TrialScribe
Clinical Research News
at University Health Network

Welcome to the January 2015 edition of *TrialScribe*, a bi-monthly e-newsletter designed to inform researchers and trainees about clinical research news and information at UHN. Included in this issue:

We hope that you enjoy reading *TrialScribe*. If you have feedback or questions, all suggestions are welcome at www@uhnresearch.ca.

- Charles Chan, FACP, FRCPC, MD, Vice President, Medical Affairs and Quality, and Christopher J. Paige, PhD, FCAHS, Vice President, Research;

Research Spotlights

Spinal Cord Injury: Developing a Customized Self-management Program

A spinal cord injury, which occurs when the spinal cord is damaged by trauma or disease, can result in partial or complete paralysis. People who have sustained a spinal cord injury are at higher risk of developing debilitating complications including pain, depression and difficulties controlling their breathing, bladder and bowels. In light of these findings, researchers are examining new approaches to promote the health and well-being of people living with spinal cord injuries.

TRI Senior Scientist Dr. Susan Jaglal is developing a self-management program for people with spinal cord injuries that will address their needs and, in parallel, engage and empower them. Recently, a team led by Dr. Jaglal and her doctoral student, Sarah Munce, consulted a group of Canadians with spinal cord injuries to obtain their perspectives on a self-management program.

For this study, 99 people with spinal cord injury from across Canada completed an online survey. Researchers found that approximately 75% of the respondents rated the development of the self-management program as "very important" or "important". The greatest proportion of respondents believed that the program should include information about exercise, nutrition and pain management, and should be delivered through an internet-based format.

"Our findings could be used to inform the design and pilot testing of a self-management program tailored to the needs of individuals with spinal cord injuries to improve their health and quality of life. Further research is required to determine how the views of individuals with spinal cord injuries change over time," said Dr. Jaglal.

This work was supported by the Canadian Institutes of Health Research, Knowledge Translation Canada and the Toronto Rehab Foundation.

Munce SE et al. BMC Neurol. *2014 Oct 21* [Pubmed Abstract]

Lung Cancer: The Molecular Makeup of Tumours

The American Cancer Society estimates that more than nine million people around the world will die from cancer in 2015. To date, there have been significant efforts made by scientists and clinicians worldwide towards identifying the many genetic mutations involved in cancer development. However, relatively little is known about how these may affect corresponding proteins and contribute to unregulated tumour growth.

PM Cancer Centre Affiliate Scientist Dr. Michael Moran led a team of researchers, including Drs. Ming-Sound Tsao, Thomas Kislinger and Frances Shepherd, in a large-scale study aimed at examining the proteins in cancerous versus normal lung tissue. To accomplish this, they used ultrahigh-resolution protein mass spectrometry, a tool that can measure the type and concentration of proteins that exist within a sample. They identified a series of proteins, called 'protein signatures', that are involved in cellular metabolism, and which were consistently observed in non-small cell lung carcinoma (NSCLC) subtypes (adenocarcinoma, squamous cell carcinoma). SHMT2 (a protein involved in metabolism from one of these signatures) levels were consistently increased in NSCLC tumours. Moreover, SHMT2 is part of a protein signature known to be associated with poor outcomes in adenocarcinoma.

This study provides critical new information that could not have been predicted by genetics alone about how these protein signatures link cancer metabolism and overall survival in lung cancer. Dr. Moran says, "Our next step will be to figure out how these protein signatures act to promote cancer, which is the next phase towards developing more targeted anticancer drugs."

This work was supported by the Canada Research Chairs Program, the Ontario Research Fund, the Canadian Institutes of Health Research, the Canadian Cancer Society Research Institute, the Ontario Ministry of Health and Long-Term Care and the Princess Margaret Cancer Foundation.

Li L et al. Nat Commun. *2014 Nov 28.* [Pubmed Abstract]

Several projects have been initiated by the Clinical Research Support Services Planning and Implementation (CRSSPI) team, chaired by Lisa Alcia, Executive Director of Research Operations. In this section you will find the new research policies available on the Corporate Intranet.

External Clinical Research Regulatory Audits/Inspections Policy

Regulatory agencies, such as Health Canada and the US Food and Drug Administration (FDA), can perform on-site inspections for any study conducted under their authority. For example, if a clinical researcher is leading a study under an FDA Investigational New Drug application (IND), the study must comply with FDA regulations and, at any time, the FDA can visit the study site to verify compliance. External regulatory inspections are often preannounced to the sponsor and the investigator.

According to UHN's External Clinical Research Regulatory Audits/Inspections Policy, researchers must notify their division heads and the Research Quality Integration (RQI) department of any upcoming regulatory audits or inspections. Also, researchers must provide both parties with all related correspondence and the agency's stated purpose of the inspection. Given sufficient notice, RQI can perform a pre-inspection audit to help researchers better prepare for a regulatory inspection.

Following the inspection, researchers must submit the audit report or a summary of the audit results with the original documentation to their division head and RQI. Major, serious and critical findings of the visit must be communicated immediately to the division head; the Vice President, Research; and the Vice President, Medical Affairs and Quality. This escalation procedure helps UHN identify institutional gaps and improve education around best practices. Please refer to the policy for the definitions of major, serious and critical findings. The policy can be accessed by clicking here or by visiting the UHN Policies webpage.

Quality Improvement and Best Practices

The Research Quality Integration (RQI) program focuses on areas critical to maintaining subject safety, data integrity and regulatory compliance. Through internal quality auditing and site support, the RQI team assists researchers in recognizing opportunities for enhancing effective processes and operations, and identifies best practices that can be shared throughout the organization. The following is a continuation of a series of case studies highlighting examples of how to manage gaps in procedure and improve research best practices.

What is an External Clinical Research Regulatory Audit or Inspection?
Certain regulatory agencies, such as Health Canada and the FDA, have programs in place to ensure the safety and to protect the rights of participants involved in the clinical trials for which they have regulatory oversight. One component of these programs is on-site inspections. In some cases, the study sponsors and investigators will be alerted of an upcoming site visit. The regulatory agency may also visit the study's Research Ethics Board (REB), and clinical and/or preclinical laboratories. Researchers must provide regulatory officials with access to and copies of records or reports with regards to the disposition of the investigational product and subjects' case histories.

External Clinical Research Regulatory Audit or Inspection – Case Study

Note: the following is a fictional case concerning the responsible conduct of research

Dr. X was conducting an FDA-regulated clinical trial evaluating the efficacy of an investigational drug to treat hepatitis C virus (HCV) infections. The REB-approved study protocol stated that express written consent would be obtained prior to enrolling participants into the study. However, given that half of the recruited participants had already provided consent for one of Dr. X's previous studies that involved the same investigational drug, Dr. X decided that it was not necessary to obtain their consent again. The REB was not notified of this protocol deviation.

Midway through the clinical trial, the FDA informed Dr. X that they would be sending an auditor to conduct an on-site inspection of the study. Dr. X was not familiar with UHN's External Clinical Research Regulatory Audits/Inspections Policy and did not notify the division head or RQI of the forthcoming inspection.

While reviewing the study documents, the FDA inspector discovered that Dr. X was missing consent for half of the study participants. Subsequently, the FDA issued an Inspection Report requesting that Dr. X provide them with a corrective and preventative action plan (CAPA). Without consulting with UHN leadership or RQI, Dr. X submitted a CAPA, which the FDA deemed as inadequate.

Quality Improvement and Best Practices

Failure to Notify RQI of Upcoming External Audits or Inspections – What are the Risks?

Without signed consent forms and accompanying documentation, there was nothing to show that Dr. X's participants were informed of the study protocol, risks and benefits prior to enrolment. Moreover, there was nothing to prove that their enrolment was voluntary. Thus, Dr. X and UHN could have been held liable should anything have happened to the participants while on trial.

Failure to obtain consent from study participants is also a clear violation of the FDA's regulations. Consequently, the FDA posted a Warning Letter identifying Dr. X and the study violations on their publicly accessible website: www.fda.gov. The FDA also prohibited Dr. X from being involved in any FDA-regulated trials for a period of five years and posted the disqualification notice on their website. These consequences negatively impacted Dr. X's research productivity and severely compromised both Dr. X's and UHN's reputation.

Why is it Important to Notify RQI of an Upcoming External Audit or Inspection?

The RQI department offers pre-inspection audits that can mimic external inspections. Accordingly, pre-inspection audits are an excellent way to identify outstanding issues and implement corrective actions before they are discovered by an external inspector. Moreover, the RQI department can help researchers prepare a CAPA if they are provided with the audit report or a summary of audit results. RQI can also develop and implement institution-wide training and education to prevent having the same violations committed by other investigators. Thus, RQI can help investigators better prepare for external inspections and respond to any negative findings if they are notified of the upcoming inspections and provided the results thereof.

News and Events

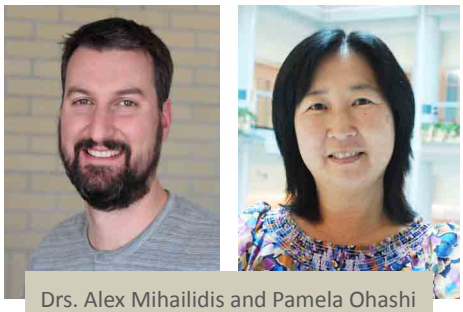
UHN Will Host a New National Research Network

On December 15th, the federal government announced the creation of four new national research networks and the renewal of an existing network. One of these new networks—abbreviated as AGE-WELL—will be based at TRI and will be co-led by Dr. Alex Mihailidis (TRI Senior Scientist). The federal government has committed $36.6 million to AGE-WELL over the next five years through the Networks of Centres of Excellence (NCE) program.

"AGE-WELL will use the world-class facilities at Toronto Rehab and Simon Fraser University and a strong research and industry partnership network across the country to establish Canada as a leader in designing and implementing technology that contributes significantly to the well-being of older people," said Dr. Mihailidis.

Dr. Pamela Ohashi (PM Cancer Centre Senior Scientist) will play an instrumental role in another newly established national research network—BioCanRX—devoted to the development of biological therapeutics for treating cancer. Biological therapeutics harness the power of antibodies, viruses and human cells to treat disease. Dr. Ohashi will co-lead the program focused on immune cell therapies. Over the next five years, BioCanRX will receive $25 million from the federal government.

The NCE program provides funding to help create networks—which bring together a critical mass of research, development and entrepreneurial expertise—and to focus these networks on strategic areas.



Drs. Alex Mihailidis and Pamela Ohashi

Custom Manufacturing at UHN

Did you know that UHN researchers have access to the Machine Shop at the PM Cancer Centre, which provides same day 3D printing?

The Machine Shop also has capabilities for:

- Sophisticated "computer numerical controlled" milling and lathing, which can shape metal and other materials into highly complex and precise shapes
- Sheet metal shaping
- Gas metal welding
- Computer assisted design (CAD)

For more details on how to access services from the Machine Shop and other UHN core facilities, please see UHN Facilities Home on www.uhnresearch.ca.

TrialScribe is brought to you by UHN Research Communications. We hope you have enjoyed reading this newsletter. If you would like to provide feedback, please email www@uhnresearch.ca.

Please note: this newsletter is designed for UHN internal purposes and, as such, contains links to some documents that can only be accessed through UHN's Research or Corporate Intranet. Some images adapted from the image archives of stock.xchng.ca.

The next issue of *TrialScribe* will be released in March 2015.