Post-Marketing

Pharmacosurveillance

In Canada

A background paper prepared for the Working Conference on
Strengthening the Evaluation of Real World Drug Safety and Effectiveness

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Note to readers:
This paper has been prepared for the *Working Conference on Strengthening the Evaluation of Real World Drug Safety and Effectiveness* as a non-technical work to facilitate discussion among a variety of stakeholders. While it is not intended to be a comprehensive overview of pharmacosurveillance activities in Canada, the examples it contains provide insight into the range and nature of post-market evaluation and monitoring of drugs, as well as strengths and limitations as the authors see them.

Report Summary

Efficacy and safety must be established before a drug may be marketed in Canada. Well-designed clinical trials are required to generate these data. However, clinical trials generally enroll small numbers of patients who may not represent the general population, and the trials are often short-term, employ surrogate outcomes, and use placebo as a comparator. Long term safety and effectiveness must therefore often be investigated after a drug has entered the market when thousands or millions of people are taking it and experiencing its benefits and harms. For such investigations, extensive data are required.

Many initiatives are underway in Canada; a number will be described in this paper. Initiatives are grouped according to type of underlying framework. For each framework, sample initiatives are provided. To the extent possible, detail on the sample initiatives includes background, goals, goal setting, advantages, limitations, measures used to determine success or failure, and evaluation capacity.

The four frameworks include:

- Drug regulatory authority frameworks (3 initiatives described)
- Health plan and drug plan frameworks (6 initiatives described)
- Drug manufacturer frameworks (2 initiatives described)
- Clinician/clinical group/disease collaborative frameworks (8 initiatives described)

Each of the initiatives described in this report has unique strengths and limitations. No single framework appears to support all needs. In general, where population-level data and relatively open access exist, resources for assessment are more limited. Where resources are more readily available (e.g., manufacturer registries and single-disease centres), data are more limited and opportunities for replication by others more restricted.

There is no clear international consensus on what "works" in pharmacosurveillance; there are no best practices currently defined for the determination of drug effectiveness and safety in the real world. Choosing the appropriate pharmacosurveillance strategy depends on the nature of the research questions, the health care system context, the availability of data sources, the required time line for results, and the availability of research expertise. Integrated, informed, and judicious use of a mixture of initiatives may ultimately provide the best information on drug safety, effectiveness, and cost-effectiveness.

List of Abbreviations[1]

AdEERS	Adverse Event Expedited Reporting System
ADR	Adverse drug reaction
AIDs	Acquired immune deficiency syndrome
AMI	acute myocardial infarction
C&W	Children's and Women's Health Centre of British Columbia
CADRIS	Canadian Adverse Drug Reaction Information System
CADRMP	Canadian Adverse Drug Reaction Monitoring Program
CDM	Chronic Disease Management (Program)
CHF	congestive heart failure
CIHI	Canadian Institute for Health Information
CIHR	Canadian Institutes for Health Information
CMIRPS	Canadian Medication Incident Reporting and Prevention System
COG	Children's Oncology Group
CPS	Compendium of Pharmaceutical Specialties
CPSP	Canadian Paediatric Surveillance Program
DAD	Discharge Abstracts Database
GATC	Genotype-specific Approaches to Therapy in Childhood
HAART	Highly Active Anti-Retroviral Therapy
HIV	human immunodeficiency virus
HOMER	HAART Observational Medical Evaluation and Research
HPRP	Health Policy Research Program
ICES	Institute for Clinical Evaluative Sciences
IHE	Institute of Health Economics
ISMP	Institution for Safe Medication Practices
MHPD	Marketed Health Products Directorate
MOXXI	Medical Office of the 21st Century
MSP	Medical Services Plan (of BC)
MS	multiple sclerosis
NBPDP	New Brunswick Prescription Drug Program
NDS	New drug submission
NIHB	Non-insured Health Benefit program
NOC	Notice of Compliance
NOC/c	Notice of Compliance with Conditions
NSAID	non-steroidal anti-inflammatory drug
PHRU	Population Health Research Unit
PMMP	Pharmacy Medication Monitoring Program
POPi	Policy Innovations Programme
QOL	quality of life
RAPPORT	Rheumatoid Arthritis Pharmacovigilance Program and Outcomes Research in Therapeutics
RCT	randomized controlled trial
TI	Therapeutics Initiative
TPD	Therapeutic Products Directorate
UBC	University of British Columbia
US	United States
WHO	World Health Organization

[1] Abbreviations relate to the report itself, not the appendix.

1. Introduction

Approval to market a drug in Canada is granted based on adequate efficacy and safety, as demonstrated through well-designed clinical trials. However, clinical trials rarely mirror the real world. In particular, they:

- include a limited number of patients,
- last for relatively short periods of time,
- under-represent patient populations,
- have more compliant patients, and require physicians to report events,
- use surrogate (short-term) outcomes, and
- generally lack direct comparison with drugs in the same therapeutic class used for the same indication.

With respect to safety and effectiveness after marketing and dissemination to the general population, a number of questions arise:

How will a drug perform once it is more widely prescribed?
How will it benefit people, as compared with alternative (probably cheaper) therapies?
If there are benefits, will they be worth the cost?
What safety concerns will arise when many people use a drug, versus few in clinical trials?
How can these issues be studied?

Post-market surveillance to evaluate drug safety and effectiveness has traditionally relied on two major data sources:

→ Clinical trials supporting the New Drug Submission (NDS) process.[2]
→ Spontaneous adverse drug reaction (ADR) reports in the post-market phase.

The limitations of clinical trials have been noted above. In the case of spontaneous ADR reporting systems, limitations include:

- Under-reporting
- Incomplete data
- Poor quality data
- Difficulty demonstrating a causal relationship between exposure and an adverse event

Useful resources for those engaged in post-market surveillance activities are the existing Canadian health databases. A summary of existing pharmacosurveillance databases in Canada, along with their strengths and limitations and the roles they can play in post-market surveillance, is contained as Appendix 1. This information was compiled in 2004 by Dr. Jun Zhang in her position as epidemiologist with the Therapeutic Effectiveness Surveillance and Evaluation Division of Health Canada's Marketed Health Products Directorate.

[2] For an explanation of how new drugs are reviewed in Canada, see: www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/fs-fi/reviewfs_examenfd_e.html. Guidance documents can be found at: www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/index_e.html and policies at: www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/pol/index_e.html.

2. Objectives

This paper will highlight the close interactions required between researchers and decision makers, and the "service" orientation of the initiatives described. If the information on individual initiatives was available, descriptions in this document focus less on methods and more on their goals, how they were established, and so forth. Of prime importance are measures used to determine success/failure for frameworks.

3. Initiatives

Drug effectiveness and safety in the real world may be evaluated through formal epidemiologic observational studies and post-market randomized clinical trials (RCTs) or large sample trials. This is particularly true when a specific health product increases or decreases the baseline incidence of a condition or illness, mortality, and/or hospitalization resulting from a specific disease. Safety and effectiveness may also be explored through initiatives arising from existing drug management systems, such as provincial drug plans. Frameworks can be developed to launch and categorize such initiatives.

The availability of relevant information and data are essential. Pharmacosurveillance frameworks may use many types of information:

- Administrative databases
- Results from pragmatic trials
- Patient registries
- Surveys
- Reporting of adverse events by clinicians or patients, whether reporting is spontaneous or mandatory.

Many initiatives are underway in Canada; a number will be described. In this paper, initiatives are grouped according to the type of framework underlying them, the four frameworks being:

1. *Drug regulatory authority frameworks*
   Example: Canadian Adverse Drug Reaction Monitoring Program (CADRMP)

2. *Health plan and drug plan frameworks*
   Example: Administrative database studies

3. *Drug manufacturer frameworks*
   Example: Clozapine patient registries

4. *Clinician/clinical group/disease collaborative frameworks*
   Example: BC Centre of Excellence for HIV/AIDS

3.1 Drug Regulatory Authority Frameworks

Health Canada is the sole regulatory body responsible for approving drugs for marketing in Canada. The ultimate authority to license and impose conditions on approval rests with Health Canada's Therapeutic Products Directorate (TPD). The Marketed Health Products Directorate (MHPD) is responsible for coordination and consistency of post-marketing surveillance and assessment of signals and safety trends for all marketed health products, and communication to health care professionals, hospitals, and others.

3.1.1 Canadian Adverse Drug Reaction Monitoring Program (CADRMP) [3, 4]

Health Canada encourages the reporting of all ADRs, especially those that:

- are unexpected, regardless of severity;
- are serious, whether expected or not; and
- occur with a product marketed for less than five years.

ADR reports are submitted voluntarily directly by health professionals and consumers to seven regional ADR centres (BC, AB, SK, MB, ON, QC, and Atlantic) as well as to the national centre in Ottawa. It is mandatory for manufacturers to report serious ADRs. ADR reports are reviewed for quality and completeness, and entered into the Canadian Adverse Drug Reaction Information System (CADRIS).[5] ADR reports are further analyzed to discover potential health product safety signals. A signal does not identify causal relationships, but triggers the need to further investigate a potential association. As of January 2004, CADRIS contained over 160,000 suspect ADR reports submitted in Canada since 1965. Annually, approximately 10,000 new ADRs are added to CADRIS. In early 2004, the Canadian Broadcasting Corporation (CBC) made the database available through its website[6] and in May 2005, Health Canada also provided open access to an online extract of the database.[7]

For one ADR episode, CADRIS data may include:

- The ADR
- Patient characteristics
- Suspected health product(s)
- Concomitant health product(s)

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[3] An Adverse Reaction Database has been developed by CADRMP and can be used to access information concerning suspected AEs to Canadian marketed health products of pharmaceuticals, biologics (including blood products and therapeutic and diagnostic vaccines), natural health products, and radiopharmaceuticals, as reported to Health Canada through voluntary and mandatory reporting measures. See: www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index_e.html.

[4] A related initiative is the Canadian Medication Incident Reporting and Prevention System (CMIRPS), a collaboration of the Institution for Safe Medication Practices (ISMP) Canada, the Canadian Institute for Health Information (CIHI), and Health Canada. CMIRPS is an independent Canadian non-profit agency established for the collection and analysis of medication error reports and the development of recommendations for the enhancement of patient safety. Some of the work of CADRMP and CMIRPS may overlap in terms of the information needed for drug safety. See: www.ismp-canada.org/index.htm.

[5] A 2004 CADRIS fact sheet can be found at: www.npha.nf.ca/Documents/ADR/CADRIS%20Fact%20Sheet.pdf.

[6] CBC Web access to CADRIS is available at: www.cbc.ca/news/adr/database/.

[7] For the press release of May 25, 2005, see: www.hc-sc.gc.ca/ahc-asc/media/nr-cp/2005/2005_46_e.html.

- Medical history and laboratory data
- Management of the ADR
- Patient outcome
- Reporter information (confidential).

Goals
The goals of CADRMP are to:
- collect and assess suspected adverse reaction reports for Canadian marketed health products: pharmaceuticals, biologics, natural health products and radiopharmaceuticals; and
- monitor the safety profile of marketed health products to ensure that benefits of the products continue to outweigh the risks.

Goal Setting
Goals are established by Health Canada. The process is not public.

Advantages
- National scope.
- Regional network, in addition to national centre in Ottawa.
- Anyone can report.
- Mandatory reporting of ADRs by manufacturers
- Database is continually updated.
- Well-established and known reporting mechanism with reporting forms available on the web, in the Compendium of Pharmaceutical Specialties (CPS), or through regional ADR centres and reports can be faxed or phoned in toll free (during regular business hours).
- Health Canada is using statistical tools under development by the World Health Organization (WHO) to complement and support systematic review and signal detection.
- Online extract of the database allows for searches to be performed by anyone.

Limitations
- Collection by spontaneous (voluntary) reporting, except from manufacturers.
- Known, significant underreporting (it is estimated that < 10% of ADRs are reported); therefore the number of reports alone cannot be used to estimate the incidence of the reaction, and numerical comparisons should not be made between reactions associated with different products.
- Health Canada cannot compel manufacturers to provide full adverse event report data, except where there is an identifiable concern, or to change product monographs, issue communications to practitioners or the public, recall products currently in the marketplace, or undertake further trials (except under NOC/c, below).
- ADRs are suspected associations only so a report does not mean the reaction was caused by the suspected product; certain reported reactions may also occur spontaneously, without causal relationship.
- Where the product has multiple ingredients, it may not be possible to determine which, if any, of the substances was responsible for the ADR.
- Terminology for coding reaction is restricted to terms used by coding dictionaries.
- CADRIS data do not represent all known safety information for products, or reports from all ADR reporting programs, e.g., medication incidences or medical errors.

- CADRIS cannot be used alone for evaluation of a health product's safety profile as it is not a complete source of information.
- Report data are often incomplete and insufficient to allow for causality assessment or to guide safety recommendations.
- Follow-up with patients and clinicians is minimal; regional staff can provide case-specific tracking numbers to facilitate follow-up and can request clarification, but information provided is often incomplete.
- The size and functionality of CADRIS do not allow for statistical analysis sufficient to include background context of previous reports, or of similar symptoms due to underlying diseases.

Measures Used to Determine Success/Failure

- The number of AEs for which a causal relationship between the drug and the AE is assessed and established.
- The number of safety signals generated and assessed
- Opinion surveys of health care practitioners and the public.

Evaluation Capacity/Capability

- Evaluation of collected information, causality assessment, safety signals, and risk/benefit profiles: conducted by Health Canada evaluators and limited by availability of staff resources.
- Evaluation of the HC post-market surveillance strategy: conducted by Health Canada evaluators.

3.1.2 Notice of Compliance with Conditions (NOC/c) [8]

NOC/c provides market authorization to products with promise of clinical effectiveness based on surrogate endpoints (e.g., lowered cholesterol or tumor shrinkage, rather than heart attack or survival) and acceptable safety evidence, but where further validation is required. NOC/c is a policy framework, not a legislative one. Thus, while additional conditions are added to the licensing approval, the NOC that is granted is otherwise the same as any other. NOC/c is granted on the condition that the product sponsor undertakes further studies to verify the clinical benefit of the drug.

Goal

The goal of the NOC/c process is to provide earlier market access for drugs to treat serious (life-threatening or severely debilitating) conditions where there is either no existing therapy or the new product provides a significant improvement in the benefit/risk profile over existing therapies.

Goal Setting

Goals are set by Health Canada.

Advantages

- Provides earlier access to drugs for serious conditions
- Establishes formal requirement for:

[8] For further information on NOC/c and a listing of drugs currently covered by NOC/c, see: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index_e.html.

    - validation studies post-market
    - ADR monitoring with regular updates to Health Canada
    - educational materials for patients and practitioners
- Restricts advertising and labeling of NOC/c drugs
- Provides a mechanism for withdrawal of market authorization if benefits are not validated

Limitations

- Surrogate endpoints which are the basis of the NOC/c approval may not accurately reflect outcomes (e.g., cholesterol lowered, but no reduction in deaths from cardiovascular disease).
- Evidence supporting NOC/c approval is often not sufficient for funding agency decisions, so drug costs may not be covered.
- Timelines for fulfillment of listing conditions are not always clear or consistent.
- The process relies on product sponsors to provide all validation studies.
- The risk profiles of NOC/c drugs may not be fully understood at time of listing.
- Promised benefits may not be borne out by further study, while patients are exposed to risks during market period.

Measures Used to Determine Success/Failure

Unknown, but could include:

- Number of drugs that proceed/do not proceed to NOC without conditions after validation studies
- Time to removal of conditions for those drugs

3.1.3 Research at the Pharmaceutical Outcomes and Policy Innovations Programme

The Pharmaceutical Outcomes and Policy Innovations Programme (POPi), based at the Children's and Women's Health Centre of BC (C&W), has a number of projects underway that fit under the drug regulatory framework heading. Examples include:

(a) Paediatric suspected ADRs reported to the CADRMP
(b) ADR reporting within the Canadian Paediatric Surveillance Program (CPSP)
(c) Genotype-specific Approaches to Therapy in Childhood project (GATC)

3.1.3 (a) Paediatric suspected ADRs reported to the CADRMP

Goals

The goals/objectives of this research are to:

- catalogue all paediatric suspected ADRs reported to the CADRMP at Health Canada from January 1, 1998, to May 30, 2002;
- identify the drugs most frequently reported;
- identify the types of reactions reported; and
- identify the demographic characteristics of the children for whom ADR reports have been submitted to CADRMP.

Goal setting

The project was funded by Health Canada, who also supplied the data to POPi. Research questions were determined in collaboration with CADRMP.

Advantages

- POPi has access to staff and expertise not readily available to Health Canada.

Limitations

- Data quantity and quality limit the ability to draw definitive conclusions regarding ADR causality.

3.1.3 (b) ADR reporting within the CPSP [9]

The CPSP is a joint project of the Public Health Agency of Canada and the Canadian Paediatric Society. Its mission is to "contribute to the improvement of the health of children and youth in Canada by national surveillance and research into childhood disorders that are high in disability, morbidity an economic costs to society, despite their low frequency". The CPSP gathers data monthly from over 2,400 paediatricians to monitor rare diseases and conditions in Canadian children. Beginning in January 2004, the reporting of serious or life-threatening ADRs in children (age <19) was included within the CPSP. In the first year of the project, 67 ADR reports were submitted, all of which were shared with the Health Canada and CADRMP.

Goal

The goal of ADR reporting within the CPSP is to develop a tracking system for ADRs in children in Canada, using an existing program.

Goal setting

The project was funded by Health Canada.

Advantages

- Collaboration with the Canadian Paediatric Society, POPi, and Health Canada provides research that enhances the work of CADMP. The clinical staff members of POPi review all cases and share results with Health Canada.
- Reporting of ADRs to Health Canada is increased.
- Newsletters, reports, and presentations at scientific meetings targeted to members of CPSP allow for dissemination of patient safety information and highlight the importance of ADR reporting.

Limitations

- Data quantity and quality limit the ability to draw conclusions regarding patient safety.

3.1.3 (c) Genotype-specific Approaches to Therapy in Childhood project (GATC) [10]

GATC is a large national project, funded in part by Genome Canada, to study ADRs in children; co-led by Dr. Bruce Carleton (POPi) and Dr. Michael Hayden (Centre for Molecular Medicine and Therapeutics). ADR data are collected by a hospital-based network of clinical surveillance pharmacists in seven Canadian hospitals, including the C&W. The surveillance pharmacists identify children experiencing a suspected ADR, collect patient-specific data, and obtain DNA samples from the affected children. DNA samples from these children are compared genetically with samples from age-matched control populations of children who are taking the same medications but not experiencing the ADRs.

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[9] CPSP information can be found at: http://www.cps.ca/english/CPSP/.

[10] GATC information can be found at: www.genomecanada.ca/GC.programmesRecherche/projets/projectDetail.asp?id=s1p11&l=e.

Goal
The goals of GATC are:

- to prevent ADRs in children by identifying predictive genomic markers for specific ADRs, and
- ultimately to provide specific dosing recommendations for commonly used drugs based on an individual's genetic make-up.

Goal setting
The project is funded by Genome Canada, Genome British Columbia, the UBC Faculties of Pharmaceutical Sciences and Medicine, the Child and Family Research Institute (BC), the Canadian Genetic Diseases Network, the Canada Gene Cure Foundation, the University of Western Ontario, Illumina, IBM, and the Canadian Society for Clinical Pharmacology.

Advantages

- This project is a trans-disciplinary cooperation among experts from hospitals, universities, research institutes, children's advocacy groups, and Health Canada.
- Designated surveillance personnel actively collect ADR report information.
- Project evaluation will allow assessment of this model of ADR surveillance to improve the quantity and quality of ADR reporting.

Limitations

- The national surveillers network is funded only for the lifetime of the project (2.5 years).

3.2 Health Plan and Drug Plan Frameworks

Drug plans in Canada seldom have internal capacity to carry out post-market surveillance, but several have developed collaborations with researchers at academic institutions for this purpose. A number of models of collaboration exist, with the most important current distinction between them being the source of funding for projects. It is important to note that the same groups may have funding from different sources for similar work at the same time, or over time. No single method of supporting post-market surveillance appears fully sufficient; each has strengths that contribute to the overall improvement of this area of work.

One noteworthy difference between Health Canada's post-marketing surveillance activities and those of health plans and drug plans is the centrality of cost-effectiveness in evaluations for the latter groups. Given their mandates to determine whether drugs should be financed for their beneficiaries, drug plans require information not only on the safety and clinical efficacy of the drugs under evaluation, but also about how their health benefits and risks compare to other drugs already on the market. Thus, they seek to determine not only whether drugs are efficacious with a safety profile that is favorable enough to warrant use, but also whether they are safer and more effective than others for the same condition. If there is a price difference between drugs for the same condition, drug plans also must determine whether price differences are justified due to increased benefit or decreased risk. Cost alone, however, is not the determining factor in listing decisions.

3.2.1 Administrative database studies: grant-funded or funded by drug plans[11]

Several Canadian academic/research units provide post-market surveillance expertise to provincial drug plans on a contract basis or with year-to-year funding. Some, like the Institute for Clinical Evaluative Sciences (ICES) in Toronto, the Population Health Research Unit (PHRU) at Dalhousie University, and the Manitoba Centre for Health Policy (MCHP), have a group of researchers who focus on prescription drug issues within a larger research unit. Others, like the Therapeutics Initiative (TI) at UBC, and the POPi at C&W, concentrate solely on the evaluation of drugs. Evaluations may be done at any time after drugs receive NOC or NOC/c approval – before initial formulary listing decisions, when listing revisions are contemplated, or to assess the impact of drugs on population health.

Some studies that focus on policy issues are funded through competitive, peer-reviewed granting processes; these may provide more independence in the choice of research questions and methods compared to those funded by drug plans, but suffer from finite funding terms and are limited by the granting agencies' priorities in each funding cycle. Some grant-funded studies include drug plans as supporters or collaborators, but not as investigators.

A number of publications result from the research in these institutions, many being disseminated in the public domain. Research publications and/or summaries can often be obtained through the Websites of the organizations.[12]

Drug plan post-market surveillance projects are seldom clinical trials; they most often rely on administrative data for utilization and observational/cohort studies. Some use patient registries based on drug funding criteria (e.g., the Nova Scotia multiple sclerosis (MS) registry and the Alberta Biologics Registry), with additional data collected from registry members or their physicians. Some groups have developed collaborations that allow data from different provinces to be used for the same study (e.g., the 2002-04 TI/ICES project funded by Health Canada),[13] thus offering larger populations to identify rare ADRs.

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[11] Electronic medical record networks may eventually replace provincial databases and may in fact have much wider potential for use. A Canadian example is COMPETE II [**C**omputerization **O**f **M**edical **P**ractice for the **E**nhancement of **T**herapeutic **E**ffectiveness], which the lead investigator suggests has a number of strengths: it routinely collects research quality data, is oriented to improve prescribing outcomes, and runs as a real-practice RCT so there is rigorous evaluation. COMPETE II is a collaboration of the Centre for Evaluation of Medicines at McMaster University and St. Joseph's Healthcare, Hamilton. Several publications on prescribing have been generated. More information can be obtained at: www.compete-study.com/overview.htm .

[12] Websites are:

- Institute for Clinical Evaluative Sciences (ICES): www.ices.on.ca
- Population Health Research Unit (PHRU) at Dalhousie University: www.phru.dal.ca
- Manitoba Centre for Health Policy (MCHP): www.umanitoba.ca/centres/mchp
- Therapeutics Initiative (TI) at UBC: www.ti.ubc.ca

[13] This collaboration led to a June 2005 report authored by GM Anderson and K Bassett titled *"Incorporating Pharmacosurveillance in Provincial Drug Formulary Decision-Making: Investigative Report".* The 46-page report is available at www.ices.on.ca/file/Pharmaco_Report_FINAL.pdf. The key objectives of the project were: (1) to work with formulary decision-makers in Ontario and BC to identify pharmacosurveillance information needs, (2) to develop and refine techniques for producing evidence and to share those techniques with research teams in both provinces; and (3) to assess the impact of pharmacosurveillance on decision-making. Within the report, Exhibit 12a (page 28) and Exhibit 12b (page 35) may of particular interest; the tables display 29 research projects used by drug benefit program decision-makers in Ontario and BC along with their perceived contribution to decision-making processes.

Goals
The goals of administrative database studies are generally to:

- inform formulary listing and drug plan policy decisions, once drugs are issued an NOC or NOC/c by Health Canada; and
- contribute to the scientific literature on drug effectiveness

Goal Setting
Topics for analysis are established by researchers or by the drug plans. In some cases, required analyses are identified with each year's funding contract. In others, topic identification is ongoing.

Advantages

- May cover full populations and "real-life" drug use situations (e.g., less selected populations).
- Analyses are relevant to policy decisions.
- Access to population-level administrative databases may be easier with collaboration between decision-makers and researchers.
- Cross-jurisdictional pooling of large datasets may allow for earlier analyses of rare events than waiting for them to accumulate over time in one area.
- Collaborations allow for comparisons of the effect of different coverage policies for the same drugs in similar populations.
- Databases may allow for collection of clinical data.
- Support ongoing communication between researchers and drug plan staff.

Limitations

- Randomization is seldom possible and statistical adjustments for bias are not always adequate; these may be most useful for detecting early signals that need to be confirmed by RCTs.
- Administrative data can be limited in scope of variables and may not include the entire population
- Choice of research topics may be limited by focus on drug plan priorities rather than effectiveness/safety monitoring.
- Such analyses involve retrospective review versus prospective study to determine drug effectiveness; this study design is unlikely to be sufficiently convincing to clinicians who argue that this type of study is not as accurate as an RCT in determining clinical outcomes due to drug therapy.
- Short time frames for policy decisions may limit type of analyses done.
- There can be long delays in data access under some privacy legislation/review processes.
- Access to peer review and ethics review may be limited, if researchers do not have academic affiliations.
- Potential benefits are limited by:
    - available funding
    - lack of long-term funding commitments, leading to difficulties in retaining research teams or carrying out long-term studies
    - lack of direct/ongoing data access (versus project-by-project review)
    - lack of access to drug plan staff support and decision-makers due to overwhelming demands and staff turnover

- privacy protection legislation may limit ability to share data between groups or jurisdictions

Measures Used to Determine Success/Failure

- Number of policies assessed.
- Development and maintenance of working relationships with other researchers and drug plans.
- Publication of peer-reviewed studies.

Evaluation Capacity/Capability

- Performance of publicly-funded groups is subject to public review and reporting.
- The same data are usually available for other researchers to examine the same topics for the same periods, providing cross-validation of methods and conclusions.
- Analyses are limited by lack of drug plan expertise, financial capacity, and time.

3.2.2 Alberta Biologics Registry

The goal of this registry is to assess the outcomes of biological therapies in patients with rheumatoid arthritis (RA) in Alberta. The registry has been developed by rheumatologists at the University of Alberta and the University of Calgary and is administered by the Institute of Health Economics (IHE), a not-for-profit research organization in Edmonton. The project is a collaborative venture between academia, government payers, and industry. A project council provides financial and program management, liaison with manufacturers and the provincial government, and guidance and direction when requested. A scientific council developed the study protocol, and arranges for the conduct and monitoring of the study. Alberta Health and Wellness has final sign-off on the study protocol. The registry is funded by industry through agreements with Alberta Health and Wellness.

All patients using biologic therapies to treat RA and who wish to receive public coverage of drug costs, as well as their rheumatologists, are required to meet coverage criteria and register before coverage begins. Data elements collected include demographics, co-morbid conditions, health-related (QOL) of life measures, measures of health care resource use, and medication history. Ongoing surveillance of the effectiveness of therapy is conducted using defined and validated criteria; patients who no longer meet the criteria are withdrawn from therapy. Several publications describing the project are available.[14]

Goals

The project intends to:

- Assess long-term safety and effectiveness of biologic therapies for RA.
- Determine the cost-effectiveness of biologic therapies for RA.
- Respond to other goals as submitted to and approved by the scientific committee.

[14] Related publications include: Maksymowych W. Reporting process of randomized clinical trials (Letter). CMAJ. 2004;170(9):1375; Barr SG, Martin L, Chung C, Maksymowych W. Mandatory pharmacosurveillance – a Canadian model for access to therapy and research. Clin Exp Rheumatol. 2004;22(5 Suppl 35):S39-43.

Goal Setting
Goals are established by the Minister's Expert Committee on Drug Evaluation and Therapeutics.

Advantages
- Provides data not available through administrative datasets, without clinical record reviews.
- Provides consistent basis for outcomes, cost, and QOL assessments.
- Provides a route for withdrawal of expensive therapies if effectiveness is not maintained.
- May provide consistent data over time, if maintained.
- Provides collaborative mechanism for stakeholders.
- Scientific oversight separated from financial and liaison roles.
- May provide model for other pharmacosurveillance studies.

Limitations
- Limited number of analysis variables collected; change over time affects ability to do longitudinal studies.
- Patients are not randomized to treatments.
- Data quality depends on individual practitioners; may not be consistent.
- Covers only patients eligible for public coverage of drug costs in Alberta.
- Enrollment is voluntary if patients are not on the Alberta Health and Wellness plan.
- May not be sustained long enough to evaluate long-term outcomes.
- No randomized control group of patients who are not receiving the drugs to provide comparisons for drug effectiveness determination.

Measures Used to Determine Success/Failure
- Ability to carry out protocol.
- Development of effective monitoring and evaluation model for pharmacosurveillance.
- Development of program to address long-term safety and effectiveness of biologics.

Evaluation Capacity/Capability
- Relies on contract arrangements; long-term capacity uncertain.

3.2.3 Modeling trends and regional variation in asthma care (POPi)

This project, funded by the Canadian Institutes for Health Research (CIHR) uses 12 years of linked administrative data (1991 to 2003) from the BC Ministry of Health and BC PharmaNet. Information includes physician services, hospital services, drug purchases, and vital statistics, and is obtained from the following databases:
- Physician services: the Medical Services Plan (MSP)
- Hospital services: the Discharge Abstracts Database (DAD)
- Drug purchases: BC PharmaNet
- Vital statistics: BC Vital Statistics Agency

Key research questions include:
- How have regional rates of utilization of various asthma medications changed over time and how do these rates co-vary?
- How do indicators of medication utilization appropriateness vary across health regions and years?

- What factors are most responsible for the variation?

Goal
The purpose of this project is to improve understanding of how patients with asthma use asthma-related medications and the effects of differences in usage on utilization of health care services. Hierarchical linear model analyses will provide information at both the patient level and the health region level. Findings from this work will be beneficial in planning and targeting interventions with patients, physicians, and policy makers to improve the quality of medication use, and ultimately the QOL of patients with asthma.

Goal setting
Goals were established by the investigative team and funding received from CIHR.

Advantages
- This study draws on data from 1.89 Million patients in BC who received respiratory-related health care services. From these, a sub-set of patients treated for asthma will be generated to form the core population for analyses. Conclusions will be generalizable to the overall patient population.

Limitations
- It is expensive and time consuming to obtain and validate the required data.

3.2.4 New Brunswick monitoring of antibiotic consumption

The New Brunswick Prescription Drug Program (NBPDP) has been monitoring antibiotic prescribing and utilization within the province, including disseminating physician profiles. The prescribing of oral antibiotics for systemic use in primary care is tracked for beneficiaries of the NBPDP using claims data. The data for each NB health region are adjusted for age and gender and compared both among NB regions and to other jurisdictions. In the first cycle, the comparators consisted of four Scandinavian countries, selected for comparison as their health care systems and populations are similar to those in Canada and they have well-established records of antibiotic use and modest drug resistance rates. NB data from 2000/2001 were used.

Goal
The NB project aims to help create awareness of antibiotic utilization rates and ultimately to reduce overall antibiotic consumption through conservative prescription.

3.2.5 Non-insured health benefit (NIHB) project on diabetes and cardiovascular drugs

The NIHB Program provides coverage for pharmaceutical and related health care products for Canada's First Nations and Inuit who are registered, employing a drug formulary similar to that of the provinces. An extensive database exists, as the program provides national coverage and has existed for a number of years. One research project that made use of the database examined a subset of clients who had been dispensed at least two prescriptions for antihyperglycemic therapy in 2002/2003 (n=35,000), seeking to determine rates of utilization of

several cardiovascular drugs which have been deemed to reduce cardiovascular risk for people with diabetes.[15] The rates of use were compared to a benchmark standard.

Goal
The goal of the project was to examine the rate of prescribing of specific protective cardiovascular drugs among claimants of the NIHB Program who are diabetic, and to compare these to a reference standard.

3.2.6 Secondary reviews and policy research related to administrative databases

As described above, provincial drug databases and other administrative databases provide rich sources of data for researchers to use for pharmacovigilence activities and initiatives. However, their existence does not guarantee their effective use. A number of experts have considered how the link between data sources and decision-making can be optimized. For example, in 2001 the Health Policy Research Program (HPRP) at Health Canada funded several projects in this area:

- *Development and evaluation of a framework for incorporating pharmacosurveillance in provincial formulary decision-making.* Bassett K, Wright JM, Warren L, et al. July 2004. HPRP Contribution Agreement 6795-15-2001/4410001.
- *Production and use of evidence of drug effectiveness: systematic review, evaluation and a guidebook for decision makers*. Carleton B. July 2004. HPRP Contribution Agreement 6795-15-2001/4410031.
- *Evaluation of data sources to support pharmacosurveillance.* Holbrook A, Keshavjee K, Sebaldt R, et al. July 2004. HPRP Contribution Agreement 6795-15-2001/4410013
- *Evaluation of an Integrated Model and Iterative Loop for Assessment of Drug Effectiveness in the "Real World".* Metge C, Soon J. In press. HPRP Contribution Agreement 6795-15-2001/4410016.

Summaries of these projects can be found at www.hc-sc.gc.ca/sr-sr/finance/hprp-prpms/final/index_e.html.

3.3 Drug Manufacturer Frameworks

Drug manufacturers participate in three major types of postmarketing pharmacosurveillance. The first framework involves reporting ADRs to Health Canada as described above. In addition, manufacturers of some drugs are required to establish and maintain registries of patients using certain drugs due to significant, known safety concerns (e.g., clozapine). In some cases, registries are a condition of the drug's original market approval; for others, they are a condition of re-entry into the market after withdrawal (e.g., alosetron). There may be one registry per manufacturer, or a common registry for all manufacturers of the same drug. Phase IV (postmarket) clinical trials of drugs that are already licensed for use in Canada may be considered another framework for pharmacosurveillance. Adverse event data are reported to CADRMP as described earlier. Efficacy and effectiveness data derived from these trials are described in research reports; many of these clinical trials end up as published manuscripts in the biomedical literature.

[15] A Drug Use Bulletin, published in November 2004, describes the research and can be accessed at: www.hc-sc.gc.ca/fnih-spni/alt_formats/fnihb-dgspni/pdf/pubs/drug-med/2004_nov_due-eum_e.pdf.

3.3.1 Patient registries

In the case of clozapine, each manufacturer of the drug maintains separate patient registries are maintained by. There is an established process for movement of patients between one registry and another, requiring written confirmation and access to previous monitoring information.[16] Conditions that must be met before drugs are dispensed include:

- Registration form completed by physician for the correct manufacturer's registry.
- Documented consent from the patient to information sharing among registries.
- Completion of appropriate monitoring with results supplied to registry.
- Pharmacist informing prescribing physician of intention to dispense.
- Confirmation of patient status, e.g., non-rechallenge status.

Goals

The clozapine registries aim to reduce deaths and other serious ADRs for a drug with significant known risks. Other registries have similar goals.

Goal Setting

Goals and mechanisms appear to be established jointly by Health Canada and the drug manufacturers but this is not entirely clear.

Advantages

- Mandates monitoring of patients at known high risk of serious ADRs.
- May reduce population exposure to high-risk drugs.
- May allow for post-market studies with registry patients.
- May provide earlier signals than population-level analysis or clinical trials for rare events, especially if there is a single registry for all manufacturers.

Limitations

- Health Canada has no mandate to monitor the registries, unless identified in a regulatory requirement.
- The processes may delay access to drug.
- Data are not available for analysis, other than by the manufacturers.
- The only current response to problems is market withdrawal.
- Unless a follow-up study is under way, monitoring is confined to known ADRs.
- Can be difficult to determine cause-effect relationship between drug and reaction since many reports are based on single cases or case series.
- Multiple adverse events reported may reflect a single patient's experience or multiple patient experiences with a drug.

Evaluation Capacity/Capability

- Determined by manufacturer; outside scrutiny minimal
- Data cannot be matched to other sources, e.g., administrative data, for outcomes analysis

[16] Health Canada letters (June, 2004) to health care professionals explain the registries. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2004/clozapine_nth-ah_e.html and http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2004/clozapine_hpc-cps_e.html.

3.4 Clinician / Clinical Group / Disease Collaborative Frameworks

Multi-site, international collaborations among clinicians and clinical groups are well established for research into specific conditions such as cancer and chronic diseases such as diabetes. While some collaborations focus intensively on clinical drug trials, including RCTs with drugs already licensed as well as experimental drugs, others do not have a clear focus on drug therapy. The latter have only limited use as pharmacosurveillance frameworks, other than offering identifiable patient populations and potential clinical partners for studies. All Canadian provinces have some type of collaborations based on disease groups or clinical groups, such as diabetes registries. Several examples are provided here.

3.4.1 BC Centre of Excellence for HIV/AIDS

Established in 1992, this centre is located at St. Paul's Hospital in Vancouver. Clinical cohort studies[17] regularly monitor and assess outcomes of patients in the Centre's drug treatment program. The best-known study cohort is the Highly Active Anti-Retroviral Therapy (HAART) Observational Medical Evaluation and Research (HOMER) group, comprised of nearly 1,500 HIV-infected individuals who have initiated HAART with three or more antiretroviral agents since August 1, 1996. The centre also conducts population health research using clinical and administrative data.

Goals

The goals of the BC Centre of Excellence for HIV/AIDS are:

- To further define the role of antiretroviral therapy for the treatment of HIV infections
- To evaluate the safety and efficacy of specific antiretroviral treatment regimens, simplified regimens, adjunctive therapies, and new formulations.
- To investigate treatments for those co-infected with viruses such as hepatitis B and C.
- To determine new approaches to the treatment of HIV-related opportunistic infections, and investigations related to HIV-associated drug toxicities and metabolic risk factors.
- To evaluate determinants of optimal antiretroviral therapy for HIV infected individuals.
- To determine patterns of hospital utilization and physician usage by linking with the BC Linked Health Database at UBC.
- To foster international collaboration with the ART Cohort Collaboration Study.[18]

Goal Setting

- Goals are set by the BC Centre of Excellence for HIV/AIDS.

Advantages

- Captures data from eligible BC patients registered for coverage of antiretroviral drugs.
- Concentrates multidisciplinary expertise in clinical and population health areas: primary care, infectious diseases, respiratory medicine, lipid disorders, counselling, psychology, clinical trial operations, statistics, epidemiology, outcomes research, and research methodology.
- Provides a direct connection between study outcomes and clinical guidelines.

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[17] Research underway at the BC Centre for Excellence in HIV/AIDS can be accessed at: http://www.cfenet.ubc.ca/content.php?id=20&sid=31#.

[18] The ART Cohort Collaboration includes 13 cohort studies from Europe and North America and was designed to allow estimation of the prognosis of HIV-1 infected, treatment-naive patients who start HAART.

- Is involved in a number of international studies, including RCTs.

Limitations

- Post-marketing studies are observational trials that are not randomized or blinded.
- Focus is largely on Phase II and III trials.
- Intense study of a single, fairly small group (7,400 people).

Evaluation Capacity/Capability

- Publications are evaluated through the peer review process.

3.4.2 BC Chronic Disease Management (CDM) projects[19]

Patient registries have been established for a number of chronic diseases such as diabetes, congestive heart failure, arthritis, and asthma, using BC health care administrative databases. The registries are structured by disease coding of physician services or hospitalizations, and/or medication history. Collaborations among the BC Ministry of Health Services, organizations of health care professionals, and regional health authorities have been established to support practitioners who provide care for registry members. The collaborations also monitor progress in therapy improvements for the specified diseases, including drug therapies.

Goals

The BC CDM projects aim to improve the quality of care and health outcomes for individuals with chronic diseases in the province.

Goal Setting

Goals are established by steering committees for each disease.

Advantages

- Establishes a mechanism for collaboration among health care administrators and a variety of health care practitioners.
- May increase awareness of drug-related issues and concerns among practitioners.
- May allow for monitoring of outcomes not usually recorded in administrative data.
- Creates identifiable consistent disease cohorts for longitudinal studies using administrative data.

Limitations

- Not necessarily focused on drug effectiveness or drug therapy outcomes.
- Not independent of funding agencies or (sometimes) manufacturers.
- Not clear who should design, fund, or carry out evaluation studies.
- The focus on all patients with a given disease means that registries are created which include a broad expanse of patients with a wide range of disease experiences, making policy-relevant analysis more difficult.

Evaluation Capacity/Capability

- Limited by resource constraints, lack of expertise.

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[19] The BC Ministry of Health Services has established a Website for its CDM program, including chronic disease statistics and utilization and cost data: www.healthservices.gov.bc.ca/cdm/research/index.html.

3.4.3 Canadian Cardiovascular Outcomes Research Team (CCORT)

CCORT, established in 2001, is funded by CIHR and the Heart and Stroke Foundation of Canada and headquartered at ICES in Toronto. Investigators from NS, QC, ON, AB, and BC are conducting research within the CCORT framework.[20] Some of CCORT's research involves cross-provincial drug studies, an example being a study examining the outcomes of elderly patients with CHF and trends in drug therapies.[21]

Goal

CCORT's goal is to measure and improve the quality of cardiac care provided to Canadians, particularly related to acute myocardial infarction (AMI), CHF, and invasive cardiac procedures such as angioplasty.

Advantages

- Able to access Ontario Ministry of health data through ICES
- Able to access registries from NS, ON, and QC containing data related to procedures, comorbidities, medications, and outcomes following hospital admittance with AMI.

3.4.4 Children's Oncology Group (COG)

COG is a cancer research organization that has treated and monitored children with cancer for more than 40 years. Over 200 medical institutions in the US and many in Canada participate in the group. Each institution has a multidisciplinary team of clinicians for diagnosis, treatment, and investigation of childhood cancer. COG currently conducts over 150 concurrent studies covering all principal cancers of infants, children, and adolescents, in which over 40,000 patients are treated according to COG research protocols.

These clinical trials compare the best available treatment with one or more experimental treatments, which are developed with the goal of yielding improved results. When a child is treated on a COG protocol, all information about the patient's diagnosis, treatment, and results is sent to a group operations center. Research findings and data are shared with the membership through ongoing communication, publications, and meetings.

Goals

The aims of COG are:

- to improve patient care; and
- to rigorously evaluate treatment protocols; i.e., head-to-head, randomised comparisons of different drugs for cancer treatment.

[20] Information on CCORT can be found at: www.ccort.ca/ccort.asp.

[21] Lee DS, Mamdani MM, Austin PC, et al. Trends in heart failure outcomes and pharmacotherapy: 1992 to 2000. Am J Med. 2004;116(9):581-9.

Goal Setting
Goals are set by the COG membership (5,000 researchers and 240 institutional members), but process is not clear.

Advantages
- Well-established data collection, including a large number of North American institutions and patients (approximately 80% of children treated for cancer at C&W are under a COG protocol).
- Randomization is frequent through clinical RCTs.
- Data can be pooled from many treatment centres for analysis.
- Data are collected by designated research assistants in each institution.
- Adverse events are captured and reported to the Adverse Event Expedited Reporting System (AdEERS)[22] in a standardized manner.
- Studies are funded independently from drug manufacturers

Limitations
- Detailed information not always widely available beyond COG membership.

Evaluation Capacity/Capability
- Appears to have high capability and evaluation capacity.

3.4.5 The MOXXI Project

MOXXI is an acronym for the "Medical Office of the 21st Century" and is a pilot research project at McGill University that is testing the potential benefits of implementing an electronic prescription, drug, and disease management tool for primary care physicians, community pharmacists, and their patients. The project started in 2002 in the Montreal area and plans recruitment of 52 physicians, 60 pharmacists, and 35,000 patients. The research team is now on phase III of MOXXI. MOXXI I, a 13-month study,[23] examined whether inappropriate prescribing could be reduced when primary care physicians had computer-based access to information on all prescriptions dispensed and automated alerts for potential prescribing problems. Data for current and past prescriptions were obtained through a dedicated computer link to the provincial seniors' drug insurance program. MOXXI II enhanced MOXXI I, improving data access, among other advances.[24] Prescription information is obtained from the Régis de l'Assurance Maladie du Québec, with drug profiles being updated daily and medication databases being updated monthly.

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[22] AdEERS is operated by the US National Cancer Institute (NCI). It is a web-based system for submitting expedited reports of serious and/or unexpected AEs. AdEERS reports are forwarded to designated recipients and the NCI for all trials using a NCI-sponsored investigational agent. See: ctep.cancer.gov/reporting/adeers.html.

[23] The research project was published in the Canadian Medical Association Journal and can be accessed at: www.cmaj.ca/cgi/reprint/169/6/549.

[24] Detail on the MOXII II project can be found at: www.moxxi.mcgill.ca/moxxihome.html.

Goal
The aim of MOXII is to allow physicians, pharmacists, and patients to manage medications safely and effectively through coordinated interventions using computerized prescribing and drug management systems.

3.4.6 New drugs for multiple sclerosis

Dr. Murray Brown and colleagues at Dalhousie University conducted a 30-month study in NS examining the effectiveness, cost, and cost-effectiveness of new disease-modifying therapies for patients with multiple sclerosis (MS).[25] At its conclusion, the study demonstrated the feasibility of using regression methods to estimate effectiveness and cost-effectiveness using 'real world' person-level longitudinal data.

Goal
The aim of the study was to estimate the effectiveness, costs, and cost-effectiveness of new MS drugs using NS MS clinical data, MS Special Therapy Program data, and NS health services administrative data.

Goal setting
Funding was provided by the Health Canada's HPRP, the MS Society of Canada, the NS Health Research Foundation, and Capital Health NS.

3.4.7 Patient survey on hypertensive management (a POPi initiative)

This project is a collaborative study between POPi and the BC Ministry of Health. The project randomly surveys 4000 PharmaCare clients, aged 65 years or older, who take hypertensive medications and have switched or discontinued medications in the past year. Patient cohort and contact information are supplied by the Ministry of Health while data analysis is conducted by POPi.

Goals
The objective is to assess patterns of patient hypertensive management in BC; in particular why people with hypertension discontinue or switch their hypertensive medications.

Goal setting
Goals were set by members of the BC Ministry of Health Hypertension CDM Program. Funding for the study was provided by the BC Ministry of Health.

Advantages
- The Ministry of Health CDM Hypertensive Working Group serves as the study steering committee to guide the research and ensure policy relevance.
- Patient privacy can be maintained using a "camouflaged sampling technique".
- Patient outcome data (from Ministry administrative databases) can be obtained for patients who consent and provide their personal health numbers. This can be used to enrich the information derived from the patient survey.

[25] A project summary can be accessed at www.hc-sc.gc.ca/sr-sr/finance/hprp-prpms/final/2005-scleros_e.html

Limitations

- Obtaining Ministry approvals can be difficult.

3.4.8 Pharmacy Medication Monitoring Program (PMMP)

This program, operated by the Centre for Evaluation of Medicines in Hamilton, has been underway for more than a decade, primarily for compliance monitoring. Patients are recruited through pharmacies in four provinces (ON, QC, NS, BC) as well as through drug registries and emergency medication release programs, in partnership with manufacturers. Patients are followed up by phone interviews conducted by trained interviewers. A computer questionnaire is employed to determine benefits and risks relevant to disease and treatment. At the outset of the project, a pilot was conducted on 1475 patients in the Hamilton area who were using non-steroidal anti-inflammatory drugs (NSAIDs).[26]

Goals

The PMMP aims to prospectively monitor new health events in patients taking selected prescription medications.

Goal setting

Led by staff of the Centre for Evaluation of Medicines.

Advantages

- Provides patient/disease/medication data to examine outcomes such as compliance, costs, and productivity.
- May be of interest for prospective pharmacosurveillance initiatives like ADR reporting or patient-reported health outcomes to drug therapy.

Limitations

- Not all eligible patients agree to participate or to be interviewed.
- There is a low recruitment rate for patients not picking up their own prescriptions.
- Pharmacy workload is increased.

4. Conclusions

There is no clear consensus on the 'best' way to carry out pharmacosurveillance in Canada at present. Each of the examples above has unique strengths and limitations. In general, it appears that where population-level data and relatively open access for others to validate research conclusions are readily available (e.g., CADRMP and the provincial drug plans), resources for assessment are more limited. Where more focused resources are available (e.g.,

[26] The pilot experience was published in 1995: Willison DJ, Gaebel KA, Borden EK, et al. Experience in the development of a postmarketing surveillance network: the pharmacy medication monitoring program. Ann Pharmacother. 1995;29(12):1208-13.

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manufacturer registries and single-disease centres), data are more limited and opportunities for replication by others more restricted. Neither of these situations is ideal.

In general, it is critical that any pharmacosurveillance framework support:

- scientific rigour in evaluation of clinically-meaningful and policy-relevant outcomes;
- collection of relevant population-level data, including endpoints;
- timely, inexpensive (or free) access to data that allows for independent assessment;
- sustainable research groups with relevant expertise;
- relevant, timely policy decisions;
- affordability; and
- transparency (of criteria and processes, and by study replicability).

Choosing the appropriate pharmacosurveillance strategy for a specific problem or jurisdiction, however, is dependent on:

- the nature of the research questions and the context of the health care system in which findings will be applied;
- the availability of data sources;
- the required time line for results; and
- the availability of expertise to carry out the research.

The drug regulatory authority framework, CADRMP, provides a well-known and established framework for submitting reports of adverse drug reactions, but is restricted by the voluntary nature of reporting, the incomplete information often contained in reports, and severe underreporting. It is estimated that only 10% of all ADR are reported; the framework cannot be used to calculate incidence rates of ADRs. NOC/c provides a policy framework to collect additional pharmacosurveillance data from manufacturers; however, it is uncertain whether NOC/c can provide sufficient patient outcome information in a timely fashion to be relevant to clinicians and health care decision makers.

Health Plan and Drug Plan Frameworks cover a wide range of pharmacosurveillance activities. Administrative database studies, supported by the drug plans in collaboration with outside researchers, can provide the advantages of more rapid access to data, increased policy relevance of research questions and access to a wide range of expertise available in the academic community. These studies may be limited by drug plan time and expertise restrictions and suffer from the drawbacks of many studies that rely on administrative databases, such as limited clinical information, limited ability to randomize or to carry out prospective studies. Grant-funded research, on the other hand, may be less tied to political priorities, but can have more restricted access to data and be constrained by the funding term and priorities of the granting agencies. Administrative database studies can be enhanced by additional information derived from, for example, surveys of clinicians and patients, or collection of supplementary data.

Registries, such as the Alberta Biologic Registry, provide additional information about patients who receive specific drugs but suffer from the problems of all observational trials; there is no randomized control group to provide comparison for drug effectiveness determination. Drug Manufacturer Frameworks, such as the clozapine registry, mandate reporting of very specific outcomes for all patients on the drug. They are not, however, often sufficient to determine drug effectiveness or safety from a population perspective. Clinician/clinical group/disease collaborative frameworks vary widely in their mandates, funding and research agendas. Chronic disease management projects focus on patients with a common disease and are

usually focused on clinical issues, such as continuity of care, rather than outcomes evaluation. Research-oriented groups, such as the COG, are able to organize and support many RCTs, which are published in respected peer-reviewed journals, while centres such as the BC Centre for Excellence for HIV/AIDs carry out observational trials on a well-studied cohort of patients.

Unfortunately, there is no clear consensus on 'what works' in pharmacosurveillance because there are no international best practices yet defined for the determination of drug effectiveness and safety in the real world. Each framework described in this paper offers some elements that are useful for either patient safety evaluations or population-level studies, but each has serious limitations; no one framework presently used in Canada appears to support all needs. It is unlikely that any one model will suffice in the long term, no matter how it is elaborated. Integrated, informed, and judicious use of whatever mix of models best addresses specific issues is likely to provide the best information on drug safety, effectiveness, and cost-effectiveness. More clarity is required on the ultimate goals that pharmacosurveillance studies should serve in an integrated pharmaceutical strategy before the most useful frameworks to support them will be clear.

Appendix I

EXCERPT FROM:

Issue Analysis Summary
Health Product and Food Branch, Marketed Health Products Directorate
Therapeutic Effectiveness Surveillance and Evaluation Division

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Dr. Jun Zhang **January 2004**

A. Canadian Outcome Databases

A1. Management of databases

Statistics Canada and the Canadian Institute for Health Information (CIHI) manage several national vital statistics and disease databases. These include:

- Canadian Mortality Database (CMD)
- Canadian Births and Stillbirths Database, and Cancer Incidence Reporting System.
- Discharge Abstract Database (DAD)
- Hospital Morbidity Database (HMDB)
- Hospital Mental Health Database (HMHDB)
- National Ambulatory Care Reporting System (NACRA)
- Continuing Care Reporting System (CCRS)
- Person Oriented Inventory of hospitalizations (POI)

A2. Core data elements

Information captured in disease/outcome databases can be summarized as:

- Personal identification
- Demographic information such as age, gender, and place of residence
- Administrative information such as date of cancer diagnosis, date of hospital admission
- Clinical diagnosis and outcome information often via the International Classification of Diseases (ICD)
- Clinical procedures captured in a standardized coding system.

Unfortunately, information about medication use is usually not captured in disease/outcome databases with the exception of the Continuing Care Reporting System.

A3. Strengths and limitations

Outcome databases provide standardized national data on cancer incidence, mortality, and hospitalization rates for major diseases in Canada. However, there are limitations:

- The ICD diagnostic coding system has recently changed from version 9 to version 10.
- Hospital procedure codes have also changed, from the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) to the Canadian Classification of Health Interventions (CCI).
- The underlying cause of death in mortality data may be poorly reported.

A4. Access to outcome databases

MHPD has established access to some of the above mentioned outcome databases through two approaches:

- DEXA query software, managed by the Data Development and Exchange Program at the Centre for Surveillance and Coordination, Public Health Agency of Canada (PHAC).
- Orius query software, managed by the Surveillance and Risk Assessment Division at the Centre for Chronic Diseases Prevention and Control, PHAC.

A5. Application of outcome databases in post-market surveillance

Cancer registry data provide baseline information about cancer incidence and survival. Mortality, general hospital, and mental health hospital files are used to generate national mortality rates and hospitalization rates and provide useful baseline information about diseases and conditions that often result in death or hospitalization, such as stroke. The national ambulatory database provides baseline information about diseases and conditions that usually result in emergency room visits and/or outpatient clinic visits.

Although outcome databases do not contain drug information, they can potentially be linked to other databases that do contain drug use information through certain identifiers, particularly at the provincial level. The data linkage between drug exposure databases and disease outcome databases has provided a great opportunity to carry out post-market surveillance activities to examine drug safety and therapeutic effectiveness.

Hospitalization files contain medical procedure codes which often include information regarding the use of medical devices, e.g., stents or artificial knees and hips. Longitudinal files like the Person Oriented Inventory can track re-admission and outcomes from surgeries.

B. Canadian Product Utilization Databases

B1. Management of databases

IMS Health Canada (IMS), provides drug utilization data for different stakeholders, including regulatory agencies. Three main core databases are provided by IMS:

- Canadian Disease and Therapeutic Index (CDTI)
- National and Regional CompuScript (CS)
- Canadian Drug Store and Hospital Purchases Audit (CDH).

Brogan Incorporated collects data from two types of sources:

- Provincial drug programs
- Private drug payment programs

(Provincial drug programs account for almost 100% of all public claims in most provinces and for nearly 50% of prescription drug purchases in Canada).

CIHI, along with the Patent Medicine Prices Review Board (PMPRB) is developing a National Prescription Drug Utilization Information System (NPDUIS) that will use federal/provincial/territorial (F/P/T) claims data to provide “national” prescription drug utilization information.

B2. Core data elements

The IMS CDTI is an ongoing survey designed to provide information about disease and treatment patterns of office-based physicians in Canada. A sample of 652 physicians is selected from 45,800 office-based physicians in Canada, stratified by region and speciality. Patient demographics (e.g., age and gender), and information about patient diagnosis and concomitant diagnosis and drug therapy (e.g. product name, strength, and form) are captured in CDTI.

Another IMS product, National and Regional CompuScript, measures the prescriptions dispensed by Canadian pharmacies. As of March 2003, IMS Health collects pharmacy dispensing data from a sample of 2,770 pharmacies (38%) stratified by province, type, and size, from about 7,200 pharmacies in Canada. Essential data items captured in CompuScript include product name, strength, ,form, prescription type (new, refill, and total) and size, physician specialty, and geographic region of patients.

CDH from IMS collects data on dollar value and unit volume of pharmaceutical products purchased by retail pharmacies and hospitals, from a representative sample of over 2,000 drugstores and 563 hospitals. Drug purchase data are collected electronically and include the following data items: corporation/manufacturer, molecule/chemical, product name, age, strength, package size, dollar sales, units, and prices.

Provincial data from Brogan Inc. covers British Columbia, Alberta, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, and Newfoundland, collectively including over 200 million prescriptions per year [217 million in 2001]. Brogan provincial data provide information on market share and average cost per claim, which has proven useful to manufacturers when making formulary submissions to the provinces. Access to these summary level data is available electronically through a product called "PharmaStat". Analysis using detailed data from Ontario Drug Benefits (ODB) is available through Brogan products and services.

B3. Strengths and limitations

As a physician-based data file, CDTI provides information about prescriptions, indications, and patient age and gender. However, several limitations have been identified, including small sample size (only 14 physician specialty groups are included in the database), lack of information on patient compliance, quarterly data (monthly data is not available), poor information about over-the-counter (OTC) products, and possible participant and selection bias.

Data collected in CompuScript are relatively accurate and reliable due to the large sample size. The physician specialty information collected in this database is also reliable. However, the sampling methodology has changed over time and it may affect the reliability of long-term trend analysis. CompuScript does not capture information about patient compliance and patient age and gender. In addition, the quality of information regarding OTC products is considered to be poor.

Data derived from CDH are relatively reliable because of the large sample size. CDH captures purchase data about OTC drugs that are often sold in pharmacies. However, drugs purchased in grocery stores and specialty health clinics (family planning centres, AIDS clinics, and cancer clinics) or through military accounts are not included in this audit. Information regarding physician specialty and patient age and gender is not captured.

B4. Application of IMS Health databases in post-market surveillance

IMS Health data play an important role in post-market utilization surveillance to examine product utilization patterns and volumes.

- CDTI data have been used to examine prescription patterns by patient demographics and physician specialty and to evaluate use of a specific medication in patients with a specific diagnosis.
- CompuScript data have been used to provide denominator data to calculate ADR reporting rates and to evaluate, as a surrogate marker, the effectiveness of risk communication strategies.
- The Canadian Drug Store and Hospital Audit can be used to monitor market trends regarding hospital and drugstore purchases by therapeutic class and geographic region and to obtain data about OTC drugs sold at pharmacies.

C. Canadian Provincial Linked Databases

C1. Management of databases

Population-based data files that link drug utilization information to physician services and hospitalization services have been reorganized as an important data source to support post-market surveillance and pharmacoepidemiology studies. In Canada, a number of provinces have established such linked databases. For example, Saskatchewan Health maintains several linkable databases; the Centre for Health Services and Policy Research in British Columbia (BC) manages the BC Linked Health Database; and the Manitoba Centre for Health Policy is in charge of the Population Health Research Data Repository.

In addition, Alberta, Ontario, and Quebec also have provincial health databases that contain health records about physician and/or emergency visits, hospitalization stays, and drug utilization, which can be linked through a common personal identification number. A relatively new federal/provincial initiative is the National Diabetes Surveillance System (NDSS) which gathers raw data at the provincial level and filters it through to the PHAC at an aggregated level.

C2. Core data elements

- Usually, a unique Health Services Number is assigned to residents as a lifetime identifier for access to health services in their province. This identification number is captured in all administrative records of health care services and enables data linkage among different health databases.
- Patient demographic information such as name, date of birth, sex, and place of residence is also captured.
- A prescription drug plan database usually captures the following information:
  - Patient identification and demographic information
  - Drug's pharmacologic therapeutic classification
  - Drug identification number (DIN)
  - Generic and brand names
  - Strength and dosage form
  - Manufacturer of the drug
  - Date dispensed
  - Quantity dispensed

- A hospital services database captures patient identification and demographic information and clinical outcome information such as diagnoses and procedures, status, and administrative information such as dates of admission and discharge, and length of stay.
- Physician services databases in each province also capture important information about patient visits. These include patient identification number, age and gender, place of residence, diagnoses and services provided.
- The computerized cancer registry database captures information about cancer diagnosis, grade and stage of neoplasm, summary of treatment status, and primary and secondary causes of death.
- Data files regarding vital statistics such as live births, stillbirths, and deaths are maintained at the provincial health departments and they can be linked with other health files.

C3. Strengths and limitations of provincial health databases

The Health Services Number is a unique identifier assigned to each individual that can be used to link data among different computerized databases. Canadian provincial electronically linkable and population-based databases (e.g., in Saskatchewan) have been used in post-market surveillance. The prescription drug plan database provides complete information regarding outpatient prescription drugs. The ICD coding system is used to record diagnosis information in all hospital and physician services. In addition, hospital charts and physician visit records are accessible for special studies. Some provincial databases (e.g., Saskatchewan health databases) have been evaluated and confirmed to be of high quality for product utilization studies and pharmacoepidemiologic studies.

However, provincial health databases have been constructed primarily for administrative purposes. Post-market surveillance is a secondary use and therefore the data may not be best suited to some specific types of studies. The population size in each province may not be large enough to evaluate rare ADRs and some provinces do not provide drug benefits for all residents. In addition, drugs must be listed in the formulary or covered under special authorization to be included in the database; therefore, some newly marketed products may not be evaluated within 12 months of market. Information on OTC drugs and drugs normally used in hospitals is not captured electronically in provincial drug plan databases.

C4. Access to provincial health databases

In order to access the data in provincial health databases, a study proposal must be prepared, submitted, reviewed, and approved by a Research Unit at a provincial health department. In addition, any data linkage must be done at the provincial health department and a formal contract must be signed to follow procedures and security measures to maintain the confidentiality of the data.

C5. Application of provincial health databases in post-market surveillance

Saskatchewan's health databases have been recognized as being among the best computerized provincial health databases in the world to be used for evaluation of safety and effectiveness of therapeutic products. The US Food and Drug Administration (FDA) has used Saskatchewan health databases to conduct a number of post-market safety evaluation studies. The quality of the health databases in other provinces requires

validation before their utilization in surveillance and evaluation of safety and effectiveness of marketed health products.