Drug Safety and Effectiveness Network

CIHR IRSC

The Canadian Mosaic of Drug Safety and Effectiveness Strategies

5th semi-annual Drug Safety and Effectiveness Network Meeting

Albert at Bay Suite Hotel

435, Albert St., Ottawa, ON

Meeting Report

October 18th, 2013, Ottawa

Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Background

The Drug Safety and Effectiveness Network (DSEN) convened its fifth semi-annual Network meeting on October 18th, 2013 in Ottawa to bring DSEN funded researchers together with decision makers working within the Federal Regulator; Federal, Provincial or Territorial (F/P/T) drug plans; and, organizations mandated to support F/P/T decision making with respect to drugs (e.g. Health Technology Assessment Organizations), to gain common understanding on the evidence needs of the Regulatory process.

The principal objectives of this meeting were:

- To understand the functioning of provincial and territorial drug plans and decision-making processes
- To engage Network members in discussion on the specific information needs of provinces and territories
- To provide network-wide interactions between DSEN funded researchers and decision makers
- To update participants on recent developments and upcoming plans and activities
- To support a culture of knowledge translation within the DSEN program

In Canada and worldwide, more information is needed on the safety and effectiveness of drugs used by diverse patient populations in real-world settings, outside the controlled experimental environment of clinical trials. DSEN has been established at CIHR in collaboration with Health Canada, and together with stakeholders from across Canada we are working to increase the evidence on drug safety and effectiveness available to regulators, policy-makers, health care providers and patients; and to increase capacity within Canada to undertake high-quality post-market research in this area.

In Canada, Health Canada reviews and approves (or rejects) new drugs for safety and effectiveness based on clinical trial evidence submitted by a drug manufacturer. The Common Drug Review (CDR) makes recommendations to provinces and territories (except for Quebec) as to which drug should be included on their formularies for reimbursement. The Pan-Canadian Oncology Drug Review (pCODR) has the same mandate for new cancer drugs. Following this process, each province and territory will make their final funding decisions. The review process and follow-up on approved drugs then varies according to provinces and territories.

Thus, a better understanding of how the provinces and territories determine which drugs to reimburse and what is the supporting research and information needed (type of research, type of reporting format, time frame) is an important component the DSEN's mandate.

Meeting Summary

This 5th semi-annual meeting, held by DSEN on October 18th, 2013 at Albert at Bay Suite Hotel, was attended by 46 participants from the research and the decision making arenas (Agenda is attached in *appendix 1* and Attendees list in *appendix 2*).

Robert Peterson, the DSEN Executive Director gave welcoming remarks and explained that the objectives of the meeting revolved around what happens in the provinces after a drug is authorized for release on the Canadian market. He then updated the participants on work done by the DSEN Coordinating Office (DSEN CO) and the network of researchers in the past few months after which participants were invited to an open discussion.

CADTH's Director of the Common Drug Review (CDR) and Optimal Use of Drugs, Chander Seghal, presented the CDR and other services offered to the provinces and territories by CADTH. Carole Marcotte, Director of drug evaluation for listing at the Institut d'excellence en santé et services sociaux (INESSS) in Québec explained the functioning of the institute and the integrated decision making in the province. Diane Forbes from the DSEN CO presented the key points and the rationale for the joint project developed between DSEN and CADTH, which aims to support the submission of Queries relevant to decision making within public drug plans.

Lunch was accompanied by a keynote presentation by Brian O'Rourke, President and Chief Executive Officer of CADTH, who spoke to synergies and opportunities in CADTH and DSEN collaborating.

The afternoon session was devoted to the work accomplishments by the network teams and collaborating centres addressing Queries submitted by provinces and territories and to a panel comprising representatives of CADTH, INESSS, P/T decision makers, and research teams who discussed new and interesting provincial and territorial opportunities for DSEN. Finally, the DSEN Executive Director announced upcoming events where DSEN will be actively engaged and gave an update on funding opportunities. A tentative date for the next semi-annual Network Meeting was given for March 21, 2014 and the meeting was adjourned.

The AM session:

After a round table introduction from the participants, Robert Peterson gave an overview of the different projects the DSEN CO has been working on since March 2013.

The DSEN CO has been considering various scenarios for team renewals, which will be discussed with the DSEN Steering Committee (DSEN SC) members on November 1st, 2013 to apprise them of the different options and gather their opinions and advices. All of the network teams, at the exception of CNODES, are up for renewal as of September 2014.

With a focus on reducing timelines and improving the process, the DSEN CO together with CIHR program delivery staff have put in place a new system for rapid review of DSEN grants that will allow for greater flexibility and adaptability for the teams and more rapid results for decision makers.
Participants were informed of the DSEN CO's workshop "Put the Drug Safety and Effectiveness Network to Work for You!" which was launched at the CADTH Symposium 2013. The workshop is designed to provide decision makers with a hands-on simulation of the DSEN Query process, using examples of successful Query submissions. Upcoming workshops, next planned in Alberta and British Columbia, would also be extended to other jurisdictions.

Dr. Peterson also provided an update on the status of the Evaluation of the Implementation phase of the DSEN. In addition to providing some context to the nature of the evaluation, he spoke to the early indications and issues identified therein. The DSEN CO has been working throughout the evaluation period to continue to refine processes and advance new activities (e.g. a strategy on network wide knowledge translation) in response to known areas of improvement. He then specifically spoke to the need for the introduction of project management in the conduct of DSEN funded research studies and presented a conceptual reporting schedule

Based on the life cycle of a research project for its teams and collaborating centres, the schedules will take into account the different methodologies used to answer a Query, the possible milestones of a project, and the expectations of decision makers, as predictability of the timing of the research output is of paramount importance to them. Decision makers need to be kept informed of the research progress and directions. The DSEN CO is ready to work with each team to align the reporting schedule on a case by case basis, which is expected to be discussed up front between the Query submitter and the researchers. Project coordinators should be mindful of their milestones throughout a project's life cycle in order to keep all parties up to date on progress, challenges to timely project conclusion.

Questions came from participants during the open discussion regarding the DSEN CO's policy towards team tabled topics. Dr. Peterson explained that currently, team tabled topics that are of interest to decision makers must be submitted by decision makers as a formal Query. The DSEN CO has already seen several team tabled topics submitted by decision makers. Some suggestions also were brought forward regarding clinical guidelines for practitioners. DSEN funds evidence based research, disseminates these results, and expects that such evidence may inform those who develop clinical practice guidelines. However, the network is not in a position to directly fund clinical practice guideline development.

Chander Sehgal, Director, Common Drug Review and Optimal Use of Drugs at CADTH explained the avenues of collaboration between DSEN and CADTH. One of the DSEN funded team has had a great experience working with CADTH on the new oral anticoagulants (NOACs) study.

Dr. Sehgal described common elements between CADTH and DSEN: policy questions, quality of the research, relevance of the research for decision makers, timeliness of the results. For CADTH, as for DSEN, the main driver is evidence to inform policy (drug formulary listing) decisions and the timelines can vary from one therapeutic review to another. Some timelines are challenging because they have to coincide with the Common Drug Review. CADTH processes, including timelines, are transparent and draft reports are open for comments. Timeliness is extremely important for therapeutic reviews as they have a distinct influence on CDR.

A question came from the participants as to the way CADTH accepts inputs from consumers and patients in their work. The CDR invites submissions from patient groups for each application it receives from a manufacturer. These submissions are summarized and presented to the Canadian Drug Expert committee (CDEC) by one or both of the public members on the committee.

Carole Marcotte, Director of the evaluation of drugs for listing at Institut national d'excellence en santé et services sociaux (INESSS) presented how the Institute evaluates drugs and makes recommendations to the Ministry of Health for the province of Quebec. Typically, the Institute receives a submission from the manufacturer. The Institute first assesses the therapeutic value of the drug based on the clinical studies presented by the manufacturer, but also considers other RCTs when available, meta-analysis, guidelines, systematic reviews, etc. The models presented by the manufacturer are adapted and tested by INESSS. The Institute evaluates price, cost effectiveness, and impact (both social and economic) of reimbursement. The Institute can perform evaluations on a new drug, a new indication for a drug already reimbursed, a modification to the reimbursement criteria, a generic, or a class review. As is the case with CADTH, rare diseases, lack of data, high cost and new cancer drugs present a challenge for INESSS.

The results are then presented to an advisory committee before a recommendation is made to the Minister. The Régie de l'assurance maladie du Québec then takes action following the Minister's decision. The whole process is transparent and is posted on the INESSS web site.

Following the presentations from CADTH and INESSS, Diane Forbes, on behalf of the DSEN CO, presented the key points of the DSEN-CADTH agreement. CADTH and CIHR have signed an Agreement for a Joint Project because of the synergy that will emerge from this collaboration in support of decision makers' needs.

The objectives of the joint project are:

- Coordinate jurisdictional input to DSEN on real world drug safety and effectiveness topics of relevance to P/T
- Produce evidence to support jurisdictional research needs of post-market drug safety and effectiveness

- Support dissemination of the DSEN evidence related to these topics through Knowledge Translation efforts to P/T

The impacts of the joint project will be measured through the increased engagement and Queries from the provinces and territories for DSEN, and better dissemination of DSEN research results.

Lunch Time:

During lunch time, Dr. Brian O'Rourke, President and CEO of CADTH gave a keynote address explaining the similitudes between DSEN and CADTH as well as the reasons for the joint project agreement.

- Similarity of organizational DNA
- Similarity and complementarity of roles
- Both organizations can provide strong linkages to the other (complementarity)
- CADTH well positioned on the provincial level
- DSEN well positioned with HC

The agreement is a first step as expenditures for drugs are getting higher for all the jurisdictions. The raise in costs is mostly due to today's niche buster era as opposed to what was referred to as the blockbuster era. For some time now, innovative drugs have been expensive drugs for a small number of patients and/or of limited general impact (e.g. cancer, rare disease, n=1 trials, etc.). Those drugs represent a challenge for all the jurisdictions and that is where post-market research on coverage with evidence development, or cost effectiveness can have a great impact.

Dr. O'Rourke indicated that the collaboration between DSEN and CADTH will improve the knowledge translation of the research outcomes and will improve the uptake by knowledge users, and will prove beneficial for both organizations.

The PM Session:

After the lunch time keynote address and lunch, three of the network teams presented their experience with addressing a provincial Query.

On behalf of Canadian Collaboration for Network Meta-Analysis (CCNMA), Shannon Kelly presented the results of the British Columbia Ministry of Health's Query on the "Real world comparative effectiveness, safety and cost-effectiveness of varenicline, bupropion, and nicotine replacement therapy for smoking cessation. The team saw a great potential for impact on the P/T reimbursement programs. Their method was meta-analysi. When the DSEN CO received an urgent request from BC to get results from CCNMA, the team was able to offer interim results and a top up of the CADTH 2010 review of smoking cessation therapies by adding new data and performing an efficacy/harm analysis. The team submitted an interim report to the province and is still working to answer all aspects of the original Query.

Andrea Tricco and Joseph Beyene followed with a presentation for Knowledge Synthesis Research Unit (KSRU). They presented the interim results of a Query submitted on "Safety, effectiveness and cost of long acting versus intermediate acting insulin for type 1 diabetes". They performed a Bayesian meta-analysis on a total of 32 primary articles encompassing 23 trials for a total of 6905 patients. The results are still preliminary and do not demonstrate a definite superiority of one type of insulin over the other; however, the final meta-analysis will ultimately cover nine different outcomes.

Brian Hutton presented the preliminary results of another BC Query "Effectiveness and Safety of Anti-hypertensives for Hypertension in Non-diabetic Patients" that was awarded to the NETMAN team. The meta-analysis considered 91 RCTs and the study protocol was published in Systematic Reviews in May 2013. The study will take into consideration nine different outcomes. Some outcomes still have to be incorporated in the study as well as subgroups, followed by a heterogeneity analysis. The report writing for verification and validation by experts is in progress and will be submitted to the Query submitter at the end of 2013.

Panel Discussion

A panel discussion on future provincial/territorial opportunities for DSEN took place after the individual presentations on provincial queries. The panel brought together representatives of CADTH, INESSS, Manitoba Health, and three DSEN funded teams. The main objective was for the panelists to synthetize what they heard during the day; explain how it related to their personal experience, and discuss P/T expectations and DSEN's research capacity. All parties were actively engaged and there seems to be a mutual understanding of the P/T needs and of how DSEN can interact with CADTH and the provincial/territorial jurisdictions. Drug plans are more in need of cost-effectiveness studies or studies with an economic component, and timeliness is a big issue for them, especially when it comes to the listing of a drug for reimbursement. P/T decision makers deal with uncertainty and DSEN can help them reduce the uncertainty. While the idea of coverage with evidence development was seen as important and interesting, decision makers mentioned that there are important structural challenges to take into account to initiate research but it could be envisioned for certain drugs.

For all, the joint project between DSEN and CADTH is of primary importance. The collaboration between the two will provide DSEN with improved contacts with provinces and territories as well as tested and robust tools of dissemination. It was also recognized that DSEN if of value to close information gaps and that provinces have to work on developing expertise to submit a Query and discuss with researchers.

After the panel, Siham Yasari from the DSEN CO gave an overview of the "DSEN Primer on Managing Researchers' Conflict of interest". The primer came to existence following some concerns about new researchers coming into the network teams who may not have been aware of the funding agreements between DSEN-CIHR and the teams. The primer reiterates that DSEN research is conducted at arm's length from the regulator and is independent from the regulated (i.e. pharmaceutical industry).

The Primer has been designed to:

- Serve as a reference tool and provide basic information to DSEN researchers
- Assist DSEN funded researchers in managing Conflict of Interest within their respective teams

- Outline questions and answers pertinent to the topic

Christian Brochu from the DSEN CO then described the several scenarios for the upcoming DSEN team renewals. All the teams in the network (at the exception of CNODES) were funded through a CIHR Team Grant tool for three years. The launch of the new funding opportunity is January 10, 2014, for a new funding start date in September 2014. It is important for DSEN to consider different scenarios and those different funding schemes will be presented to the DSEN Steering Committee for guidance and advice. Given that three network meta-analysis teams were funded back in 2011 and that those teams work well together, a possible "merger" is under consideration. The funding tools will also be assessed to select the mechanism most appropriate to the Network's needs.

Closing Remarks

Robert Peterson adjourned this fruitful network-wide meeting by mentioning that the interactions that we witnessed during the meeting were all in favor of the DSEN-CADTH joint project and that this agreement will allow DSEN to develop contacts with 19 different drug plans. DSEN will also work with the research teams on addressing timeliness as this is an important element for decision makers. The development of a methodology-based reporting schedule and dialogue with the Network researchers will inform the DSEN CO as to the different existing possibilities and milestones. Again in the view of addressing timeliness, the DSEN CO has improved the peer review process that was applicable to the Rapid Funding tool, making it more flexible and responsive to the needs of decision makers.

The tentative date for the next semi-annual Network Meeting was announced for March 21, 2014.

APPENDIX 1 - MEETING AGENDA

5th semi-annual Drug Safety and Effectiveness Network meeting

The Canadian Mosaic of Drug Safety and Effectiveness Strategies

October 18, 2013

Albert at Bay Suite Hotel
435 Albert St. Ottawa, ON K1R 7X4

8:00	Continental breakfast (provided)	
8:30	Welcome and Introductory remarks	Robert Peterson, DSEN, CIHR
8:45	DSEN Update o Reporting schedule o Workshops for Provincial and Territorial Decision Makers o DSEN Implementation Evaluation	Robert Peterson, DSEN, CIHR
9:30	Open Discussion	All
10:15	Health Break	
10:30	Serving the provinces and territories: the roles of CADTH and INESSS o CADTH - The Common Drug Review and other services o INESSS – Integrated Decision Making in Quebec	 Chander Sehgal, CADTH Carole Marcotte, INESSS
11:15	Partnership between CADTH and DSEN	Diane Forbes, DSEN, CIHR
12:00	Networking Lunch – Keynote Address	Brian O'Rourke, CEO, CADTH
13:00	Work to date on queries submitted by provinces or territories 3 speakers (researchers) X 15 minutes (with questions)	
	o CCNMA: What is the real world comparative effectiveness, safety, and (ideally cost-effectiveness) of varenicline, bupropion, and nicotine replacement therapy for smoking cessation?	Shannon Kelly, CCNMA
	o KSRU: How does real world use of insulin glargine compare to NPH insulin in terms of effectiveness and safety (and ideally cost-effectiveness) for the management of type 1 diabetes mellitus?	Andrea Tricco, Joseph Beyene, KSRU

	o NETMAN: How do thiazide diuretics compare to ACE inhibitors and combination antihypertensive products in terms of effectiveness (and cost-effectiveness) for the management of hypertension in non-diabetic patients?	Brian Hutton, NETMAN
14:00	Panel: Provincial and Territorial Opportunities for DSEN	Kristen Chelak, CADTH Carole Marcotte, INESSS Robert Shaffer, Manitoba Health Michael Paterson, ICES George Wells, OHRI Ingrid Sketris, Dalhousie University
14:45	Health Break	
15:00	DSEN primer on researchers' conflict of interest	Siham Yasari, DSEN, CIHR
15:15	Process for team renewals	Christian Brochu, DSEN, CIHR
15:30	Closing remarks	Robert Peterson

APPENDIX 2 - List of Attendees

Abrahamowicz, Michal	McGill University/CAN-AIM
Bailey, Chantelle	University of British Columbia
Beyene, Joseph	McMaster University/KSRU
Bjerre, Lise	University of Ottawa/NETMAN
Brochu, Christian	DSEN
Catalá-López, Ferrán	Centro Superior de Investigación en Salud Pública
Chapman, Laurie	Health Canada
Chateau, Dan	University of Manitoba/CNODES
Chelak, Kristen	CADTH
Coyle, Doug	University of Ottawa/CCNMA
Crain, Janet	CADTH
Delage, Johanne	DSEN
Dolovich, Lisa	McMaster University/DSECT
Filion, Kristian	McGill University/CNODES
Forestell, Stuart	Health Canada
Forbes, Diane	DSEN
Furlan, Andrea	University of Toronto
Gamble, John-Michael	Memorial University
Griffiths, Jenna	Health Canada
Haas, Marion	Health Canada
Hohl, Corinne	University of British Columbia
Hutton, Brian	University of Ottawa/NETMAN
Jimenez, Ricardo	University of British Columbia/SEARCH
Kelly, Shannon	University of Ottawa/CCNMA
Kim, Richard	McMaster University/PREVENT
Kowalec, Kaarina	University of British Columbia/SEARCH
Law, Barbara	Public Health Agency of Canada
Legan, Robin	McMaster University/PREVENT
Levy, Adrian	Dalhousie University/CNODES
Macdonald, Erin	ICES/CDSERN
Marcotte, Carole	INESSS
Mizrahi, Corine	CNODES
Moher, David	University of Ottawa/NETMAN
O'Rourke, Brian	CADTH
Paterson, Michael	ICES/CNODES
Peterson, Robert	DSEN
Ross, Colin	University of British Columbia/PREVENT
Saggar, Jas	McMaster University/DSECT
Sehgal, Chander	CADTH

Shaffer, Robert	Manitoba Health
Shaw, Kaitlyn	University of British Columbia/SEARCH
Sketris, Ingrid	Dalhousie University/CNODES
Tricco, Andrea	University of Toronto/KSRU
Wang, Tongtong	Health Canada
Wells, George	University of Ottawa/CCNMA
Yasari, Siham	DSEN