CNODES: The Canadian Network for Observational Drug Effect Studies

Samy Suissa[1,2], David Henry[3], Patricia Caetano[4,5], Colin R. Dormuth[6], Pierre Ernst[2], Brenda Hemmelgarn[7], Jacques LeLorier[8], Adrian Levy[9], Patricia J. Martens [5,10], J. Michael Paterson[3], Robert W. Platt[2], Ingrid Sketris[11], Gary Teare[3,12] for the Canadian Network for Observational Drug Effect Studies (CNODES)

[1] Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Quebec

[2] Departments of Epidemiology and Biostatistics, and of Medicine, McGill University, Montreal, Quebec

[3] Institute for Clinical Evaluative Sciences, Toronto, Ontario

[4] Manitoba Health, Winnipeg, Manitoba

[5] The University of Manitoba, Winnipeg, Manitoba

[6] Departments of Anaesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, British Columbia

[7] Department of Medicine, University of Calgary, Calgary, Alberta

[8] Departments of Medicine and Pharmacology, University of Montréal, Montreal, Quebec

[9] Department of Community Health and Epidemiology, Dalhousie University, Halifax, Nova Scotia

[10] Manitoba Centre for Health Policy, Winnipeg, Manitoba

[11] College of Pharmacy, Dalhousie University, Halifax, Nova Scotia

[13] Saskatchewan Health Quality Council, Saskatoon, Saskatchewan

Please address correspondence and request for reprints to:
Dr. David Henry (Guarantor)
Institute for Clinical Evaluative Sciences
Sunnybrook Health Sciences Centre

2075 Bayview Avenue
Toronto, M4N3M5
E-mail: david.henry@ices.on.ca

Words: Abstract: 264; Body: 1988

Tables: 2, Figures: 1, References: 24

Running title: CNODES

Funding: The Canadian Network for Observational Drug Effect Studies (CNODES) is a collaborating centre of the Drug Safety and Effectiveness Network (DSEN), which is funded by the Health Canada and the Canadian Institutes of Health Research. The funding bodies had no role in the conduct of studies or writing of the manuscript

Key words: pharmaco-epidemiology, drug safety, administrative health data

Samy Suissa <samy.suissa@mcgill.ca>
David Henry <david.henry@ices.on.ca>
Patricia Caetano <Patricia.Caetano@gov.mb.ca>
Colin R. Dormuth <colin.dormuth@ti.ubc.ca>
Pierre Ernst <pierre.ernst@mcgill.ca>
Brenda Hemmelgarn <Brenda.Hemmelgarn@albertahealthservices.ca>
Jacques LeLorier <jacques.le.lorier@sympatico.ca>
Adrian Levy Adrian Levy <adrian.levy@DAL.CA>
Patricia J. Martens <Pat_Martens@cpe.umanitoba.ca>
J. Michael Paterson <michael.paterson@ices.on.ca>
Robert W. Platt <robert.platt@mcgill.ca>
Ingrid Sketris <Ingrid.Sketris@DAL.CA>
Gary Teare <GTeare@HQC.sk.ca>

Author Contributions:

All authors were involved in the creation of CNODES, by contributing to the original funding application, negotiating access to data through their respective Ministries or health authorities, and establishing the local resources needed to undertake the work of CNODES. All authors contributed to conception and design, acquisition of data, local and/or central analysis of data and all assisted in drafting and editing of the manuscript.

ABSTRACT

Background

Although administrative health-care databases have long been used to evaluate adverse drug effects, responses have been slow and uncoordinated. Here we describe the establishment of the Canadian Network for Observational Drug Effect Studies, a collaborating centre of the Drug Safety and Effectiveness Network.

Methods

CNODES is a distributed network of investigators and linked databases in British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec and Nova Scotia. Principles of operation are: 1) research questions are prioritized by the coordinating office of DSEN; 2) the linked data stay within the provinces; 3) for each question, a study team formulates a detailed protocol enabling consistent analyses in each province; 4) analyses are run 'blind' to the results obtained elsewhere; 5) protocol deviations are permitted only for technical reasons; 6) analyses using multivariable methods are lodged centrally with a methods team, which is responsible for combining the results to provide a summary estimate of effect. These procedures are designed to achieve high internal validity of risk estimates and to eliminate the possibility of selective reporting of analyses or outcomes.

Results

The value of a coordinated multi-provincial approach is illustrated by projects studying acute renal injury with high potency statins, community-acquired pneumonia with proton pump inhibitors and hyperglycemic emergencies with anti-psychotic drugs.

Interpretation

CNODES is an academically-based distributed network of Canadian researchers and data centers with a commitment to rapid and sophisticated analysis of emerging drug safety signals in study populations totaling over 40 million.

INTRODUCTION

The need for drug safety research using an epidemiological approach has been clearly understood for decades.[1,2] Prescription medications remain one of the commonest causes of severe adverse reaction in clinical medicine. It has been claimed that they account for between 1800 and 10000 deaths annually in Canada[3,4]

Canadian population health databases have been used to assess the risks and benefits of NSAIDs, beta-agonist inhalers in asthma, anti-psychotic drugs, gastric-acid suppressants, and many others.[5-8] A population-based approach is particularly important for less frequent, severe, or long-term adverse effects that cannot be detected by the randomized controlled trials (RCT) required for initial drug approval. Such trials are not powered for rare outcomes, exclude vulnerable populations, and do not provide sufficient follow-up for quantification of long-term effects.[9]

Recent experiences of the cardiovascular effects of COX-2 inhibitors and thiazolidinediones, demonstrate the need to rapidly detect and confirm low relative risks, in the order of 1.2-1.5, to be able to distinguish risk between individual members of drug classes, and identify clinical factors that increase risk.[10,11] This requires very large sample sizes, which can only be achieved by use of population databases.

To date, such research has not been coordinated. Investigations of the adverse cardiovascular effects of Vioxx® (rofecoxib) were conducted using databases in Ontario, Quebec and Saskatchewan. [12-14] The time taken to respond to the first safety signal published in November 2000 ranged from three to nine years – excessive considering the potential threat to public health posed by a very widely used drug. Investigators employed different

approaches in the design and analysis of these studies, obtained discrepant results, and individual risk estimates were imprecise.

The challenges are to organize sufficient financial and human resources, co-ordinate responses to such safety signals, standardize methodological approaches, and obtain rapid access to data-sets that are large enough to give precise estimates of risk The Canadian Network for Observational Drug Effect Studies (CNODES), an investigator-led multi-province distributed network of data repositories, has been established to do this.

THE DEVELOPMENT OF CNODES

CNODES is part of the Drug Safety and Effectiveness Network (DSEN), a joint initiative of Health Canada and the Canadian Institutes of Health Research (CIHR) (.http://www.cihr-irsc.gc.ca/e/40269.html). The principal aim of CNODES is to use collaborative, population-based approaches to provide rapid answers to questions about drug safety and effectiveness. Funding of the infrastructure for CNODES was granted in January 2011 on the basis of a single, directed, internationally-refereed application to CIHR, with representation from seven provinces (British Columbia, Alberta, Manitoba, Saskatchewan, Ontario, Quebec and Nova Scotia). The application added a mechanism for accessing data from the United Kingdom General Practice Research Database (GPRD) because of its size, direct and rapid access to comprehensive data, including drugs marketed in the UK prior to their licensing in Canada.[15] Work in CNODES commenced March 2011.

Database structure

Legal and privacy concerns meant it was unfeasible to pool data from multiple provinces in a single central repository. There was a strong preference for a distributed network because the data remain and are analysed ‘in situ’, meaning local regulations about data access and approval processes for research are respected, and local knowledge, expertise and analytical capacity is valued and supported. The main disadvantages are that

those same features can lead to delays in accessing data or obtaining approvals for individual studies. Some barriers to timely data access persist in British Columbia and Quebec. CNODES data sources are summarized in Table 1. The provincial databases vary in their capacity to answer different questions. If the question concerns a drug used primarily in patients under age 65 years, this can only be studied comprehensively in 3 provinces – British Columbia, Saskatchewan, and Manitoba – plus the GPRD (Table 1).

Governance

Prospective research questions regarding safety and effectiveness of drugs marketed in Canada come from Health Canada and are directed to the DSEN coordinating office (Figure). Federal and provincial drug plans may refer questions to Health Canada. The questions are assessed and prioritized by a scientific advisory committee of DSEN, prior to consideration by CNODES (Figure). The CNODES Database Team (Figure), comprising the provincial leads, is responsible for ensuring access to the linked provincial data-sets and maintaining analytical capacity at each site. If a study is feasible within CNODES the Database Team selects a Project Team (Figure). The Project Team comprises nominees from each province with relevant methodological and content expertise, and a liaison member from the Methods Team. They develop the scientific and analytical protocols, organize local approvals for the research and arrange for the analyses to be conducted in each database. The Methods Team provides methodological leadership and supports the development of each research protocol, assists the development of the scientific and analytical protocols for each project, and conducts meta-analyses of the results across databases. The Methods Team also reports on bias, precision and validity of results, and is charged with developing new methods for the design and analysis of multiple observational studies.

Methods

Linked prescription drug and outcome data are analysed separately in each province using a range of multivariable techniques; the results from the provinces and GPRD are combined to give a summary estimate. In the studies conducted to date (see Table 2) a range of methods and tools have been used, including high-dimensional propensity scores to generate and compare exposed and reference cohorts, a nested case-control analysis with propensity score adjustment, and a highly restricted cohort, selected to minimize confounding by indication and protopathic bias (Table 2).

Measures to reduce bias

The complete coverage of provincial populations and sub-populations minimizes selection biases. The initial screening of study questions ensures their appropriateness for evaluation using observational methods and administrative data. There is strong clinical and methodological input into the design of scientific and analytical protocols. The standardization of these reduces variation in results due to study design and analysis. We use common exposure, co-variable, and outcome definitions and make maximum use of shared common, tested, SAS code. Sophisticated analytical techniques reduce confounding. All research protocols are logged at the CNODES and DSEN coordinating offices, and will be registered with www.Clinicaltrials.gov. All study outcomes and analyses are pre-specified, and site-specific protocol deviations are permitted for technical reasons only. Each participating site lodges results in a secure drop box without knowing the results obtained at other sites. The Study Team and Steering Committee jointly review and interpret results and a Publications Committee reviews all reports prior to submission and publication. These procedures should reduce publication and reporting biases.[16,17] All CNODES researchers are required to make a full disclosure of their relationships with life sciences companies. Open-ended relationships, such as stock holding and membership of speakers' bureau are discouraged; researchers with such relationships

cannot take primary responsibility for leading specific CNODES research projects, including developing study protocols or drafting study reports.

Studies undertaken since commencement

Since March 2011 CNODES has commenced five studies. Analyses were completed in 12 months for three studies (Table 2). Initial study questions were designed to use data from all member provinces. The details of the studies illustrate the capacity of the network to assemble very large cohorts, agree on standardized analytical protocols and carry out suitable adjustments simultaneously in multiple data-sets. Early experience indicates that important questions can be addressed in most provinces within 4 months. Full results of studies are being published separately and are not provided here. Briefly, the results documented a small increase in the relative risk of acute kidney injury with high versus low potency statins and no increase in the risk of community-acquired pneumonia with proton pump inhibitors.[18,19]

Limitations

The main limitations are those of the datasets themselves. Eight of the nine repositories used by CNODES comprise linked health administrative data, which generally lack information on risk factors such as obesity, smoking, non-prescription drugs and complementary therapies.[20] The GPRD database in the UK comprises electronic health records that include some of this information[15]. We found no difference in the results obtained to date with this and the provincial administrative data. Data-bases do not include hospital drug use, and capture information on drug prescribing (GPRD), or dispensing, rather than consumption. Controlled observational studies are subject to a range of sources of bias, most significantly information biases and confounding by indication and disease severity.[21] These are limitations of all non-randomised pharmacoepidemiological studies, but reviews suggest that there is good agreement between properly designed non-randomised and randomised studies when investigating adverse effects of drugs.[22]

Capacity building and knowledge translation

Training and knowledge translation teams have been established to support the work of CNODES. Key objectives of the network are to train graduate students and analysts, and to inform clinical practice, and health care programs and policies.

DISCUSSION

The main advantages of the multi-provincial distributed network are the generalizability, statistical power and timeliness of the study results. The standardization of design and analyses minimizes variation. The large group of researchers in seven provinces is building substantial capacity in pharmaco-epidemiology across Canada.

In establishing CNODES we considered that a distributed network, where the data are analysed in each province and outputs combined by meta-analysis, would be the only feasible model. This overcame the substantial legal and privacy obstacles to pooling the raw data. However, the distributed network approach has not guaranteed timely access in every province. There were, and still are, substantial delays in accessing data in British Columbia and Quebec.

CNODES exploits the scientific principle of replication. A single study is rarely sufficient to provide definitive information on a serious adverse drug effect unless it finds an extremely high risk for a drug. In CNODES the drug /disease association is examined in up to nine databases simultaneously, and early experience has shown that heterogeneity in the estimates is low. This contrasts with the typical situation where studies are conducted in a haphazard sequential manner over several years before a meta-analysis is performed to assess the totality of the evidence.[10] In CNODES, meta-analyses are planned prospectively as part of the study protocol, providing immediate summary evidence. The value of such a network is illustrated by the study

of high-dose statins and acute kidney injury, which explored an uncommon serious outcome and a small excess risk in a widely-used medication. [18]

CNODES exploits the enormous statistical power that results from combining provincial health databases. This discriminatory power is necessary in order to detect small but important increases in risk and to make comparisons between drugs, so that benefit/ harm relationships can be quantified and contrasted. Drug regulation is moving from a traditional 'all or nothing' attitude to safety to a 'risk management' approach throughout the lifecycle of the drug.[23] This necessitates more rapid access to larger and more comprehensive data-sets and people with the skills to analyze them.

The strategy used to establish CNODES is different from that taken in the creation of a prominent drug safety network in the USA, the Mini-Sentinel. Mini-Sentinel is a distributed network of 17 data partners in the USA with a total population of 99 million.[24] Much development work went into the creation of data extraction tools that generate identical core data sets within each node. These data nodes can be queried directly and simultaneously from the co-coordinating center using common code with rapid response times (days rather than weeks).[24] While not capable of functioning on this time scale CNODES has the advantages of complete population coverage and the academic and methodological capacity that is being built at each provincial site. This new expert network will be in the long-term interests of Canada. .

Currently, CNODES has access to data from a total population of over 40 million, and many pharmaco-epidemiologists in Canada either already have or will have some connection with the enterprise. Studies that are independent of CNODES will continue and hopefully increase as a result of the larger capacity engendered by the network. The first real test will be the ability of CNODES to quantify the next major drug safety signal. Experience suggests that we will not have to wait very long for that event.

References

1. Strom BL, Carson JL, Morse ML, LeRoy AA. The computerized on-line Medicaid pharmaceutical analysis and surveillance system: a new resource for postmarketing drug surveillance. *Clin Pharmacol Ther* 1985; 38(4):359-364.

2. Slone D, Shapiro S, Miettinen OS. Case-control surveillance of serious illesses attributable to ambulatory drug use. In: Colombo F, Shapiro S, Slone D, Tognoni G, editors. *Epidemiological Evaluation of Drugs*. Littleton, MA: PSG; 1977:59-82.
3. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998; 279(15):1200-1205.

4. Bains N, Hunter D. Adverse reporting on adverse reactions. *CMAJ*1999; 160 (3): 350-351

5. Guess HA, West R, Strand LM et al. Hospitalization for renal impairment among users and non-users of nonsteroidal anti-inflammatory drugs in Saskatchewan, Canada, 1983. In: Rainsford KD, Velo GP, editors. *Side-Effects of Anti-Inflammatory Drugs*, Part 2: Studies in Major Organ Systems. Lancaster, PA: MTP Press; 1987:367-374.

6. Spitzer WO, Suissa S, Ernst P et al. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992;326(8): 501-506.

7. Gill SS, Bronskill SE, Normand SL et al. Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med* 2007;146(11):775-786.

8. Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S, Leslie WD. Use of proton pump inhibitors and risk of osteoporosis-related fractures. *CMAJ* 2008;179(4):319-326.

9. Rothwell PM. Treating Individuals External validity of randomised controlled trials: “to whom do the results of this trial apply?” *Lancet* 2005; 365: 82–93

10. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006;296(13):1633-1644.

11. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356(24):2457-2471.

12. Mamdani M, Rochon P, Juurlink DN et al. Effect of selective cyclooxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. *Arch Intern Med* 2003;163(4):481-486.

13. Levesque LE, Brophy JM, Zhang B. The risk for myocardial infarction with cyclooxygenase-2 inhibitors: a population study of elderly adults. *Ann Intern Med* 2005;142(7):481-489.

14. Varas-Lorenzo C, Castellsague J, Stang MR, Perez-Gutthann S, Aguado J, Rodriguez LA. The use of selective cyclooxygenase-2 inhibitors and the risk of acute myocardial infarction in Saskatchewan, Canada. *Pharmacoepidemiol Drug Saf* 2009;18(11):1016-1025.

15. Rodriguez LAG, Perez- Gutthann S. Use of the UK General Practice Research Database for pharmacoepidemiology. *Br J Clin Pharmacol*. 1998; 45(5): 419–425.

16. Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, et al. Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias. *PLoS ONE* 2008; 3(8): e3081.

17. Peters J, Mengersen K. Selective Reporting of Adjusted Estimates in Observational Epidemiology Studies: Reasons and Implications for Meta-analyses. *Eval Health Prof* 2008 31(4): 370

18. Briefing Document for Endocrinologic and metabolic drugs advisory committee meeting of December 15, 2009. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM193833.pdf Gaithersburg, Maryland. (Accessed June 26th 2012)

19. Johnstone J, Nerenberg K, Loeb M. Meta-analysis: proton pump inhibitor use and the risk of community-acquired pneumonia. *Aliment Pharmacol Ther* 2010;31(11):1165-1177.

20. Strom BL. Overview of Automated Databases in Pharmacoepidemiology. In: Strom BL, Kimmell SE, Hennessy S editors. *Pharmacoepidemiology* 5th Edition. Wiley 2012. p. 158-162

21. Collet JP, Boivin JF, Spitzer WO. Bias and confounding in Pharmacoepidemiology. In: Strom BL, editor. Pharmacoepidemiology. 2d Edition. John Wiley & Sons; 1994. p. 609-27.

22. Golder S, Loke YK, Bland M. Meta-analyses of adverse effects data derived from randomised controlled trials as compared to observational studies: methodological overview. *PLoS Med* 2011; 8 (5): e10011026.

23. Lifecycle management. Drug and Health Products. Health Canada. http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/model/life-cycle-vie-eng.php (Accessed June 26th 2012)

24. Platt, R., Carnahan, R. M., Brown, J. S., Chrischilles, E., Curtis, L. H., Hennessy, S., Nelson, J. C., Racoosin, J. A., Robb, M., Schneeweiss, S., Toh, S. and Weiner, M. G. The U.S. Food and Drug Administration's Mini-Sentinel program: status and direction. Pharmacoepidemiol. Drug Saf 2012; 21(Suppl 1): 1–8.

FIGURE – How questions are prioritized and answered in CNODES

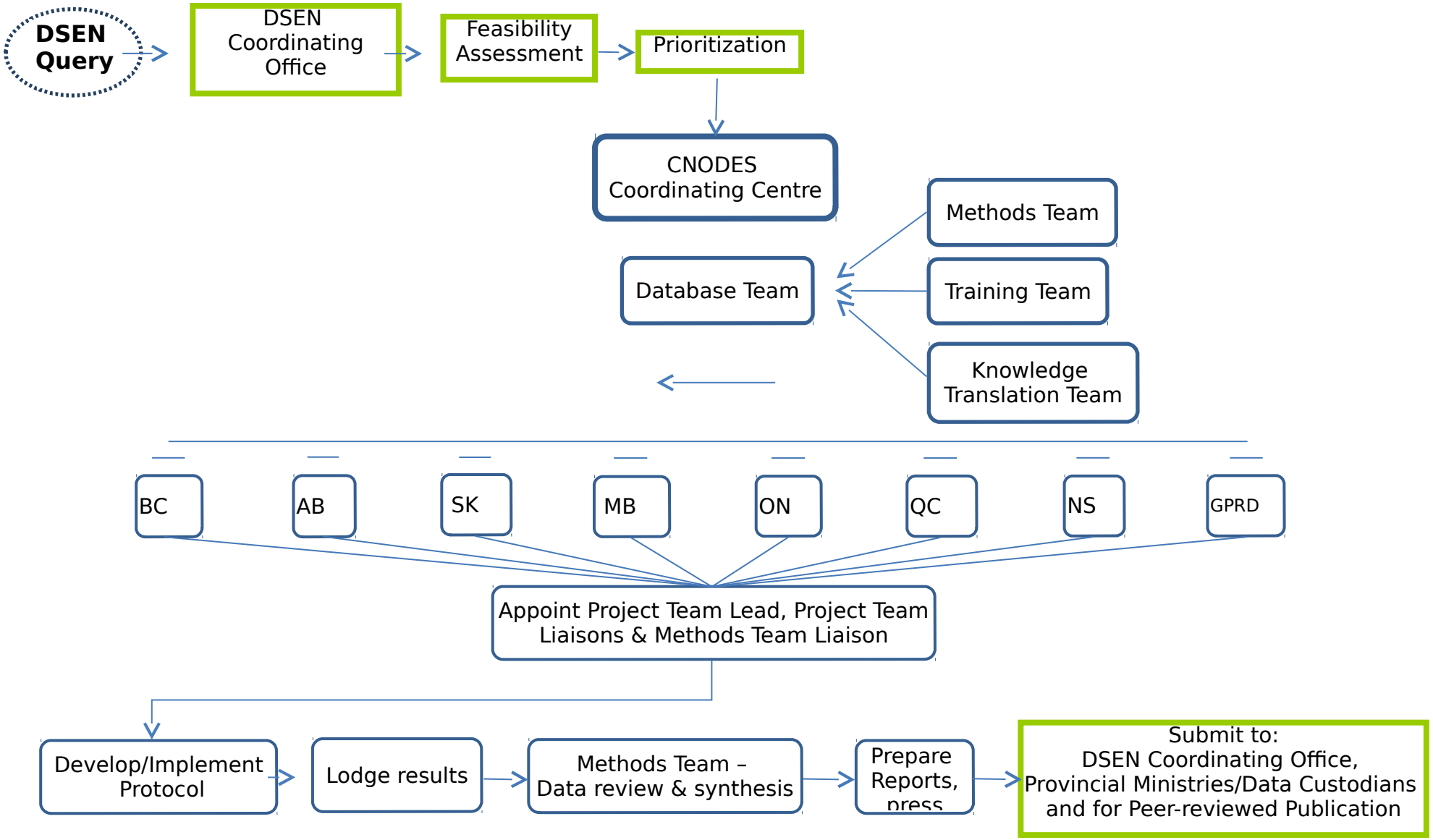

Table 1. Overview of CNODES Canadian provincial databases and the GPRD (as of June 2012)*

Site	Total Population (000)	Prescription Drug Data: People Covered; Time Period Covered	Update Frequency	Vaccine Data	Emergency Department Encounters	Outpatient Laboratory Data	Cancer Registry	Time to Data Access
British Columbia	4,573	All; from 1996	Weekly	Partial	No	No	No	Weeks
Alberta	3,779	≥ 65; from 1994	Monthly	Yes	Yes	No	No	Days
Saskatchewan	1,058	All; from 1996	Quarterly	No	No	No	No	Days
Manitoba	1,251	All; from 1995	Quarterly	Yes	Yes	Partial (Public Health)	Yes	Days
Ontario	13,373	≥ 65 + social assistance; from 1997	Bimonthly	No	Yes	No	Yes	Days
Quebec	7,980	≥ 65 + social assistance; from 1983	Monthly	No	Yes	No	Yes	Months
Nova Scotia	945	≥ 65 + social assistance/ Family Pharmacare; from 1989	Quarterly	No	Yes	No	Yes	Days
GPRD	11,829	All; from 1988	Monthly	Yes	No	Yes	Yes	Immediate

*All sites have access to data on demographics, vital statistics, dispensed outpatient prescriptions, physician encounters, and hospitalizations.

Table 2: Summary of CNODES projects completed between March 2011 and May 2012

Study Question	Design	Analysis	Data-sets used in the analyses	Sample Sizes
Do high dose statins increase the risk of acute renal damage?	Retrospective cohort study of high versus low dose statins	Meta-analysis of site-level, propensity score-adjusted intent-to-treat and as-treated (case-control) analyses	BC, AB, SK, MB, ON, QC, NS plus GPRD and	646,803 users of high dose statins and 1,351,162 users of low dose statins
Do proton pump inhibitors increase the risk of community-acquired pneumonia?	Restricted retrospective cohort study (of patients who commenced PPI and NSAID therapy on the same day)	Meta-analysis of site-level, propensity score-adjusted intent-to-treat analyses	AB, SK, MB, ON, QC, NS plus GPRD	93,835 PPI/NSAID users and 4,228,184 non users
Do all second generation anti-psychotic drugs increase the risk of hyperglycemic emergencies?	Retrospective cohort study	Meta-analysis of site-level, propensity score-adjusted intent-to-treat and as-treated analyses	Age 18-65y: BC, SK, MB, GPRD Age 66y+: BC, AB, SK, MB, ON, NS plus GPRD	215,591 aged 18-65y 298,580 aged 66 y+