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The Canadian Network for Observational Drug Effect Studies (CNODES): Reflections on the First Eight Years, and a Look to the Future

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Introduction

The Canadian Network for Observational Drug Effect Studies (CNODES – www.cnodes.ca) was established in 2011 as a coordinating centre and research network funded by the Drug Safety and Effectiveness Network (DSEN)(1). DSEN was formed as a joint initiative of Health Canada and the Canadian Institutes of Health Research (www.cihr-irsc.gc.ca/e/40269.html), with the overall objective of providing high-quality and comprehensive information on the safety and effectiveness of pharmaceutical products after they enter the Canadian market. CNODES' primary mission is to use population-based Canadian and other databases through a distributed network to perform rapid assessments of drug safety and effectiveness. The research questions are usually proposed by Health Canada, the national drug regulator, but can also come from other stakeholders such as provincial and territory drug plans. In 2016 funding was granted for an additional five years.

CNODES is one of several such networks that have been created worldwide over the past two decades; Sentinel, IMI-PROTECT, AsPEN, and others have been productive and successful. These networks use distributed analysis of population data-bases to perform observational studies that generate 'real world' data to inform regulatory processes. Historically, regulatory science has relied primarily on randomized trials. While trials provide the best available evidence on efficacy, they are not usually designed to observe the effects of medications as used in practice, nor are they suitable for the study of rare safety outcomes, which require large sample sizes to estimate associations with sufficient confidence. Observational studies can provide such evidence on rare safety outcomes, along with evidence on other key indicators, such as disease incidence and drug utilization. CNODES has had considerable success in developing a framework to conduct observational studies of safety and utilization.

In this supplement, we review the progress of CNODES, its structure and operations, scientific training and knowledge translations activities, and the types of questions that have been addressed. We then discuss challenges and opportunities that networks like CNODES will face in the future.

CNODES Progress

Funding Structure

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CNODES's funding structure is unique among similar networks. CNODES is funded under a joint initiative of Health Canada, DSEN and the CIHR. But CNODES researchers report to the health science research funder, CIHR, through DSEN, a mechanism that keeps CNODES researchers and research products independent of Health Canada, stakeholders, and other interested parties, such as the pharmaceutical industry. Other networks have a variety of different structures. Sentinel, for example, is run under a contract with the US FDA(2), leading, at least potentially, to closer connection between the researchers and the regulator. The IMI-PROTECT project was funded by a consortium of the EU and European pharmaceutical companies (www.imi.europa.eu). CNODES' funding structure has strengths and weaknesses relative to the other systems. The independence that arises from funding run through a research funding organization, rather than a contract, preserves CNODES researchers' academic independence, ensures freedom from industry pressures, and leads to substantial opportunities for methods development and training. However, it makes it more challenging to ensure an appropriate degree of collaboration between the stakeholder and the research team.

Process

CNODES receives queries from stakeholders via the DSEN Scientific Advisory Committee. This committee is composed of DSEN representatives, members of the DSEN teams, including CNODES, and representatives from query submitters (typically Health Canada). The bulk of CNODES studies are on comparative safety; others have included drug utilization studies, studies of quality of care, and of comparative effectiveness. The stakeholders (mainly federal drug regulators, federal and provincial drug benefit funders) provide important input at key points in the CNODES research process. They provide the initial queries and review protocols for CNODES research projects and help refine research questions and scientific protocols. They also aid in the interpretation and contextualization of results and tailor this information to their target knowledge users.

Queries are first assessed for feasibility by CNODES members, who are scientists and analysts working in eight Canadian provinces. Work usually starts with a literature review to assess the state of the literature to date. Queries are then refined into research questions in close collaboration with the relevant stakeholders. Once the query is deemed feasible a scientific protocol is prepared and a

project management action plan (PMAP) is created. The scientific protocol is registered with clinicaltrials.gov. A detailed statistical analysis plan is produced, to ensure reproducible results and minimize unnecessary heterogeneity across sites. Analyses are conducted independently in each site and sent to the coordinating site without unblinding of analysts and investigators to other sites' work. When appropriate, results are meta-analyzed by the study team. Finally, several summary reports are produced, including a one-page "fact sheet" and a full study report. Publication in peer-reviewed journals typically follows these reports.

As of April 2019, CNODES has assessed over 80 queries from stakeholders, including approximately 50 from Health Canada and 30 from other stakeholders. Close to 50 of these queries were deemed infeasible by CNODES, or low priority by DSEN and the stakeholders. 34 queries/projects were undertaken by CNODES, leading to 19 completed studies, and 15 studies that are currently in progress. These have involved over 100 analyses of linked population data-bases. From these 34 queries, CNODES has written 17 literature reviews or reports and 20 published query-related manuscripts. Key query-response papers are summarized in Table 1. In addition, CNODES has produced more than 100 papers addressing methodological problems and other related topics at various stages of publication.

Crosscutting Teams

Financial support for CNODES' includes funding for four overlapping teams. The Methods team is responsible for ensuring that the research conducted in response to queries is of the highest quality and for the development and evaluation of novel methods for pharmacoepidemiologic research. The Methods team has conducted over 20 methodological studies, with 17 publications. These have dealt with topics such as appropriate use of the high dimensional propensity score(3,4), methods for meta-analysis (5,6), and the use of targeted maximum likelihood in pharmacoepidemiology(7,8). Methods team members have also supervised more than 30 trainees and more than 20 analysts in continuing education.

The Training team has worked with the Methods team to develop web-based educational initiatives, to support trainees and analysts to attend courses and other educational programs

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(<https://www.cnodes.ca/training/online-lectures/>). This team is also developing a certification process for data analysts who participate in CNODES studies. During the first phase of CNODES, over 100 trainees were involved in projects, 17 projects were led by new investigators, and 55 new investigators or trainees were authors/ co-authors of CNODES reports.

The CNODES Knowledge Translation team, in collaboration with specific stakeholders, uses a comprehensive dissemination strategy to condense results into actionable messages, targeting query submitters and other relevant stakeholders. The KT team also conducts research into innovative methods for dissemination, collaborates with the training team to train CNODES team members in KT practice, and studies the impact of CNODES research on health care practice(9).

The Database team maintains the data repositories and determines feasibility and site participation in each study. The CNODES database team is responsible for management of data access at the individual CNODES sites, and for projects related to data access and data structures. The database team is currently conducting research on the use of electronic medical records with detailed clinical data as a supplement to claims data, and leading an initiative to develop a common data model (CDM)(10). Based closely on the Sentinel CDM, CNODES is implementing a common data structure across sites that have rapid data access and expedited IRB approvals for research purposes. This will enable CNODES to run queries using the Sentinel semi-automated tool kit and creates the potential for collaboration between Health Canada and FDA on regulatory questions of international importance.

Future Directions

Funding Structure

Given the substantial start-up costs required to develop and initiate a network, sustainable long-term funding is necessary to maintain capacity; sustainable funding must be in place to ensure that the infrastructure built in the start-up phases is maintained and used. A related long-term challenge for distributed data networks such as CNODES is personnel. CNODES was initiated by established researchers; most other networks were as well. If networks are to survive long-term, it will be important to transition from the current set of leaders to a new generation of research teams.

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CNODES has attempted to integrate junior investigators into projects, with multiple projects led by junior investigators. These investigators should be well-placed to take leadership roles in CNODES in the future. CNODES has also had training as a primary mandate; substantive and clinical investigators, methods researchers, and, perhaps most importantly, data analysts are encouraged to maintain and develop skills, and to take on leadership roles when possible. This has led to an increased capacity in pharmacoepidemiology in Canada in general and has placed CNODES in good standing to ensure sufficient capacity for the future. Finally, data holding sites are expected to develop long-term plans for development of capacity and long-term sustainability of both scientific expertise and data access at sites.

Communication with Regulatory Agencies

It will remain important to develop and maintain strong relationships with regulators responsible for queries. This requires ongoing bi-directional communication, so that network scientists, who are almost exclusively university-based, understand the needs of regulatory scientists. Central to this is the fact that, while scientific considerations are very important in the conduct of studies, studies need to be designed with regulatory scientists' needs in mind.

Both regulatory and academic scientists need to continue discussing the role of observational research in the drug regulatory process, and on the drug regulatory process as a continuum across the life-cycle of a product. While it is self-evident to most in the pharmacoepidemiology community that observational research can add value, regulatory professionals used to a clinical trials framework may continue to need reassurance that observational data can provide valuable and necessary information in the drug surveillance process.

Cross-jurisdiction Collaborations

One opportunity for future development of networks is the potential for cross-network and cross-jurisdiction collaborations, and for networks of networks. If regulators, who are responsible first to their own constituencies, can develop processes to share queries and results and to plan studies of emerging safety issues prospectively, networks may then be used effectively to be more pro-active

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about these emerging safety questions. CNODES and Health Canada are currently collaborating with researchers in Europe and the EMA on a study of oral anti-coagulant drugs.

The natural heterogeneity between networks may provide informative data that could serve multiple regulators at once. Sentinel is by far the largest network but subjects have relatively short follow up in the US due to the nature of the insurance markets. CNODES, on the other hand, includes fewer subjects but subjects are followed for much longer on average(1). European and Asian networks by nature of their multi-country structure include a wide variety of health systems. This may provide complementary data that may be able to address different parts of the same research question (or, the same question from different angles).

This will pose challenges as well; can regulatory agencies develop protocols for sharing information and queries, and do they have the incentive to do so? Will regulators and networks have the appropriate incentive structure to prioritize between national and cross-network projects? Imminent local needs will almost always pre-empt international collaborations, but these latter projects may simultaneously provide informative results for multiple authorities.

When considering international collaborations, one principal challenge will be data heterogeneity, both in content and in structure. When heterogeneous results are observed between countries, regions, or networks, it will be important to understand the potential reasons for this heterogeneity, and to provide explanations for it. It will be important, to the extent possible, to plan research in advance acknowledging the possibility of between-region heterogeneity and providing plans for decisions under heterogeneous results.

Substantive structural differences between patient populations in different countries may, on the other hand, be used to the benefit of research. Through a network study, researchers and regulators will be able to learn about treatments in populations that would be potentially inaccessible in their own network. Difference in treatment patterns may also be used to advantage. If differences in treatment protocols result in a natural instrumental variable [REF] this may be leveraged to provide unbiased estimates of treatment effects across populations.

Common data models and related analytic tools, like those developed by Sentinel (11) and the Observational Health Data Sciences Initiative (OHDSI) (12) provide structure and a framework to

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organize data and may help address differences in structure between health data systems. There are several approaches to development of a common data model; these have been discussed extensively (10,13), and revolve around the degree of centralization and control required. Ideally, regulators around the world may organize around one or more platforms for ease of collaboration.

Data Access and Data Sources

Distributed data networks require rapid and secure access to administrative claims data and future electronic health record data. It will remain a priority to maintain access and preserve privacy. It will be important to demonstrate the usefulness of new sources such as free text from electronic health records, prior to their implementation on a broad scale.

Methodological Development

Networks like CNODES should continue to be a source of methodological development. It is imperative that methods development be supported by the networks and by funders. Areas of natural interest for methods development include efficient use of large datasets, privacy-preserving analyses, incorporation of electronic medical record data, effective use of machine learning, and other topics. Cloud-based computing methods and new developments in encryption may provide additional technological methodological advances for networks.

Summary

In collaboration with Health Canada and under the auspices of the Canadian Institutes of Health Research and DSEN, CNODES has created a Canada-wide network for observational drug research, along with an infrastructure and set of processes for the conduct of high-quality studies into the effects of drugs in the population. CNODES has been productive over the first seven years of its mandate and has built a framework, sustainable infra-structure and the human capacity to sustain a long-term partnership with Health Canada and other Canadian stakeholders to supply high-quality information to guide quality use of medicines in Canada. Continued development work, including stable funding, better and faster data access, training, methods development, and international collaborations will help these networks continue to effectively serve public health. In this supplement, we describe several research results that have arisen as a consequence of CNODES' work.

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Table 1: Selected CNODES Query Publications

Query	Submitter	Publication
Demo 1	demo	Dormuth C et al. Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases; BMJ 2013;346: f880
Demo 2	demo	Filion KB et al. Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis. Gut. 2014;63(4):552-558
Q10-04	Health Canada	Azoulay L et al. The use of atypical antipsychotics and the risk of breast cancer. Breast Cancer Research and Treatment 2011;129(2):541-8.
Q10-12	Health Canada	Lipscombe et al. Atypical antipsychotics and hyperglycemic emergencies: multicentre, retrospective cohort study of administrative data. Schizophrenia Research 2014;154(1-3):54-60
Q10-23	Health Canada	Henry D et al. Occurrence of pregnancy and pregnancy outcomes during isotretinoin therapy. CMAJ. 2016;188(10):723-730
Q12-02	Health Canada	Dormuth C et al. Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases. BMJ. 2014;348: g3244
Q12-08	Health Canada	Renoux C et al. Serotonin-norepinephrine reuptake inhibitors and the risk of acute kidney injury: a cohort study of eight administrative databases and meta-analysis. Clin J Am Soc Nephrol. 2015;10(10):1716-1722
Q13-02	Health Canada	Renoux C et al. Ventricular tachyarrhythmia and sudden cardiac death with domperidone use in Parkinson's Disease. Br J Clin Pharmacol. 2016;82(2):461-472
Q13-03	Canadian Agency for Drugs and Technologies in Health	Gomes T et al. Trends and uptake of new formulations of controlled-release oxycodone in Canada. Pharmacoepidemiology and Drug Safety. 2018;27(5):520-525.
Q13-06	Health Canada	Azoulay L et al. Incretin based drugs and the risk of pancreatic cancer: international multicentre cohort study. BMJ. 2016;352:i581
Q13-06	Health Canada	Azoulay L et al. Association Between Incretin-Based Drugs and the Risk of Acute Pancreatitis. JAMA Intern Med. 2016;176(10):1464-1473
Q13-06	Health Canada	Filion K et al. A Multicenter Observational Study of Incretin-based Drugs and Heart Failure. N Engl J Med. 2016;374(12):1145-54.

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Q14-02	Canadian Agency for Drugs and Technologies in Health	Jun M et al. Comparative safety of direct oral anticoagulants and warfarin in venous thromboembolism: multicentre, population based, observational study. BMJ 2017;359:j4323
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