Knowledge Translation in the Post Market Evaluation of Drug Safety and Effectiveness Data

Report from a workshop held Nov. 25 & 26 2007 at the University of Ottawa, hosted by the McLaughlin Centre for Population Health Risk Assessment

Background and Context

The need for post-market surveillance of drugs

Prescription drugs are typically approved for sale, for very specific medical conditions, based on clinical trials that involve a limited number of people for a relatively short time. However, many drugs are then used by a large number of people, sometimes for a very long time. And some drugs are used to treat medical conditions for which they have not been tested or approved. This situation has given rise to concerns in Canada and internationally that not enough is known about the ongoing safety and effectiveness of drugs, especially those taken by persons with complex conditions, elderly persons and children.

Currently, no single organization or group in Canada has the mandate, responsibility or capacity to systematically track the safety and effectiveness of drugs once they are approved for marketing. Meanwhile, the post market evidence about the impact of drugs that does exist, such as from some observational studies and adverse reaction drug reports, is not well communicated to policy makers, prescribers or the public because of the absence of a comprehensive and coordinated system to evaluate safety and effectiveness through a drug's life cycle. When information about safety and risks is not effectively communicated, then no risk management is possible.

This situation has been a concern among some groups for a long time, but more recently the risks of a lack of drug safety information have been underscored for the public through the media reports about:

- drugs withdrawn from the market because of the harm caused (the most recent and highly publicized case being that of Vioxx® and the increased risk of heart attack and stroke);
- the unsettling results of a major study tracking women on estrogen/progestin therapy for menopause (In a study of 16,000 women, harm (from an increased risk of breast cancer, heart disease, stroke) was found to outweigh the combination's purported benefits (decreased risk of heart attack, breast cancer & hip fracture in women at risk).)
- concerns about the widespread use of drugs in populations where there is little, equivocal, or no evidence of benefit. For example, the use of anti-depressant drugs (including selective serotonin reuptake inhibitor (SSRIs)) among children and

adolescents. Another example is the use of antipsychotics in elderly persons with dementia, where there is evidence of harm and lack of benefit.

Harm resulting from insufficient safety information about prescription drugs is not new, as evidenced by tragedies in the past century such as the effects of thalidomide on the fetus and DES (diesthylstilbestrol) on the daughters (vaginal cancer) of women given the drug during pregnancy. But there is a growing recognition of the need to better determine the risks and benefits of prescription drugs, after they are marketed and become widely used. In 2006, the U.S. Institute of Medicine report, *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, examined changes needed in that system to avoid future preventable drug catastrophes. Italy, Australia and the United States are trying to respond to the need for more post-market surveillance of prescriptions drugs. And in the U.S., the Agency of Healthcare Research and Quality (AHRQ) has helped to fund 14 Centers for Education and Research on Therapeutics (CERTs).

Proposals for coordinated & comprehensive post market surveillance strategies

In Canada, there is mounting consensus among policy makers, researchers, patient groups and health care professionals that this country needs a system of post market surveillance. And impetus for such a system is coming from several different sources: 1) Health Canada is interested in a formalized surveillance system because of its plans to introduce a system of progressive licensing for prescription drugs which will allow for ongoing assessment of risks relative to therapeutic benefit through the licensing stages 2) The National Pharmaceutical Strategy working with key partners such as the Canadian Institutes of Health Research (CIHR), the Canadian Patient Safety Institute (CPSI) and the Canadian Drug Policy Development Coalition (a group of concerned researchers, academics, policy makers and health professionals), has proposed a network of independent research centres, to operate at arm's length from government and industry in determining the impact of the use of prescription drugs in society. The business plan for this network proposes a model for developing an integrated and comprehensive approach to support the evaluation of drug safety and effectiveness in Canada and estimates its potential costs.

Provinces have a strong interest in the area of post-market surveillance and must decide whether or not to list a new drug on provincial formularies — for example, they can require more safety and effectiveness information before making a decision to pay for the drug. As well, provinces could also direct under what circumstances particular drugs should be used (an example is the restriction the Manitoba government has put on the use of the drug Aricept in individuals with advanced Alzheimer's disease). However, at the provincial level, it is difficult and potentially repetitious to gather the needed information (such as a comparison of standard and newly approved treatments) to guide listing decisions. Information produced from observational studies conducted by groups like the Institute for Clinical Evaluative Sciences (ICES) have been useful in identifying risks associated with marketed drugs.

Knowledge Translation[1]: What it is, why it is needed

In the context of this workshop, Knowledge Translation was understood to mean finding ways to

1) communicate existing and future post-market evidence about prescription drug safety, effectiveness and use to the appropriate parties in a way that is easily understood, and
2) ensure, through proper targeting, understanding of barriers, and the use and evaluation of interventions, that the evidence is acted on *so that patients benefit from improved drug safety and effectiveness.*

In his keynote address, *Principles of Knowledge Translation*, Prof. Jeremy Grimshaw underscored the need for knowledge translation (KT) by citing studies that indicate 30 to 40 per cent of patients do not get treatment of proven effectiveness, and 20 to 25 per cent of patients receive care that is not needed or that is harmful.

He later cautioned, however, there are no "magic bullets" in KT interventions. Their impact varies across professions and settings and reviews of KT interventions indicate that they lead to a level of change in practice that is modest -- between five and 10 per cent uptake. This may seem to be a small amount but from an overall population perspective, Dr. Grimshaw points out, it is important and can lead to improvements for many, many people. Further, he said a major gap in the world literature is that there are no up-to-date studies on how to change prescribing habits of health professionals.

At its most basic, Grimshaw said KT is about ensuring that:

- Stakeholders are aware of, and use, research evidence to inform decision making and that
- Research is informed by the current available evidence and the experience and information needs of stakeholders.

To illustrate the range of stakeholders and their varying evidence needs for KT, he listed six categories of stakeholders (researchers, health professionals, patients, administrators, policymakers and industry) and considered their relative needs for four different types of research (basic, clinical, health services and population health). In addition, there are more universal barriers to KT cited by Grimshaw which include:

[1] Knowledge Translation was the term used in this workshop but there is a dizzying array of terms, and even more definitions, that address the practice of finding ways to communicate and act on scientific/medical evidence. In his address, Grimshaw listed 27 others (including Knowledge Transfer, Knowledge Implementation, Translational Research and Knowledge Exchange) and noted that the morass of terminology is an impediment.

- Structural/health system including financial. As an example, he noted that an important life-saving drug was not available to Zimbabweans because it was not listed in the World health Organization's essential drug list.
- Organizational. For example, when there are drugs available to improve outcomes after certain types of strokes, but the diagnostic imaging equipment to determine eligibility is not universally available.
- Peer group effects. These occur when local standards of care are not in line with desired practice
- Knowledge, attitudes and skill of the person requiring the evidence
- Professional/patient interaction. The interaction is imperfect, in part, because of the human brain's limited ability to undertake the complex information processing needed to understand and transmit the KT message.

The need for accumulated evidence: Grimshaw stressed that it is vital that people "don't believe the hype" and "don't generate the hype" and should not base KT on early single studies Grimshaw listed four sources of high quality guidelines and systematic reviews:

- The Cochrane Collaboration
- The U.S. Agency of Healthcare Research and Quality (AHRQ) evidence-based practice reports,
- The Human Genome Epidemiology Network (HUGEnet), and
- Multiple guidelines.

But he added that none of these sources provide enough information on relative safety/harm. Grimshaw noted that two new Cochrane subgroups examining behaviour change have been commissioned by the Canadian Agency for Drugs and Technologies in Health (CADTH) and its Canadian Optimal Medication Prescribing and Utilization Service (COMPUS):

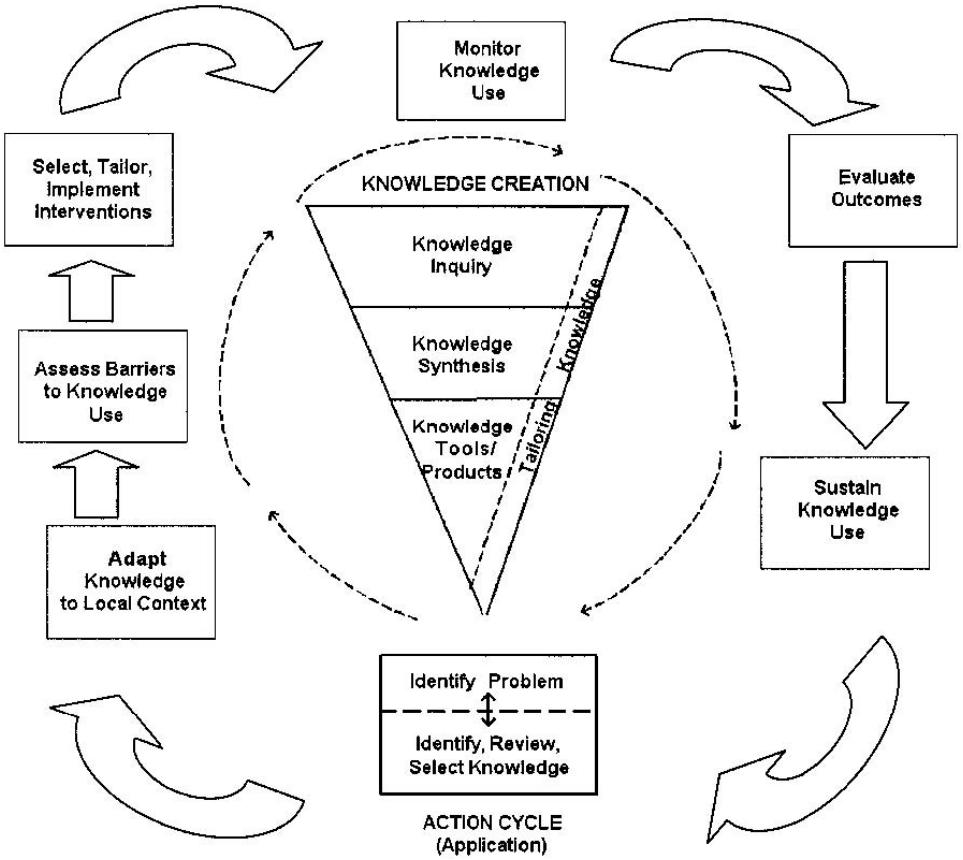
- The Cochrane Effective Practice and Organization of Care (EPOC) group, which is reviewing systematic reviews on changing prescribing behaviour and contributing to the CADTH/ (COMPUS) linked website, Rx for Change.
- The Cochrane Consumers and Communication Review Group, which is reviewing interventions aimed at improving communications with patients/consumers. For example, the group has looked at studies of the use of decision aids for treatment options and how their use improves patients' knowledge and reduces the conflict they feel about the medical decisions that they face.

Strategies to facilitate KT: When it comes to targeting policymakers and managers, KT strategies found to help facilitate KT (based on in-depth interviews) include personal contact, the timeliness and relevance of the evidence/information being communicated, and the inclusion of summaries and recommendations. The barriers to KT include the absence of the first two strategies mentioned above, as well as mutual mistrust and power and budget struggles. Grimshaw said current, but not yet evaluated, ideas for KT with these stakeholders include the targeted push of "actionable messages" and the use of knowledge brokers.

Educational outreach — an approach derived from social marketing, which highlights the communication of three messages in 10 to 15 minutes — involves the use of a trained person to meet with providers in their practice setting to give information aimed at changing the provider's practice. This particular KT intervention—also known as "academic detailing"-- has proven to be effective for changing prescribing habits. A 2007 systematic review of studies and trials found that the median "absolute improvement" in prescribing behaviour was about 4.8 per cent (with the range between from 3 to 6.5 per cent) — a "relatively expensive" but perhaps still efficient intervention, according to Grimshaw.

In his conclusion, Grimshaw stressed the need to embed KT and its evaluation in the creation of knowledge (e.g., studies). The Knowledge to Action Loop diagram[2] which he drew attention to, underscores the need to adapt and tailor KT intervention tools to local circumstances and, subsequently, to monitor and evaluate their use in the translation of knowledge.

Knowledge to Action Loop



[2] From: Graham ID et al. Lost in Knowledge Translation: Time for a Map? *Journal of Continuing Education in the Health Professions*, Winter 2006; 26(1):13-24.

The challenges associated with Knowledge Translation of research/evidence about the "real world" safety, effectiveness and use of prescription drugs

Key challenge**:** To find ways to ensure that useful evidence/information about patients' 'real world' experiences with drugs is communicated effectively to the appropriate parties (stakeholders) in ways that benefit patients and improve the safe, effective and efficient use of drugs for society. Current evidence indicates that, for some widely-used drugs, there are large deviations from optimal use. At the same time there is, on the part of some, an "extraordinary resilience to beat back change" in how drugs are prescribed.

Research challenges

How to identify the true risk/benefits of new drugs, especially when adverse side effects may be common (such as cardiovascular problems) rather than rare.

Dr. Anne Holbrook drew attention to this issue in her discussion of the use of COX 2 inhibitors and NSAIDS (non-steroidal anti-inflammatory drugs). The former drugs were developed to have fewer gastrointestinal complications (compared to NSAIDs), but they presented an increase in cardiovascular risk for some who took them. Still, it was a rare adverse effect — liver toxicity — that led to the market withdrawal of one drug in the COX-2 inhibitor class (lumiracoxib), not the more common adverse effect of increasing the risk of cardiovascular problems. This illustrates how "rare and unusual ADRs (adverse drug reactions) drive decisions when common adverse events cause far more harm." The "rare and unusual" are easier to identify clinically and easier to pick up retrospectively in observational studies. Dr. Holbrook also drew attention to the cardiovascular risks associated with the use of glitazones (a class of drugs, less than a decade old, to control Type 2 diabetes). She noted that because congestive heart failure is so common in the population with Type 2 diabetes, the increased risk does not always "trigger a signal" that the CHF may be due to the drug.

- *How to test claims that a new drug is better/more efficient than the standard treatment.* To be granted marketing approval by the regulator, new drugs do not have to be compared to the existing standard drug treatment. Depending on the drug they may be compared to placebo or a less commonly used drug treatment. Also, clinical trials are costly and there is little funding or even an opportunity for independent trials to compare a new drug with an old standard drug.[3]

[3] This particular research challenge was driven home recently by the need for the National Institutes of Health in the US to sponsor a $16.2 million clinical trial to compare two treatments for age-related macular degeneration (AMD). The currently used treatment (bevacizumab) is being used off-label for AMD but has not been proven safe and effective in a clinical trial. The company that manufacturers bevacizumab and a newly developed drug for AMD (ranibizumab) is unwilling to stage the direct head-to-head comparison.

- *How to test claims that the use of a new drug leads to savings in other parts of the health care system.* This is a claim routinely made by pharmaceutical companies, but one that is difficult to test given the way that health care is funded; that is, funding for prescription drugs is typically allocated quite separately from hospitals and clinical services.

- *The need to ensure there is enough accumulated evidence to feel confident before acting, since the findings of initial trials and studies are often contradicted by newer evidence*. This point was emphasized by Prof. Grimshaw in his keynote address (see above, Knowledge Translation: What it is, why it is needed.)

- *Understanding what constitutes 'enough' evidence; knowing when the evidence base is actionable*

- *How to collect evidence in a timely fashion.* Too often evidence and decision making pass each other like two ships in the night. In large part this is because evidence is not produced until after a decision is taken.

- *The potential tension between the benefits to the public of acquiring new evidence about risks and benefits as soon as possible versus the demands on the researcher to publish in a peer reviewed journal which has a lengthy review process etc.*

Knowledge Translation challenges

Several of these challenges were discussed by Prof. Grimshaw in his key note address (see above: Knowledge Translation: What it is, why it is needed.)

- *Making a meaningful difference in patients' lives.*

- *Involving the public more in the decision-making process.* Workshop participants suggested, for example, using citizen juries to help make decisions.

- *Ensuring that the "communicator" is considered to be credible to the audience.* This point was emphasized by several speakers. Most Canadians get their health risk information from the media (see below, Challenges to the Regulator), but one participant stressed that health charities are also considered trustworthy sources. Charities are often are invited to contribute to government policymaking yet government cut-backs mean that their funding is derived more and more from the pharmaceutical industry which may introduce a bias in communications.

- *Identifying and addressing barriers to uptake. Barriers* — whether structural, organizational, cultural/ethnic, related to the peer group, the individual or the relationship between patient and health professional —should be identified and strategies to overcome them adapted to local circumstances.

The question of relative efficacy (and safety) is of importance as ranibizumab at a cost of $1950 per injection is 50 times more expensive than bevacizumab.

- *Tailoring relevant information (for example, clinical or health services) for different audiences (policy makers, health professionals, the public, administrators)*.

- *Keeping information simple (and, therefore, useful).* There are limits to what people can comprehend and act on, and several presenters stressed the need to limit the number of key points to be communicated (three is the upper limit) and to keep the points simple.

- *Bringing the public into decisions about how to allocate resources.* Given the high cost and limited evidence about the effectiveness of some new drugs (for example, cancer drugs), the public should be involved in deciding whether to fund the drugs or, for example, use the money to hire more nurses.

- *Learning from social marketing & adult education strategies.* Knowledge translation is not a new field, though it may be relatively new as it is applied to clinical evidence. These fields can provide useful information about how best to communicate information.

- *Ensuring that KT itself is evidence based.* KT strategies should be evaluated to ensure they work.

- *Being realistic about the scope for changing behaviour and practise*. As noted by Prof. Grimshaw, successful KT interventions with respect to drug prescribing practises typically have a modest effect — perhaps from 4 to 6 per cent change in behaviour—versus changes in reimbursement policy which may have a more profound and encompassing effect although not always with the preferred impact.

Point of care/ prescribing challenges for health professionals

Health professionals:

- *Do not all have the technical/electronic capacity to use advanced treatment decision-making tools.* The Canadian health care system has been slow to adopt electronic medical records. As well, some decision-making tools (such as E-therapeutics, from the Canadian Pharmacists Association) are costly for subscribers. These tools, however, are helpful because individuals cannot process too much complex information about a patient's multiple medication use at one time and electronic algorithms assist with this.

- *Have problems explaining risks to patients in ways that they understand*: For example, how to explain the consequences of not taking a drug and how not to exaggerate benefits (and/or risks) of a drug: the concepts of absolute and relative risk are not well understood by, or explained to, patients. (The top ten drugs in terms of costs to the system tend to relate to cardiovascular health and yet they have only a modest benefit — how can that information be communicated?)

Also, health professionals may need support to encourage non-drug approaches, hence the "Alternative prescription pad" intervention as promoted by COMPUS.

- *Lack incentives to act on evidence.* Peer comparison can be helpful in encouraging a change in practice but in general there are not many incentives.

- *Are uncomfortable acknowledging the futility of treatment*, hence sometimes over-prescribe and use drugs off-label in an attempt to "try/do something". For example, there is no effective safe drug treatment for dementia in the elderly, yet the costly new anti-psychotics are widely prescribed for the elderly in care — one study indicated that 24 per cent of elderly persons admitted to long-term care are prescribed anti-psychotics within 12 months of admission.

- *May be unduly influenced by drug manufacturers, who work very hard to promote their drugs*. Pharmaceutical companies would not spend the money that they do on advertising or sending drug representatives (salespersons) to physician offices unless it worked.

Challenges to the regulator (Health Canada)

- *Health Canada does not have the authority, under legislation, to require: drug manufacturers to issue a risk communication; prior approval of any risk communications issued by a manufacturer; or manufacturers to update the labelling of a product to include new risk information.* Health Canada's only recourse, if it believes there is serious risk of harm to the public, is to withdraw market authorization for a drug.

- *There are no regulatory requirements governing the responsibilities for development and dissemination of new risk information about marketed prescription drugs (or any marketed health products).* However, Health Canada has a policy of working with drug manufacturers in developing such information, and of approving risk communication information developed by manufacturers. The exception to this is when there is a concern that relates to multiple drug products or multiple manufacturers (e.g., a generic version of a drug) and it is not feasible to get all the manufacturers together to vet the risk communication.

- *Drug manufacturers have, in the past, challenged the validity of evidence that Health Canada considered when developing risk communication information*. (Health Canada has considered including the pertinent sources of information in its risk communication information, but there is concern about obscuring the message with excessive detail.)

- *Health Canada is not perceived to be a credible or useful source of information about risk, according to survey results*. Indeed, the workshop was told that health professionals have as much or more confidence in information coming from a manufacturer because they believe a manufacturer would not send out such

information unless the risk was serious. In two surveys undertaken by Health Canada (2003 and 2007) most health professionals reported they were familiar with the regulator's sources of information about risk, but barely half found it relevant, most found it was not current, and only about a quarter of respondents deemed the information to be important. Less than 20 per cent of health professionals had confidence in HC as a source of information, and the same number did not consider the information to be clear, concise, comprehensive or timely. Only four per cent of health professionals said they used HC risk information in their practices (2003 survey). Meanwhile, results of the survey of the public (administered in 2003 and 2006) revealed that most respondents — 64 per cent — identified the media as their source of risk information, and only 10 per cent or less consulted HC's website for information, relying instead on pharmacists, doctors and the internet amongst others.

- *Notwithstanding the above, both health professionals and the public identified Health Canada as the body most responsible for health product safety.*
- *Health Canada has multiple audiences for information about risk and there is a need to target risk information so recipients are not overwhelmed with communications that are not relevant to them*. The public is the target audience for Health Canada's public warnings, public advisory's, product recall notices, It's Your Health circulars, fact sheets and backgrounders, foreign product alerts and information updates. Health professionals and hospitals are the target audience for Dear Health Care Professional Letters, Notices to Hospitals and the Canadian Adverse Reaction Newsletter. (Risk information issued jointly by Health Canada and drug manufacturers include industry-issued public communication, Dear Health Care Professional letters and Notices to Hospitals.)

KT strategies aimed at improving the prescribing of drugs

Presenters stressed that there is no "magic bullet"to KT strateges. However, some successful (and evaluated) examples of KT strategies/resources, as well as some promising (but not yet evaluated) ideas, include:

- *Pharmacists embedded in primary care settings* so that they can consult with doctors, meet with patients and review charts to ensure the optimal use of medication. One such trial, known as the IMPACT (Integrating Family Medicine and Pharmacy to Advance Primary Care Therapeutics) project, took place in Ontario: pharmacists worked part time in seven family medicine group practices. Pharmacists met with patients and with doctors and reviewed charts with the aim of optimizing medication use, identifying cases where patients were over and under treated, and providing timely follow up to ensure both the safety and effectiveness of the medicines. Pharmacists found, on average, four drug related problems for each patient. The most common findings were the underuse of effective drug therapy, and after six months of co-location of the pharmacists with the physicians, there was better medication monitoring and use.

- *Pharmacists trained in academic detailing who visit physicians and provide unbiased information about drugs using materials and approaches similar to*

those used by the pharmaceutical industry. One such service is operated out of Dalhousie University (the Academic Detailing Service under the Faculty of Medicine's Continuing Medical Education) and one project has focused on the care of patients with osteoarthritis. A key message during the detailing visit by a pharmacist to a family physician has been the benefits of exercise and physiotherapy. Physicians were told about adverse events related to COX 2 — and that those drugs were not more effective than NSAIDS (non-steroidal anti-inflammatory drugs). One result of the detailing was a 23 per cent decrease in the use of COX-2 s, with significant effects maintained for 3 months.

- *Computerized decision support*. A couple of examples were given: 1) the COMPETE II diabetes tracker system, developed at McMaster University and available for primary care practices with electronic records capacity, which profiles patients (for level of exercise, smoking, drugs being use) and identifies those at high risk for disease complications and 2) E-Therapeutics, the subscription-based service developed by the Canadian Pharmacists Association, which provides ready information on diagnosis, drug interactions, side effects, alternative treatments and related concerns.

- *Prompting service for preventive care*: A simple reminder system that was initiated for 350 Ontario doctors (350,000 patients) and resulted in a 5 – 6 per cent increase in simple preventive measures, such as mammograms and pap smears. Reminders were sent by email, fax and regular mail.

- *The production of practice profiles for health professionals*, so they can see how they prescribe compared to their peers.

- *Patients' access to their medical records.* One such system is in place at the Sault Ste. Marie Health Centre, where patients have access through a secure portal to their records. Prof. Lisa Dolovich predicted that a social networking approach for drug information will become a reality before there is any widespread use of electronic medical records. She noted that there is already an initiative underway in Hamilton where a social network of clinicians shares information about drugs.

- *Changes in policy, especially reimbursement policy*. For example, when evidence revealed that the then-standard use of wet nebulization for the treatment of acute asthma was equivalent to (and less convenient and more expensive than) the use of a metered dose inhaler for delivering beta-2 agonists, changes in reimbursement policies, together with guidelines and a 1-800 line to provide information, helped to make a significant change in treatment practice.

- *The KT processes and intervention tools designed by the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS).* For example, to improve the use of proton pump inhibitors, COMPUS used 11 tools including academic detailing, a quick reference prescribing aid and interactive presentations for physicians and pharmacists. (The time frame for producing such processes

and interventions is about 15 months.) COMPUS, which is part of the Canadian Agency for Drugs and Technologies in Health, also sponsors Rx for Change, a KT intervention database.

KT strategies for a Drug Effectiveness and Safety Network

Workshop participants suggested the network could:

- Consider KT needs before conducting research; embed KT in the process of conducting the research
- Foster methods development and KT activities among groups like the Institute for Clinical Evaluative Sciences.
- Collaborate with existing KT ventures (such as COMPUS, etc.) and link to the Public Health Agency of Canada to address broader public health considerations
- Develop media strategies, in light of information that more than 60 per cent of the Canadian public get their health risk information from the media
- Establish citizen juries to help with KT and with resource allocation decisions with respect to prescription drugs
- Encourage the creation of a resource where all patients would be required to go, after they receive a prescription for a non-acute condition, for more credible, trustworthy information and counselling. A related suggestion was that that the first "prescription" given to a patient could be for information, not for a drug.