical staff, did not report adverse events suffered by four patients even though the side-effects were "known to be associated with the study drug," the FDA found.

With Health Canada inspecting just a sliver of the country's clinical trials, much of the responsibility for oversight falls to the drug companies sponsoring the trials, as well as the research and ethics boards.

These boards, often set up by the hospital or university where the doctor works, review and approve clinical trial procedures to make sure human subjects are protected. They monitor a trial's progress and can shut it down if patients are put at unacceptable risk.

However, Turgay left the board in the dark for as many as four months about serious reactions that sent two child subjects to the emergency room. In one of these cases, Turgay had to be told to provide parents with information on how to safely give medications after a child was accidentally given 10 times the study dose of a powerful antipsychotic. The child's tongue swelled, his eyes rolled back and speech faltered.

The FDA suggested there was a lapse in oversight by the research board supposedly supervising the experiment.

"I knew of (research ethics boards) in the U.S. that would suspend all research of a (clinical investigator) because of his late reporting of (serious adverse events)," the FDA inspector wrote in her 2004 report. "(In this case), it certainly would have been reasonable."

Turgay died in 2010. Hospital spokeswoman Holly-Ann Campbell said no current employees were involved in the study or its oversight and said "we cannot speak to how this situation was managed at that time."

The pharmaceutical company that sponsored the trial refused to say how much it paid Turgay in grants, consulting fees or to give lectures about medical conditions and drug treatments.

At the University of Calgary, Dr. Remo Panaccione's has received money for consulting and lecturing from at least 26 different pharmaceutical companies.

Panaccione, a leader in inflammatory bowel disease research who was inspected by the FDA in 2007 and cited for a violation, said it is "necessary" to interact with drug companies to ensure research is beneficial for patients.

"With research dollars being harder and harder to get, both researchers and academic institutions need to look at other partnerships to insure we continue to move our respective fields forward," he told the Star.

The number of drug makers that have given him money "demonstrates an involvement across the field and not with one company in particular," he added.

Two studies funded by one of those companies, AbbVie, was the focus of the 2007 FDA inspection.

The FDA found Panaccione had not told the university's ethics board about three test subjects who were hospitalized during a trial studying the use of the drug Humira to treat Crohn's disease.

Panaccione blamed his staff for the "oversight." He said the hospitalizations were reported to the sponsoring drug company but not the university's ethics board. He said the hospitalizations were due to a Crohn's flare-up and not the study drug. An AbbVie spokesperson said, "all clinical trials get audited by regulatory agencies and we fully support and respect this process."

Some Canadian doctors who have been subject to FDA inspections describe the U.S. agents as hard-nosed investigators hell-bent on finding problems.

In Alberta, Dr. Alexander Paterson remembers the first time he met an FDA inspector in 1988.

"He looked like Dick Tracey with a fedora and a turned-up overcoat. . . . He wouldn't shake my hand. He produced his ID," Paterson told the Star. "They're actually trained detectives and they come up with discrepancies."

Paterson, who works out of Calgary's Tom Baker Cancer Centre, is a renowned cancer researcher who sits on Health Canada's advisory panel on oncology treatments.

He also holds the dubious distinction of being cited for violations in three FDA inspection reports — in 1988, 2002 and 2004 — more than any other Canadian doctor, according to a Star analysis of available FDA data.

The unfavourable report card could be the result of being at the forefront of research into new cancer drugs, he said, which could prompt more FDA inspections than those of the average Canadian researcher.

During the first inspection, the FDA inspector uncovered a series of problems with the trial, including one the FDA said was "extremely" concerning: Patient information submitted by the pharmaceutical company to the FDA (to get the drug tamoxifen approved to treat cancer) did not match medical records found in Paterson's possession.

In several cases, the copies given to the regulator suggested the treatment worked better than the doctor's own progress notes indicated.

The inspection also found "possibly ineligible patients being enrolled in the study . . . and patients being incorrectly dosed."

Speaking to the Star, Paterson chalked some of the findings up to an “out-of-his-depth” inspector with no clinical trial experience and who used the most up-to-date standards to grade a study started years earlier.

In one case, the inspector’s report says, the record submitted by the drug company said the patient’s response to the treatment involved “no change.” This was in direct conflict with the doctor’s record, which “lists the patient’s response as ‘worse.’ ”

The inspector said he found several records at Paterson’s clinic where information was crossed out and changed, “especially in the ‘patient response’ section.”

At the time, Paterson and the drug company both denied making the changes.

“I certainly don’t think there was any tampering with the data,” Paterson told the Star. “You can never exclude that. (But) I really don’t think that would happen.”

He said it was “a good study” that led the FDA to approve the drug “to the benefit of many patients.”

The Star found numerous Canadian doctors broke the rules put in place to protect the safety and welfare of clinical trial subjects.

Nearly 20 doctors across the country enrolled patients into their studies who should have been excluded, many because of pre-existing health conditions that could make experimental treatments risky.

While researching a new drug for chemotherapy, the Saskatchewan Cancer Agency’s Dr. Muhammad Salim enrolled a patient who should not have been accepted because of uncontrolled hypertension, a 2003 FDA inspection found. Salim did not remove another patient, as required by the study’s rules, when his disease worsened. Salim’s trial also did not report two cases of side-effects, including a gastrointestinal bleed.

A spokeswoman for the cancer agency told the Star that Dr. Salim “won’t be made available” for an interview.

In one case, a clinical trial by Canadian doctors became the focus of the court.

A 2013 lawsuit claimed drug maker Boehringer Ingelheim misrepresented the safety of Pradaxa, a blood thinner that some patients and their families have blamed for causing serious bleeding and death.

The lawsuit went after three Hamilton institutions: McMaster University, Hamilton Health Sciences and Population Health Research Institute, a centre jointly operated by the university and the hospital network and that runs clinical trials in Canada and across the world.

SCOTT GARDNER
After poring over study datasets following a U.S. FDA review of a blood thinner drug, Hamilton's Dr. Stuart Connolly and his team uncovered 81 new adverse events.

The institute's Drs. Stuart Connolly and Salim Yusuf led the sole clinical trial for Pradaxa that played a significant role in the drug being approved in the United States and Canada.

The lawsuit alleged the clinical trial failed to report side-effects and produced "tainted data" to get the drug approved.

The road to Pradaxa's approval had been bumpy. The FDA had initially rejected the drug maker's request to have Pradaxa approved because patient datasets included transcription and auditing errors that "called into question the overall quality of those datasets and (the FDA's) confidence in them."

Then, in August 2010, U.S. inspectors descended on the research institute and found more deficiencies. Among them, there was no data management plan in place until months after the first of the 18,000 patients were enrolled.

"If you do an inspection in a huge study like that . . . there is always going to be some finding. There were some findings, but none of them were considered major," Connolly told the Star.

Spurred by the FDA's initial rejection, Connolly's team pored through its datasets. In a 2010 correction to their research article published in the New England Journal of Medicine, Connolly's team said they uncovered 81 adverse events that were never reported — including a stroke, heart attacks and major hemorrhages — spread across the patients taking either Pradaxa or the medication it was tested against.

The drug was resubmitted and approved — a testament, Connolly says, to the overall quality of the study and its findings.

"In a database with close to a billion data points, there are sometimes going to be errors," he said. "There were some deficiencies. I totally agree. We had some of the data that wasn't perfectly accurate on the first filing.

There were some events that we found when we went back and took a second look. But those are relatively small issues compared to the clarity and robustness of the initial results."

In May, Boehringer announced it would pay $650 million to settle 4,000 lawsuits against Pradaxa, emphasizing in a press release that it stands firmly behind the safety of the drug. The lawsuit naming the Hamilton institutions is one of them. The institutions told the Star they had no comment as the settlement process "is not complete." They said they have "complete confidence" in the research.