

MOTHERISK PROGRAM SUMMARY OF FINDINGS TO DATE

Motherisk is a program founded by Dr. Gideon Koren in 1985 for research and clinical care related to the safety and impact of drugs on the developing fetus and newborn. The Motherisk Program consists of a call centre that provides information to approximately 120 women per day about drug and chemical exposures during pregnancy and lactation, a research laboratory that examines patterns and impacts of drug and chemical exposures during fetal and early childhood development, and a clinic for the evaluation of children suspected of having Fetal Alcohol Spectrum Disorder. The Motherisk Program also operated a drug testing laboratory (MDTL) that conducted analyses of hair and other material to identify exposure to drugs and other chemicals. Originally developed to conduct analyses for research, the MDTL also conducted testing at the request of government agencies and private parties for a variety of purposes including child protection and criminal prosecution. The MDTL ceased operating in March 2015 and closed permanently in April 2015 (for all purposes except research).

Over the last 11 months, concerns have been raised about the MDTL as well as other components of the Motherisk Program. The Hospital for Sick Children (SickKids) has taken those concerns extremely seriously, cooperated fully with an independent review, and conducted its own investigation of the concerns that have been raised. This document outlines the learnings and actions taken by SickKids to date.

MDTL

In late 2014, concerns were raised about the quality and validity of drug tests performed by the MDTL for use in legal proceedings. Retired Justice Susan Lang was appointed by Order in Council in November 2014 to conduct an independent review of MDTL with the complete support of SickKids. The review was originally expected to be concluded in June 2015 but the scope of the review was broadened in March 2015 and is now expected to be concluded in December 2015. In addition to Justice Lang's review, SickKids has been conducting its own review of the MDTL and is providing the following learnings to date:

1. **Lack of forensic accreditation:** Forensic laboratories use carefully documented procedures to ensure the integrity of data submitted for consideration by the court system and in some jurisdictions have specific accreditation verifying the application of those special procedures. In Ontario, there is no registry for forensic toxicologists. The

MDTL was not operating as a forensic laboratory, and its staff did not have formal forensic laboratory training.

In responding to requests for laboratory testing for use in legal proceedings, the MDTL did not hold itself out as a forensic lab. Indeed, when staff testified, we have been advised that they identified themselves as clinical scientists or clinicians rather than as forensic scientists. However, staff may not have routinely identified for the courts the limitations of the results and how their operating procedures differed from those in forensic laboratories.

SickKids' Action:

The reliance on medical evidence in legal proceedings is complex. There is a shared responsibility between the judicial system and health care providers to develop a common understanding of what standards are acceptable for different purposes. SickKids is implementing a program to ensure that staff who testify in court understand their roles in the judicial system.

2. Processes, standards and proficiency testing: Accurate and reliable drug testing requires strict adherence to established processes for the preparation and analysis of samples, sample storage, and results reporting.

Laboratories such as the MDTL that provide data for clinical or forensic use should have a robust quality assurance program and standard operating procedures to guard against such inconsistencies. The MDTL had neither in place until 2007 when pre and post analytic policies were implemented. By early 2011, standard operating procedures for MDTL were in place.

For many years, MDTL has participated in the Society of Hair Testing's (SoHT) "proficiency testing" program, through which the SoHT sends out hair samples containing known quantities of drugs to participating organizations for testing. This process provides an opportunity for participating organizations to validate that their testing processes are reliable as compared to the results achieved by other participating organizations. Initially, SickKids believed that MDTL's participation in the SoHT's proficiency testing with good results was assurance that the MDTL's results were reliable. However, in February 2015 we learned that for several years, results from another laboratory used to confirm results from the MDTL were submitted to the SoHT as MDTL's results. As a result, for those years, the SoHT process does not provide any assurances with respect to the MDTL testing results. This is clearly completely unacceptable and deeply regrettable. This issue was resolved by 2011.

SickKids' Action:

As soon as SickKids became aware of this information, it temporarily suspended and then permanently closed the MDTL for all purposes except research.

3. Testing methodology: The initial approach to drug testing by MDTL for research purposes relied on immunoassay testing and these tests were used for results reported to the judicial system. However, definitive testing for a particular drug requires confirmation by an additional method. Mass spectrometry (“MS”) based testing is the accepted standard for confirming the presence of a drug identified by a presumptive test like immunoassay and for determining quantities of a drug present in a sample.

Whereas the MDTL changed to gas chromatography-mass spectrometry (GC/MS) for testing cocaine and some other drugs in 2010 and liquid chromatography-mass spectrometry (LC/MS-MS) in 2014, it continued to use immunoassay testing for some drugs including cannabinoids until the MDTL was closed in 2015.

SickKids’ Action:

MDTL has been permanently closed.

4. Oversight of MDTL operations: Opportunities for interactions between clinical and research colleagues are one of the many strengths of SickKids, and the “bench to bedside to backyard” principle has resulted in many significant contributions to the understanding, treatment and prevention of disease. While this principle allows the hospital to provide world class and ground breaking care to its patients, it also carries the risk of a new and novel technology, procedure or treatment being available for patient/client use before robust infrastructure is created to protect against any risks associated with such novel technology, procedure or treatment. This is what the hospital now believes occurred with the MDTL.

The technology relied upon by the MDTL and the expertise developed grew out of the largely independent domain of an individual Principal Investigator within the hospital’s Research Institute. As the research and work being done was cutting edge and novel, as most research is, the Research Institute did not oversee the activities or results of MDTL at a granular level. When it became apparent to the Hospital that the activities of the MDTL involved a significant non-research (“clinical”) component, which is unusual for a research laboratory, steps were taken to align the MDTL with the Department of Paediatric Laboratory Medicine to ensure appropriate quality oversight. While well intentioned, the execution of these steps was too slow, due in part to assurances from the MDTL of their successful participation in external proficiency testing, as well as an initial focus on improvement of non-analytical policies and procedures. It is clear in hindsight that there should have been tighter oversight of the lab.

SickKids' Action:

As concerns became clearer in late 2014 and early 2015, the hospital closed the MDTL and appointed a new Director of the Motherisk Program, Dr. Shinya Ito, Division Head, Clinical Pharmacology and Toxicology at SickKids.

SickKids has amplified efforts to confirm that there is a rigorous quality review system for all clinical laboratories to ensure that they have a high level of appropriate oversight, that the results produced are valid and reliable and that testing is performed in a manner that meets all quality and safety standards.

Research

Dr. Gideon Koren has had a very active research program at SickKids for many years, encompassing many different areas of research related to pharmacology, toxicology and maternal/child health. SickKids has been looking into several areas related to Dr. Koren's research, including scientific integrity, potential conflicts of interest, and the ongoing research studies.

1. Scientific Integrity

The media has reported on a disagreement over the interpretation of one scientific paper published in 1997 by Dr. Koren and colleagues that reviewed and analyzed a series of papers studying the safety and efficacy of antihistamines in pregnancy to treat morning sickness. The disagreement arose when a 2013 publication could not recreate the analysis that Dr. Koren's group conducted. The authors of the 2013 study noted that they could only identify 22 of the 24 publications cited in the 1997 study and that they could only identify 139,414 subjects, rather than the larger number ("over 200,000" cited in one line of the paper; 174,568 subjects described in a table in the paper) identified in the Koren publication. They also questioned the validity of claims made in the paper regarding the safety and protective effect of antihistamines.

Dr. Koren has had research funded by Duchesnay Inc., the manufacturer of Diclectin, and has received payment from Duchesnay for various services. Some media reports on this scientific disagreement appeared to question Dr. Koren's scientific integrity, suggesting the possibility that scientific bias might have been created by the financial relationship between Dr. Koren and Duchesnay. These concerns are separate and distinct from concerns about the MDTL except for the commonality of leadership.

SickKids Action:

SickKids leadership asked SickKids' Research Integrity Advisor (who is responsible for reviewing any allegations of scientific misconduct) to investigate whether data had been falsified or fabricated.

The investigation by the Research Integrity Advisor noted that there had been errors made in the citation of references in the 1997 meta-analysis and that the total number of subjects had been overstated but found no evidence that data had been fabricated or falsified. The Integrity Advisor identified 174,568 subjects across 24 studies – so found the missing citations and subjects. He did note however that “the over 200,000” subjects referenced in one part of the Koren paper was an overstatement.

The review by the Research Integrity Advisor did not address the safety or protective effect of anti histamines during pregnancy in the 2013 study. We believe this is a scientific debate based on different interpretations of data. To confirm this, we are asking an expert in the field to conduct an independent reanalysis of the original data in the 1997 meta-analysis.

Issues of scientific misconduct are serious and must be examined. SickKids is committed to the highest standards of research. If further concerns are raised regarding Dr. Koren's research we will investigate and ensure any issues identified are appropriately addressed. It is important to separate scientific misconduct from legitimate scientific controversy which is healthy and is what leads to advances in science that improve the care we can provide to patients.

2. Potential conflicts of interest

Questions have been raised regarding a potential conflict of interest, based on the fact that pharmaceutical company Duchesnay Inc. Canada, the manufacturer of Diclectin – the only drug approved by Health Canada to treat nausea and vomiting in pregnancy – is a source of funding for Motherisk programs and research and some of the research and clinical work of Motherisk has focused on the use of Diclectin. The former Director of Motherisk, Dr. Gideon Koren, also consulted for Duchesnay. Motherisk has provided information on Diclectin on its call lines and in its pamphlets, without consistently declaring Duchesnay's role as a funder of Motherisk.

Collaborations between industry and hospitals/researchers are critical for encouraging innovation that leads to the discovery of new health care products/services/methods; however, such relationships may lead to perceived or actual conflicts of interest. Significant potential conflicts should be disclosed and managed. Through SickKids' annual conflict of interest declaration process, Dr. Koren has disclosed funding received from various sources including Duchesnay.

Dr. Koren's long-standing academic and funding relationship with Duchesnay was typically disclosed on publications that directly relate to Diclectin, and his online profile noted that he consulted for Duchesnay. However, Duchesnay's support and the support of other companies was also not consistently acknowledged on the Motherisk website and in several Motherisk pamphlets. In a number of publications, Dr. Koren also acknowledged funding through the "The Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation". This is a name Dr. Koren gave to an aggregate of donated funds in support of his research. These unrestricted funds were donated by a variety of individuals and organizations to be used at the discretion of Dr. Koren to fund his research. The primary donor of unrestricted funds in recent years was Duchesnay, pursuant to a contract between Duchesnay and The Hospital for Sick Children Foundation. In some cases where "The Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation" is acknowledged, Duchesnay funding is also acknowledged. In other cases, Dr. Koren only acknowledged that fund.

SickKids' Actions:

SickKids has since added disclosures to the Motherisk website and Motherisk publications, noting all corporate funding received by the program of over \$5,000 for the past four years. On pamphlets/sites that specifically mention Diclectin, a disclosure statement noting Duchesnay's support for Motherisk has been added. SickKids asked Dr. Koren to stop using the "Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation" designation for donated funds in December 2014.

We acknowledge that funding received by a hospital or scientist from industry may raise concerns for members of the public and the medical community regarding conflicts of interest. When potential conflicts occur, it is important that steps are taken to guard against bias and to ensure transparency allows for bias to be considered in interpreting findings. This allows other experts in the field to replicate or refute findings for findings that are published in peer-reviewed scientific journals. Bias is difficult to determine and we are committed to providing any information necessary for the scientific community to evaluate the work on its own merits.

SickKids is refreshing its Conflict of Interest policy, to ensure (a) it takes into consideration health sector best practices as they relate to disclosure and management of conflicts of interest; and (b) that all relevant information is accessible and analyzed in a consistent manner across the organization.

3. Other Research-related Questions

SickKids' Action:

SickKids' requested that the SickKids Research Ethics Board (REB) undertake a formal review of all active research studies under Dr. Koren's name, in light of concerns over the MDTL and its association with the research program.

Fourteen studies are currently active, with a new Principal Investigator and the remaining studies have, or will be, closed. SickKids will ensure continuing oversight of the continuing studies as well as support of the trainees involved in the studies to complete their academic programs.

Call centre

The Motherisk Program has an active call centre with four helplines, each of which provides evidence-based information to women, their partners and their health care providers. The general Motherisk Helpline provides information about the risk or safety of prescription and over-the-counter drugs, herbal products, chemicals, x-rays, chronic disease and infections during pregnancy and while breastfeeding. The Alcohol and Substance Use Helpline is a resource that provides information about the effects of alcohol, nicotine and drugs like cannabis, cocaine and ecstasy during pregnancy and breastfeeding. The Nausea and Vomiting of Pregnancy Helpline provides information on managing morning sickness. The Exercise in Pregnancy Helpline provides information on how to exercise safely during pregnancy and breastfeeding.

Six to 8 counselors respond to about 120 calls per day, and provide relevant information. Approximately 10% of the calls are referred to medical staff for detailed analyses and discussion. On average, 250 patients per year are seen in follow-up at a weekly Motherisk maternal-fetal clinic.

SickKids' Actions:

In the interest of a thorough evaluation of all Motherisk operations, and as part of the new Director of Motherisk Dr. Shinya Ito's initial program assessment, SickKids has been reviewing and updating all processes and practices of the Motherisk helplines, including enhancing technology that supports the call centre operations, expanding existing quality assurance activity and quality audits, updating Motherisk-generated information resources and reviewing resources for potential conflict of interest.

As noted above, in any cases where they did not exist before, conflict of interest statements have been added to the call centre protocols.

Summary

Over the course of the last eleven months since concerns regarding the MDTL came to light, SickKids has proactively investigated and addressed these concerns and continues to cooperate with the independent review. Significant and completely unacceptable issues were discovered regarding the MDTL, which led SickKids to cease operations of the MDTL in March 2015.

A review of other areas within the Motherisk program has led to improvements in processes specific to these programs and well as broader organizational learnings.

SickKids is committed to ongoing resolution of the issues that have arisen, and to addressing outstanding concerns and any recommendations that may arise as a result of the independent review.

It is deeply regrettable and completely unacceptable that practices in this particular program did not meet SickKids' standards of excellence. We extend our apologies to anyone who feels they may have been impacted.