Gaps in the evaluation and monitoring of new pharmaceuticals: proposal for a different approach

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The marked increase in spending on drugs[1] has led payers such as provincial governments to restrict funding for many drugs to specific clinical indications that are thought to be cost-effective.[2,3] Some have argued that this unreasonably deprives patients of access to beneficial drugs.[4] In this article we argue for a new approach to drug evaluation in Canada that combines the strengths of randomized trials and observational studies, and places more emphasis on the use of drug evaluation after marketing for decision-making.

At least 4 different types of clinical studies are required to inform rational drug policy: (1) randomized trials to determine efficacy and safety (which are required for licensing), (2) real-world randomized trials to determine effectiveness and safety in regular practice, (3) observational studies that use administrative databases and (4) targeted primary data collection (Table 1). Currently, most randomized trials are done to determine efficacy and safety under ideal conditions, whereas the other designs, which are less frequently used, attempt to determine a drug's pattern of use and effectiveness under real-world conditions. For some drugs, the results of randomized trials of efficacy will be so straightforward and the possibility of real-world use outside the conditions of the trial so small that no other study designs will be required. However, for other drugs there may be concern about the impact of the drug upon clinically important outcomes (e.g., if surrogate outcomes were used in the efficacy trials) or concern that the drug

Table 1: Characteristics of clinical studies used to inform drug policy

Type of study	Purpose	Timing	Usual sponsor(s)	Strengths	Weaknesses
Randomized trial	Determines drug efficacy and safety, usually compared with placebo	Before licensing	Industry	Provides unbiased evidence about efficacy Detects major side effects	Real-world effectiveness may not be reflected Important but rare side effects may not be detected New drug is often not compared with commonly used alternatives
Real-world randomized trial	Determines drug effectiveness and side effects in the real world	Before and after licensing	Industry Granting agencies	Provides evidence about real-world effectiveness and side effects of the drug, compared to usual practice	Large sample sizes are often required Comparator treatments are often not standardized
Observational study with administrative databases	Evaluates drug use, compliance, use of concomitant drugs, and the association between drug use and outcomes in the real world	After licensing	Drug plans Granting agencies Industry	Is relatively inexpensive and fast Can be population-based Can detect rare side effects	Databases often lack detailed information needed to characterize patients or determine outcome Determination of causation is difficult because of biases resulting from lack of randomization
Primary data collection	Provides detailed information about patient characteristics and outcomes	After licensing	Granting agencies Industry Drug plans	Provides detailed information about clinical relevance Can combine information with administrative data	Data collection can be time-consuming, especially if large sample size needed If not randomized, biases can make determination of causation difficult

will be used for patients on whom it has not been studied or for whom it is cost-ineffective. In these circumstances, 2 or more of the study designs would be required to adequately assess the impact of the drug in the real world and to guide clinical and policy decisions.

A proposed model for optimal drug evaluation in Canada is shown in Fig. 1. We would suggest more large, head-to-head randomized trials to convincingly determine the relative benefits and risks of competing medications in regular practice. The greater use of observational studies and chart reviews after licensure would increase the use of real-world evidence to monitor the use of drugs. Payers might become more liberal in their initial decisions about paying for drugs if they knew that their decisions would be re-evaluated over time and that they could change their decision if the use of a drug seemed to be beyond that which the evidence would support.

Observational studies that use administrative data to link drug claims to physician and hospital use can play a key role in drug evaluation after marketing. Although work is underway to create a national drug-claims database[5] this database will not link drug claims to other administrative data and will therefore be of limited use. Linked databases do exist in many provinces. Several research groups have

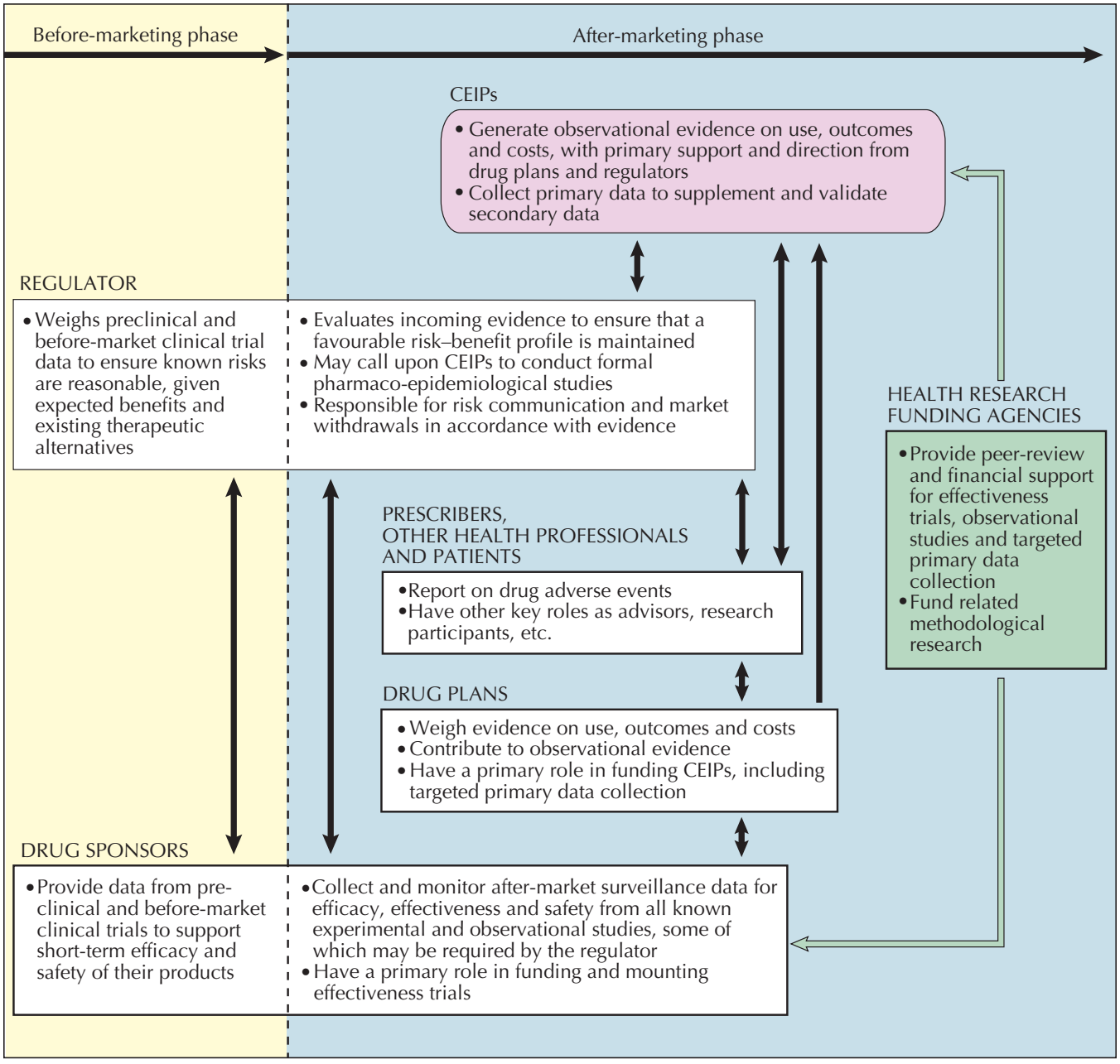

Fig.1: A proposed model for drug evaluation in Canada. CEIPs = Centres of Excellence in Pharmacosurveillance.

the expertise and experience to use these databases for evaluation after marketing[6–13] (for a list of these groups and Web sites, see the online appendix at www.cmaj.ca).

We refer to each of these groups as a Centre of Excellence in Pharmacosurveillance (CEIP). Ideally each CEIP should be affiliated with an academic institution or institutions to ensure independence and methodological rigour, and should work closely with provincial drug plan decision-makers and others to help identify priorities for research.

A national research infrastructure should be developed to allow researchers from a CEIP to access data from other provinces under appropriate conditions of security and confidentiality. If transfer of data between provinces is not possible analytical methods developed in one province could be used in other provinces (unpublished data). Collaboration among CEIPs would not only promote collegiality and shared methods, but also make it possible to increase sample size and detect rare outcomes. As well, analysis of natural experiments that occur when provinces make different formulary decisions (e.g., coverage for rofecoxib and celecoxib is restricted in British Columbia and Ontario, but unrestricted in Alberta and Quebec) could play an important role in informing drug policy.

The recent establishment of Health Canada's Marketed Health Products Directorate[14] and the emergence of a national drug review process[15] could provide a fresh emphasis on coordinated drug evaluations after marketing. In the United States, the Food and Drug Administration (FDA) uses signals from its adverse-event reporting system (AERS) as a trigger for targeted pharmacoepidemiological research conducted in academic centres with access to linked administrative databases.[16,17] These studies, funded by the FDA, include support for focused efforts to collect primary data to supplement and validate the administrative data. Given efforts to establish a joint US–Canada AERS,[18] we wonder why a similar network of CEIPs could not operate in Canada, perhaps in collaboration with the FDA. As well a forum and sufficient funding should be provided to permit all those involved in drug policy to meet formally to ensure that the most important questions are being examined, and that all available and appropriate methods and data sources (including clinical registries and electronic medical record databases) are being used to examine them. This new strategy will require more investment in research and outcomes assessment, and there will be considerable discussion about who should pay for what. However in the end the benefits generated by the more appropriate use of medications will be considerable.

Because of the societal importance of pharmaceuticals the act of writing a prescription, which used to be a private interaction between a physician and a patient, is now being scrutinized and manipulated by those who pay for drugs (to try to decrease the amount paid), by those who make drugs (to try to increase the amount paid) and by those who are interested in quality of care (to try to ensure that the right patients get the right drugs). Many of us wear more than one hat. The challenge for all of us is to ensure that drugs are used in the most appropriate, cost-effective manner possible. The large number of stakeholders involved and their conflicting self-interests make the development of effective drug policy difficult. The changes that must be made to the current system will require considerable courage and commitment on the part of all groups involved. Time will tell whether societal good will win over self-interest.

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Why don't we initiate more large simple randomized controlled trials?

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When new drugs come to market and are prescribed by physicians to real-world patients, their costs and effectiveness may vary considerably from those measured in carefully controlled randomized controlled trials (RTCs). Physicians, patients and provincial governments that fund pharmacare programs must base their prescribing and funding (coverage) decisions on the very limited information available from RCTs. In the real world, such drugs are prescribed not only for the relatively healthy and usually younger patients who enter RCTs, but also for patients with comorbidities and for older patients. As well, serious but less common side effects might not be detected in clinical trials; if any are detected, their frequency may not be precisely determined. Thus the real-world cost-effectiveness may not mirror that shown in RCTS.

In this issue, Laupacis and colleagues (see page 1167),[1] build on previous work[2] in proposing a model for drug evaluation in Canada that might reduce the uncertainty. A good example of this type of problem is the recent introduction of a new class of drugs for the treatment of arthritis, the COX-2 selective nonsteroidal anti-inflammatory drugs (NSAIDs). Laupacis and colleagues[2] have previously documented the rapid uptake of COX-2 selective NSAIDs in Ontario and the cost of this to the Ontario Drug Benefit Program. One of the surprising findings is that, despite approval for payment for these NSAIDs as limited-use products, the availability of the COX-2 selective NSAIDs not only led to a shift away from nonselective NSAIDs, but also created a large new cohort of anti-inflammatory drug users.

The widespread use of COX-2 selective NSAIDs has created a familiar dilemma. What do we do when the evidence for a widely prescribed class of drugs is insufficient to know whether the benefits outweigh the harms as compared to those of the standard therapy? The concern about harm in this example comes from the results of 2 large RCTs[3,4] designed to look at the incidence of complicated peptic ulcers in patients with arthritis, treated either with COX-2 selective NSAIDs or with nonselective NSAIDs. For this serious adverse-event outcome, rofecoxib showed a significant benefit[3] and celecoxib showed a trend toward a benefit.[4,5] However, a more comprehensive analysis of these trials suggests that, rather than being safer than nonselective NSAIDS, rofecoxib and celecoxib are more harmful; the number of patients with at least one serious adverse event of any kind was higher with the COX-2 selective NSAIDs than with the nonselective NSAIDs.[6,7]

The authors[8] acknowledge that the controversy is unresolved and propose a model for drug evaluation in Canada that might prevent such dilemmas. The component of their model that I believe has the most chance of providing a solution is the mandated conduct of a large simple RCT after marketing.[1,9]

In this particular example the optimal opportunity for initiating the RCT would have been immediately after the COX-2 selective drugs were first marketed in Canada. At