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Evaluating the Cost-effectiveness of Pharmaceuticals in Canada

Katherine Boothe, *McMaster University, Hamilton, Ontario, Canada*

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A Comparative Health Reform Analysis

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Abstract

Canada adopted guidelines for the economic evaluation of pharmaceuticals in 1994, and a central process for drug assessment in 2003. The context and the way the issue reached the agenda in the two time periods differed. The guidelines were adopted amidst growing academic interest in methods for economic evaluation of pharmaceuticals in Canada and internationally, and were first promoted by an entrepreneur from the pharmaceutical industry. The Common Drug Review (CDR) was adopted in a context of broader intergovernmental negotiations over health reforms, and came onto the agenda as a policy option that addressed pharmaceuticals but avoided the fraught question of public insurance. Both processes aim to harmonize drug assessment in Canada and ensure that publicly reimbursed drugs are cost-effective. Neither is the subject of legislation or regulation, but the CDR enjoys greater uptake as a result of an intergovernmental agreement that all new drugs will be subject to its review. Evaluation of the CDR has been more robust, and finds a split in opinion among stakeholders concerning the CDR's benefits. This article describes the reforms using information drawn from government and CCOHTA/CADTH documents, published reflections of participants and secondary literature, and nine expert interviews. It finds that although the CDR's design and implementation respond to some of the shortcomings of the Canadian guidelines, there are still important unresolved tensions between harmonization and transparency in drug assessment, and new challenges regarding pharmaceutical pricing and use of evidence. The way these tensions are resolved has important implications for broader attempts to reform public drug coverage in Canada.

Le Canada a adopté en 1994 des recommandations pour l'évaluation des médicaments et, en 2003, un processus centralisé d'évaluation des médicaments. Le contexte et la façon dont le problème a émergé sur l'agenda différaient d'une période à l'autre. Les recommandations ont été adoptées dans un contexte d'intérêt croissant des universitaires pour les méthodes de l'évaluation pharmaco-économique, au Canada comme à l'étranger, et ont été d'abord portées par un entrepreneur politique issu de l'industrie pharmaceutique. Le Programme Commun d'Évaluation des Médicaments (PCEM) a été adopté dans un contexte plus vaste de négociations inter-gouvernementales à propos des réformes de santé, et a émergé sur l'agenda politique comme une solution au problème posé par les médicaments qui évitait de poser la question complexe de leur prise en charge publique. Les deux processus partageaient un objectif d'harmonisation de l'évaluation pharmaceutique au Canada, et de garantie de coût-efficacité des médicaments couverts par l'assurance publique. Aucun n'a fait l'objet d'une loi ou de régulation, mais les décisions du PCEM sont plus suivies en raison de l'accord inter-gouvernemental stipulant que tout nouveau médicament doit être soumis à son approbation. Le PCEM a été plus sérieusement évalué, ce qui a dévoilé une opinion divisée sur son bilan au sein des parties prenantes. Cet article décrit les réformes, en utilisant

l'information recueillie dans les documents gouvernementaux et du OCCETS/ACMTS, des réflexions publiées par les participants et les données secondaires, ainsi que neuf entretiens avec des experts. Il montre que, bien que, dans sa conception et sa mise en place, le PCEM ait tenté de répondre à certaines lacunes des recommandations de 1994, il reste des conflits non résolus entre harmonisation et transparence dans le processus d'évaluation, ainsi que des défis nouveaux sur la détermination des prix et l'utilisation de l'évidence. La façon de résoudre ces conflits aura des conséquences importantes sur les tentatives plus générales de réformer la couverture publique des médicaments au Canada.

Key Messages

- Canada was an early adopter of cost-effectiveness analysis of pharmaceuticals as part of public drug plans' decisions regarding which drugs to reimburse.
- The introduction of the Canadian Guidelines for Economic Evaluation of Pharmaceuticals (in 1994) and the creation of the Common Drug Review (in 2003) made progress towards a harmonized nation-wide process of drug assessment in Canada, but barriers to harmonization remain.
- Compared to the earliest use of the guidelines, the Common Drug Review has developed significant new mechanisms for transparent decision-making, which is a major concern for stakeholders but may be in tension with new approaches to harmonization in drug listing decisions.

Messages-clés

- *Le Canada a été parmi les premiers pays à intégrer l'analyse coût-efficacité des médicaments dans la prise de décision de remboursement public.*
- *L'introduction des Recommandations Canadienne pour l'Évaluation Économique des Médicaments (en 1994) et la création du Programme Commun pour l'Évaluation des Médicaments (en 2003) ont permis de progresser en direction d'un processus harmonisé sur le territoire national pour l'évaluation des médicaments au Canada, mais il reste des obstacles à l'harmonisation.*
- *Comparé à l'utilisation initiale des recommandations, le Programme Commun d'Évaluation des Médicaments a permis de développer des mécanismes transparents de prise de décision, ce qui représente un souci capital pour les parties prenantes mais peut aussi être en conflit avec les tentatives récentes en vue d'une harmonisation des décisions de mise sur le marché.*

1 INTRODUCTION

In 2015, a group of Canadian academics and experts issued a report entitled *Pharmacare2020* calling for universal public drug coverage in Canada. It noted that:

> Equitable access to medically necessary prescription drugs does not require that every drug be covered for every use. It requires that all patients have access, without barriers, to medicines *selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness* (Morgan et al. 2015, 8, emphasis added).

The report acknowledges the crucial task of assessing which drugs to fund, for which patients, something that Canada's existing limited public drug plans have struggled with for decades. This article describes and compares the adoption and implementation of two drug assessment processes in Canada: the Canadian Guidelines for Economic Evaluation of Pharmaceuticals in 1994, and the Common Drug Review (CDR) in 2003. Both processes aim to harmonize drug assessment in Canada and ensure that publicly reimbursed drugs are cost-effective. This article describes the reforms using information drawn from government and CCOHTA/CADTH documents, published reflections of participants and secondary literature, and nine expert interviews (see Appendix A for interview details). It finds that although the CDR's design and implementation respond to some of the shortcomings of the Canadian guidelines, there are still important unresolved tensions between harmonization and transparency in drug assessment, and new challenges regarding pharmaceutical pricing and use of evidence. It argues that understanding the goals of existing processes of drug assessment in Canada, as well as the barriers to realizing these goals, is an essential component of broader attempts to reform public pharmaceutical coverage in this country.

2 OVERVIEW OF REFORMS

In June 1993, a diverse group of pharmaceutical policy stakeholders and experts met in Sainte-Adèle, Québec, to discuss methods for evaluating the cost-effectiveness of pharmaceuticals. The Canadian Collaborative Workshop on Pharmacoeconomics included representatives from Health Canada, provincial and territorial ministries of health, the pharmaceutical industry, professional organizations for physicians and pharmacists and Canadian and international academics. Together they produced the first draft of the Canadian Guidelines for Economic Evaluation of Pharmaceuticals. These guidelines were endorsed by the Canadian Coordinating Office of Health Technology Assessment (CCOHTA, now CADTH)[1] in 1994, and subsequently by federal, provincial and territorial deputy ministers of health

[1] CCOHTA is funded by federal, provincial and territorial governments, and is independent from them. In 2006, its name was changed to the Canadian Agency for Drugs and Technologies in Health (CADTH). This article will refer to the agency by the name in use at the time of mention.

(Torrance *et al.* 1996). They were some of the earliest formal methods for economic evaluation of drugs being considered for public reimbursement, preceded only by Australia's draft guidelines in 1990 and Ontario's provincial guidelines in 1991. The Canadian guidelines were updated in 1997 and were entirely voluntary. A CCOHTA study in 1998 found that eight of ten provincial drug plans required pharmacoeconomic analysis to be submitted by manufacturers seeking public reimbursement for new drugs, and four of those required use the Canadian guidelines (Otten 1998).

In 2003, federal, provincial, and territorial health ministers created a central drug assessment process known as the Common Drug Review (CDR), which significantly expanded the use of the revised Canadian guidelines. The CDR is housed within CADTH and provides advice to participating provincial and territorial drug plans (all expect Québec) as well as the plans managed by the federal government for Aboriginal peoples, the military, and federal inmates. Its mandate is to review all new, patented drugs except oncology drugs, which since 2010 have been assessed by the pan-Canadian Oncology Drug Review (pCODR). It also reviews old drugs or conducts class reviews as requested by drug plans or Formulary Working Groups (Canadian Agency for Drugs and Technologies in Health 2013). The CDR has no connection to reimbursement or pricing: participating drug plans are not bound by the CDR's recommendations, but have agreed that new drugs must go through the CDR before they are considered by the provincial or territorial agencies (McMahon, Morgan, Mitton 2006).

3 HISTORY AND CONTEXT

Research on economic evaluation of health interventions goes back to the 1970s, but in the early 1990s academics and experts were becoming increasingly interested in the economic evaluation of health technologies in general and pharmaceuticals in particular (Torrance, Thomas, Sackett 1972; Cochrane 1972; Drummond, Stoddart, Torrance 1987; Drummond 1991). The journal *Pharmacoeconomics* published its first issue in 1992 (Milne 1992), and pioneering researcher Dr. George Torrance mentions the sense of excitement and innovation regarding this research at McMaster University in Ontario at this time, with "a sense of doing things differently."[2] The work of Dr. Torrance and others at McMaster influenced the creation of guidelines for the economic evaluation of drugs in Ontario, authored by Dr. Alan Detsky, then a member of the provincial drug plan's expert advisory committee (Detsky 1993).[3] As discussed below, guideline development in Ontario and Australia helped push national guidelines onto the policy agenda in Canada.

Although the CDR uses a revised version of the Canadian guidelines, there was not a continuous process of development from the voluntary guidelines to the required (but non-binding) recommendations of the CDR. Rather, the CDR was created in a context

[2]George W. Torrance, interview via Skype, 11 June 2014.
[3]Torrance, interview.

of ongoing negotiations among federal, provincial and territorial governments on broader health reforms. A central drug review body for Canada was mentioned in the September 2000 First Ministers' Meeting communiqué on health, which called for "strategies for assessing the cost-effectiveness of prescription drugs," potentially to include "a common intergovernmental advisory process to assess drugs" (Canada 2000). The intention to establish "a single, common review process for coverage of new drugs in Canada" was announced at the September 2001 meeting of federal, provincial and territorial ministers of health (Canada 2001), and reinforced by the 2002 Romanow Report on health reform in Canada, which called for "a comprehensive, streamlined, and effective process...[for] ensuring the safety, quality and cost-effectiveness of all new drugs" (Commission on the Future of Health Care in Canada 2002). The September 2002 federal, provincial and territorial health ministers' meeting announced the final agreement to create the CDR, noting that the review process would be housed in CCHOTA and would "streamline the drug assessment and drug plan listing processes" (Canada 2002).

4 GOALS OF THE REFORM

The explicit goals of the Canadian guidelines and the CDR are quite similar. Both aim to improve the use of evidence in making drug listing decisions (Torrance et al. 1996; Canadian Agency for Drugs and Technologies in Health 2013). Both aim to reduce balkanization in drug assessment and streamline the process across the country (Menon, Schubert, Torrance 1996; Canada 2002).[4] Two interviewees mention an implicit goal that the CDR's streamlined process would eventually lead to greater harmonization between public plan formularies, or lists of reimbursed drugs, although one of these interviewees calls this hope "fairly naïve."[5]

The Canadian guidelines and the CDR aim to ensure that listed drugs are cost-*effective*, a goal that is distinct from (and may at times be in conflict with) a goal of cost-containment. In keeping with this, there is limited explicit mention of cost containment with regard to either process (Menon, Schubert, Torrance 1996 is the exception regarding the Canadian guidelines). However, there is evidence that drug plan officials had implicit goals related to controlling drug costs and gaining political cover for difficult decisions during the development of the Canadian guidelines and the CDR.

One interviewee who was closely involved in the guidelines' development cites goals related to value for money, saying the guidelines were meant to determine "how to allocate a limited budget for the maximum good in patients' lives." However, he also notes the possibility that provinces thought economic analysis would help them justify decisions not

[4]Devidas Menon, interview, Edmonton, 7 August 2014; and Francois Schubert, interview via phone, 25 August 2014.

[5]Interviews with a former expert committee member, Toronto, 13 June 2014; and an Associate Deputy Minister of Health, Ottawa, 16 October 2008.

to list very expensive drugs, a view that is echoed by another participant in the guidelines' development.[6]

An associate deputy minister in Health Canada said since the CDR was a relatively low cost option to implement, it was popular with federal and provincial health ministers. Ministers also appreciated the ability to attribute difficult reimbursement decisions to a third party.[7] However, the CDR has faced more criticism than the Canadian guidelines related to the perception that it is motivated by cost-containment. Interviewees note that patients tend to see the CDR as punitive and mainly motivated by cost-cutting goals.[8] A CADTH official who was involved in setting up the CDR notes that at the time there were concerns with specific new drugs for multiple sclerosis and Alzheimer's disease, which were very expensive and where expert advice varied.[9] In a "myths versus facts" memo (Canadian Agency for Drugs and Technologies in Health 2011), CADTH responds by arguing there is little difference in cost between drugs that are recommended for listing compared to those that are not recommended; this has been supported by independent research (Rocchi et al. 2012).

The preceding discussion focuses on the goals of officials and experts, but the pharmaceutical industry was instrumental in putting guideline development on the policy agenda in the early 1990s, and it had sometimes conflicting goals regarding their creation. An industry representative involved in creating the guidelines says pharmaceutical manufacturers hoped that economic evaluation would help justify price premiums for truly innovative drugs, and that a central process with scientific expertise would be an advantage at a time when requests for economic analysis were seen by industry as inevitable. However, manufacturers also saw risks in adding "a fourth hurdle" to the process of getting a drug approved for reimbursement, and raised concerns that a binding centralized review process ran the risk of making reimbursement a "100% win or lose" situation, whereas previously rejection by one Canadian province did not necessarily mean that others would make the same decision.[10]

Although industry was consulted on the design of the CDR, there is less information about their goals at that time. A CCOHTA-commissioned study after the CDR's first year in operation found that industry respondents were dissatisfied with what they perceived as the lack of transparency and timeliness of the process (Ekos Research Associates Inc. 2005).

[6] Torrance; Menon interviews.

[7] Interview with an Associate Deputy Minister of Health.

[8] Interviews with a former expert committee member; and an expert committee member, Hamilton, 21 August 2014; and a former public member of CEDAC, via phone, 19 August 2014.

[9] Interview with a CADTH official, Ottawa, 14 October 2008.

[10] Schubert, interview.

5 HOW THE ISSUE CAME ONTO THE AGENDA

The Canadian guidelines and the CDR can be understood as responses to an ongoing set of problems in Canadian pharmaceutical policy. However, the way these problems reached the public agenda in the two time periods differs. In the early 1990s, the main pressure to act came from an interest group, the pharmaceutical industry, and was spearheaded by external policy entrepreneurs from industry and academia. In the early 2000s, the pressure appears to have been mainly internal, in the form of federally-commissioned expert reports and discussion between federal, provincial and territorial officials and ministers.

The 1993 workshop that produced the first draft of the Canadian guidelines included a full range of stakeholders, but the impetus came from the pharmaceutical industry. Specifically, it came from Francois Schubert, who was a member of a new pharmacoeconomics working group within the Pharmaceutical Manufacturers Association of Canada (PMAC, now Innovative Medicines Canada), the umbrella group for research-based pharmaceutical companies. Schubert organized a steering committee consisting of academics and representatives from Health Canada and provincial ministries of health, and this committee identified additional stakeholders and held the Canadian Collaborative Workshop on Pharmacoeconomics in June 1993 (Menon, Schubert, Torrance 1996), chaired by Dr. George Torrance, a leading academic expert on the economic evaluation of health interventions.[11]

Interviews with three key participants in the workshop (Torrance, Schubert, and Dr. Devidas Menon, then chair of CCOHTA), indicate that industry wanted a collaborative process of guidelines development because, as Torrance put it, industry felt "the writing was on the wall" when it came to requirements for economic analysis in drug assessment.[12] After Ontario released its draft guidelines for economic analysis in 1991, PMAC was concerned that each province would develop its own guidelines (Torrance et al. 1996). PMAC was also concerned that national guidelines would be imposed as they were in Australia: according to Schubert, spearheading the collaborative process "was to try to be proactive rather than reactive."[13] Menon reiterates the importance of industry in setting the agenda and argues that the drug plans themselves were not involved at the agenda-setting phase, saying industry "complained of different sets of rules, unclear rules, that were more or less rigid depending on the province...did anyone else perceive it as a problem?...I'm sure there was interest because drug plans were more and more dealing with cost issues. But government...often doesn't see the problem until it is in the room with them."[14]

The CDR responds to a similar set of problems concerning fragmentation in drug assessment processes across the country and corresponding variation in public drug formularies, but in the early 2000s there was no push from industry or external entrepreneurs like Schubert and Torrance. Perhaps industry was satisfied with the Canadian guidelines status

[11] Torrance; Schubert, interviews.
[12] Torrance, interview.
[13] Schubert, interview.
[14] Menon, interview.

quo, especially given that the guidelines did not make expert recommendations regarding cost effectiveness binding on formulary decision-makers, as some in industry had initially feared. Although industry was apparently consulted on the creation of the CDR, manufacturers were very critical after the process was in place (Ekos Research Associates Inc. 2005). Instead, pressure from governments, particularly elected officials, appears to be more important in initiating the CDR. Commentators argue that federal and provincial ministers of health "were concerned with the notable differences in coverage of prescription medications within their formularies and with the significant duplication of effort in reviewing new medicines" (Tierney and Manns 2008, 432; see also Clement *et al.* 2009), and note that variation in provincial formularies had "become a politically sensitive issue in Canada" (Laupacis 2005, II-6). Broader health reforms, including calls for nation-wide pharmaceutical insurance, were on the agenda at this time, and the CDR gave federal and provincial governments an opportunity to work together and, as one interviewee puts it, "make progress on pharmaceuticals without opening the insurance can of worms,"[15] which had proven an intractable policy problem in the past (Boothe 2013).

6 HOW THE REFORMS WERE DESIGNED AND IMPLEMENTED

Once formal guidelines for economic analysis (in 1993) and a centralized review process (in 2003) were on the intergovernmental policy agenda, there were two types of decisions to be made. First, there was a set of technical decisions about the content of the guidelines and review process. Second, there was a set of political decisions about how and where the guidelines or review process would apply, and these were very much informed and constrained by the institutions of Canadian federalism.

The Canadian guidelines innovated in terms of the scientific methods, and the CDR in terms of the centralization of the process. In the case of the Canadian guidelines, the scientific content was created by academics participating in the collaborative workshop,[16] building on Australia's recently published guidelines (Menon, Schubert, Torrance 1996).[17] By contrast, the scientific content of the CDR is more the product of translation than creation as it uses an updated version of the Canadian guidelines, but it made progress in the design of the process, building on analogous provincial processes, especially Ontario's. The first chair of the Canadian Expert Drug Advisory Committee (CEDAC), the independent body that makes reimbursement recommendations, was Dr. Andreas Laupacis, who had previously chaired Ontario's Drug Quality and Therapeutics Committee. A former CEDAC member notes that most members had experience with regional drug assessment committees, and that moving from a provincial process to the CDR "was pretty seam-

[15] Interview with a former Associate Deputy Minister of Health, Ottawa, 15 October 2008.
[16] Torrance, interview.
[17] Schubert; Torrance; Menon, interviews.

less."[18] Another expert who sat on both CEDAC and a provincial committee notes that by the time the CDR process was instituted, "the principles of cost-effectiveness and process of assessment and quality of evidence were quite well-established [among experts]."[19]

The two reforms differ much more in their governance than in their content even though both have been shaped by the federal division of authority and financial responsibility in Canada, where provinces have constitutional jurisdiction over health, and outpatient drugs are excluded from the federal-provincial cost-sharing arrangements that support public hospital and medical insurance. Neither the Canadian guidelines nor the CDR was or is linked to any legislative or regulatory requirements. The Canadian guidelines were adopted in the sense that they were endorsed by the Pharmaceutical Manufacturers Association of Canada, CCOHTA, and then federal, provincial and territorial deputy ministers of health, but there was no mandate to require that public drug plans use the Canadian guidelines when conducting drug assessments. In the early 1990s, there was no push at the political level to make regulatory changes, and it appears that the potential benefits of harmonized reviews were trumped by differences in provincial capacity to conduct reviews, and the determination of provincial drug plans to maintain their autonomy over formulary decisions.

CCOHTA was given the task of communicating the guidelines across the country, but Menon notes that this was passive diffusion, and that the guidelines were actually picked up more outside of Canada, a view echoed by another workshop participant.[20] Menon recalls his impression at the time that provinces didn't really want the guidelines—the push for their creation had come from industry, and those provinces with the capacity and the desire to do economic evaluation (Ontario and later British Columbia) had their own methods for doing so.[21] The guidelines' creators noted early on that communicating the results of economic evaluations to formulary decision-makers was a challenge, given decision-makers' lack of expertise in the methods, and acknowledged that "even with a set of national guidelines, [formulary] decisions made regionally could be different across the regions" (Menon, Schubert, Torrance 1996, 82).

The implementation of the CDR differs in that it involves federal, provincial and territorial agreement on the creation of an independent expert advisory committee and a new mandate for CADTH to manage the process, but it is still affected by issues of formulary control. The creation of a central institution to conduct evaluations addressed one barrier to harmonization by allowing smaller provinces to access expert advice they did not have the capacity to produce individually. However, like the Canadian guidelines, the CDR is not the subject of regulation and its recommendations are non-binding (Canadian Agency for Drugs and Technologies in Health 2013). According to the associate deputy minister at Health Canada, when the CDR was set up, provincial and territorial health ministers

[18] Interview with a former expert committee member.
[19] Interview with an expert committee member.
[20] Menon; Schubert interviews.
[21] Menon, interview.

wanted advice, but did not want to be obligated to list particular drugs.[22]

This means that the CDR did not replace existing provincial processes of drug assessment (Laupacis 2005).[23] Public plans consider CDR recommendations, but conduct their own processes to assess factors such as budgetary impact and increasingly to negotiate prices. This is of particular interest in Ontario, which had the most developed process for economic evaluation prior to the CDR. An interviewee comments that the CDR allowed the provincial committee to rely on higher quality, more consistent literature reviews than previously, when these reviews were prepared *ad hoc* by provincial committee members or outside clinicians. The interviewee comments that the CDR "makes our lives easier...and I think it's made the process [of drug listing] much shorter."[24]

Another difference in how the CDR is implemented is the inclusion of mechanisms to improve the transparency of its assessments. Interviewees see these mechanisms as a response to concerns with existing processes of economic evaluation in the provinces, and to "a secular trend" in greater transparency in health system decision-making.[25] The CDR publishes summary reports of CEDAC decisions on its website, which committee members see as very important.[26] In 2006, public members were added to CEDAC. These members are citizens who are not representatives of patient groups but who collect information from these groups and bring their concerns into CEDAC evaluations. A former public member of CEDAC noted that the role of the public members was sometimes challenging, as experts on the committee found it difficult to appreciate how public members' input could fit with the evidence-based mandate of the committee, while patient advocacy groups did not necessarily understand the idea of cost-effectiveness analysis and saw the CDR as "a political body to save the government money."[27] The former public member notes that there was sometimes a sense of being "token taxpayers" on the committee, a view echoed by an expert member who says "public and patient involvement is mainly an exercise to be seen."[28] However, both these interviewees also argue that the public members offer a valuable perspective on quality-of-life issues such as sleeplessness and pain. The expert member offers, "I think we are fairly competent to weigh the evidence without public input, but how do you deal with values?...There is definitely merit in public and patient input."[29]

[22]Interview with an Associate Deputy Minister of Health.
[23]Interview with an expert committee member.
[24]Interview with an expert committee member.
[25]Interviews with an expert committee member and a former expert committee member.
[26]Interviews with an expert committee member and a former expert committee member.
[27]Interview with a former public member of CEDAC.
[28]Interviews with a former public member of CEDAC and an expert committee member.
[29]Interview with an expert committee member.

7 EVALUATION

The explicit goals of the Canadian guidelines and the CDR regarding harmonization of drug assessment are sometimes at odds with the voluntary, non-binding design and implementation of the processes, and this has been reflected in evaluations to date. Two key metrics that have been used to evaluate both the Canadian guidelines and the CDR are stakeholder satisfaction and uptake. Researchers conducted surveys of users in 1999 and 2005, and the House of Commons Standing Committee heard evidence from a range of stakeholders in 2007. For uptake of the Canadian guidelines, researchers asked the extent to which provincial and territorial drug plans were using the guidelines when conducting drug assessments. For the CDR, researchers ask about the degree of concordance between CDR recommendations and public plans' listing decisions.

Other evaluation measures specific to the CDR include the time to listing for new drugs, the percent of new drugs that receive a positive recommendation (often compared to jurisdictions outside Canada)[30], and degree of transparency in the process. A final measure that has been important in evaluating the CDR is the reasons for negative recommendations: explaining trends in which drugs receive "do not list" recommendations helps the CDR respond to perceptions that it is driven by a mandate to control costs, and also highlights shortcomings in the process regarding certain types of drugs, such as those for rare diseases that tend to have limited clinical evidence about efficacy.

Evaluation of the Canadian guidelines was somewhat limited. At a conference shortly after the guidelines' adoption, Menon noted that there were no immediate plans for CCOHTA to evaluate implementation of guidelines, although the agency would be considering its entire mandate for pharmaceutical assessment in the next two years (Menon and Schubert 1996). In an interview, he notes that CCOHTA was never able to measure how compliant users were with the technical elements of the guidelines.[31] After updating the Canadian guidelines in 1997, CCOHTA surveyed users and found some specific areas of the guidelines (such as changes to the format and reporting structure) were seen as improved, but others (such as the use of quality-adjusted life years) still needed work (Glennie *et al.* 1999).

Other research from around this time found that studies commissioned by CCOHTA mostly complied with the Canadian guidelines (Baladi, Menon, Otten 1998). Provincial use of the guidelines was more limited at this time: of the eight provinces requiring economic evaluation, only four required the use of the Canadian guidelines (Otten 1998). This falls short of the goal of a harmonized review process, and another study in British Columbia found that after the first year of requiring economic evaluation, only five out of twenty-one manufacturer submissions of economic evaluations complied with the guidelines (Anis, Rahman, Schechter 1998).

Evaluation of the CDR has been more robust, and has included both interviews with

[30] This criterion is measured as a response to patient and industry criticism that the CDR restricts access to new drugs, compared to other countries (Tierney and Manns 2008; Lexchin and Mintzes 2008).

[31] Menon, interview.

stakeholders and analysis of CDR decisions. A small set of interviews in 2006 asks participants about perceived fairness of central drug reviews in Canada, Australia, New Zealand and the UK, and concludes that while Canada did well in publicizing decisions and providing an appeals process for manufacturers, it could make improvements by including additional enforcement (either voluntary or regulatory) and developing a broader understanding of standards for evidence and use of economic evidence (Mitton et al. 2006). Another international comparison of reimbursement recommendations conducted in 2008 finds that although the CDR's decisions on specific drugs often differed from comparable bodies in Australia and Scotland, these differences "likely reflect discrepancies between countries in national markets and health," and the three agencies in fact have similar proportions of drugs recommended for listing, restricted listing, or no listing (Lexchin and Mintzes 2008). In 2004, CCOHTA commissioned a study to evaluate the CDR's first year in operation, which interviewed a range of stakeholders and examined a variety of topics from the consistency and rigour of reviews to the extent to which the CDR decreased duplication in review, improved the use of resources and expertise, and integrated the central review process into drug plan reviews (Ekos Research Associates Inc. 2005).

The Ekos study found the opinions of government stakeholders, academics and health professionals diverged sharply from the opinions of industry and patient advocacy groups. Governments (including public drug plan managers) were very positive about the CDR, reporting that it was fair and rigorous, reduced duplication in reviews across participating drug plans, and increased efficiency (Ekos Research Associates Inc. 2005). Industry and patient groups were much more negative, arguing that the process was not fair and objective, was linked to access problems when drug plans fail to adopt positive CEDAC recommendations in a timely fashion (which the study notes is not within the CDR's control), and resulted in longer times to listing. The study notes that although industry and patients perceive that the time to listing increased under the CDR, this is not in fact supported by available evidence. All stakeholders agreed on the need for more public input into the CDR process, and the study "found evidence of much frustration and misunderstanding with respect to the CDR process and recommendations. The patient advocacy groups in particular appear to have little awareness of the purposes and benefits of an evidence-based review," which the authors argue points to a need for an improved communication strategy from the CDR (Ekos Research Associates Inc. 2005, vi).

A similar split in opinion among stakeholders is found in the report of the House of Commons Standing Committee on Health, which heard testimony about the CDR process in 2007. By this time, the CDR had made some changes to its transparency and public outreach mechanisms, such as the addition of public members to CEDAC, and was in the process of making others, such as publishing lay-language versions of CDR reviews and recommendations online. Patient advocacy groups still expressed frustration with the transparency and timeliness of the process. Industry was similarly unhappy, although the report acknowledged evidence from experts who concluded that "more transparency would be possible if the pharmaceutical industry was willing to disclose the clinical trial data,

prices, and other information that is currently protected under confidentiality agreements with CADTH" (Standing Committee on Health 2007, 15).

With regard to the uptake of CDR recommendations, a 2006 analysis finds provinces varied in how quickly they responded to CDR recommendations. It also finds their decisions were generally consistent regarding whether to list, although not necessarily how to list (for example, they might put different restrictions on the population eligible to receive the subsidized drug). The study authors cautioned that more detailed analysis is required after the process has been in place longer (McMahon, Morgan, Mitton 2006).

More recent studies have found that concordance between drug plan decisions and CDR recommendations varies across the country, ranging from 60% in Ontario to 90% in New Brunswick and Nova Scotia (Gamble *et al.* 2011, 6; Paris and Belloni 2014, 15). Gamble *et al.* (2011, 6) interpret this variation between drug plan decisions and CDR recommendations as "substantial" and point out that their results "suggest a lower overall percent agreement" than the 90% concordance rate reported by the agency in 2007 (Canadian Agency for Drugs and Technologies in Health 2007). This report did not provide details of how the concordance rate was calculated.

With regard to percentage of new drugs listed and time to listing, Gamble *et al.* (2011, 6) found a "substantial" decrease in the number of new drugs listed for public reimbursement since the introduction of the CDR and note that the decrease in the percent of new drugs listed is likely caused by a number of factors, mentioning particularly "the considerable clinical uncertainty seen in recent drugs submitted for review." The authors found that the time it took provinces to list a drug decreased for a number of the smaller provinces after the introduction of the CDR.

A 2012 study assesses the reasons drugs receive a "do not list" recommendation from the CDR, and in doing so provides a useful evaluation of the process as a whole. Similar to Gamble *et al.* (2011), it finds that clinical uncertainty (not enough evidence about a drug's efficacy) is the strongest predictor of a "do not list" recommendation and that certain types of drugs (such as those for rare diseases) are particularly susceptible to problems with insufficient evidence (Rocchi *et al.* 2012, 241). It concludes that the CDR is "a successful institution...It maintains the full support of the funding provinces, it consistently meets timelines for review, it scrupulously follows well documented processes and it has made modifications over the years to respond to criticisms" (Rocchi *et al.* 2012, 240). However, the authors point out that until their study, its decisions had not been subject to a high level of external scrutiny, especially compared to other central review bodies like NICE in the UK, as previous studies and evaluations have been completed by "individuals who are or have been engaged in the CDR process" (Rocchi *et al.* 2012, 231).

8 ANALYTICAL COMPARISON

This article has noted a key tension between the stated goals of the Canadian guidelines and the CDR with regard to more harmonized drug assessment, and the design and implementation of the processes, which in both cases must confront institutional barriers to harmonization. The most important of these barriers is that Canadian provinces have sole authority and financial responsibility for their public drug plans. A truly harmonized assessment process would require each plan to make the same decisions about any given drug and thereby relinquish control over their formularies. Comparing the uptake of the Canadian guidelines to the CDR demonstrates that there is value in having a central structure to help in meeting harmonization goals: certainly government stakeholders and experts report a greater degree of harmonization with the CDR. However, absent institutional change at the drug plan level, the degree of harmonization that can be realized is limited. This is a key contention of the call for a national pharmacare plan, which argues that a single national formulary (fully harmonized decision-making regarding which drugs should be covered) is necessary to ensure access, safety, and value for money (Morgan *et al.* 2015).

Even without a fully unified pharmacare program, an understanding of these barriers to harmonization may be particularly relevant to current efforts to increase collaboration in drug price negotiations in Canada with the pan-Canadian Pharmaceutical Alliance (pCPA). The pCPA is a project of the Council of the Federation, an organization of Canada's premiers that aims to promote interprovincial-territorial cooperation on a range of issues. Since 2010, the pCPA has concluded 83 joint price negotiations for branded drugs reviewed by the CDR or pCODR (Council of the Federation 2015). This collective price negotiation could address an important barrier to harmonized formularies under the CDR if it allows jurisdictions to list the drug at the same price. Prior to the work of the pCPA, the CDR might give a drug a "do not list" recommendation based on the manufacturer's stated price, but larger provinces like Ontario would often negotiate a confidential price with the manufacturer that made the drug cost-effective and allowed the province to list it. The challenge for harmonization is that smaller provinces often lack the capacity to undertake these negotiations or the bargaining power to achieve a cost-effective price (Morgan et al. 2013). The pCPA may address this barrier by allowing all provinces to get the same lower, confidential price for a drug. However, currently the negotiations are not binding, which industry stakeholders identify as a major source of frustration (IBM Consulting 2014). Even after the pCPA's lead jurisdiction for the negotiation signs a Letter of Intent with the manufacturer, each participating drug plan must "make their final decision on funding the drug product" and enter a jurisdiction-specific pricing agreement with the manufacturer (Council of the Federation 2014).

It thus appears that the same institutional barriers to harmonization that affect the CDR are relevant to the pCPA. However, even if these barriers were resolved by making the collective price negotiation binding, there is an additional tension between harmonization and transparency. Lower drug prices and potentially greater harmonization come at the

expense of transparency to the public, to private drug plans, and to prescribers. According to one interviewee, if a drug plan agrees to list the drug at a lower, confidential price, it can "skew prescribing, because it signals the product is better," whereas it may not offer value for money at the published price. The interviewee continues, "the [drug plan] stamp of approval counts for a lot."[32] It may be that the value of lower prices and greater harmonization outweighs the value of transparency in this case, but to date there has been limited public discussion of these trade-offs (but see Dhalla and Laupacis 2008).

The increased emphasis on transparency is an important difference between the Canadian guidelines and the CDR. Interviewees report that, when the Canadian guidelines were designed and adopted, communicating the results of drug assessments to the public was not a high priority, although there were concerns about communicating to assessment users such as drug plan managers (Glennie *et al.* 1999).[33] However, in the decade after the Canadian guidelines' adoption, transparency became a much higher priority for stakeholders, reflecting perhaps increased awareness of cost-effectiveness evaluation of pharmaceuticals as well as a broader move to transparency in health policy and government decision-making. The CDR has responded to this issue in ways the Canadian guidelines could not, and has led the way for greater transparency in some provincial drug assessment processes. The CDR's non-technical summaries of decision rationales were an important innovation in communicating with the public, and Ontario's Committee to Evaluate Drugs (CED) now publishes summaries of decisions as well (Ontario Ministry of Health and Long Term Care 2013). The CDR innovated in its introduction of public members of CEDAC, and later, a template for patient advocacy groups to submit information to the committee (Canadian Agency for Drugs and Technologies in Health 2015). This is another area where some provincial plans are following suit—Ontario's CED now includes patient members.

If this focus on transparency is a key part of the ongoing development of drug assessment processes in Canada, it also leaves us with unanswered questions. Attempts to increase the transparency of the process are mainly focused on increasing its legitimacy with the public, and particularly patients—indeed, there is strong consensus among experts about the value and rigour of the methods. Now, almost ten years after public members were added to CEDAC, it is worth asking the degree to which these attempts have succeeded, given the highly concentrated costs and diffuse benefits of a negative CDR recommendation or formulary listing decision, and the highly technical nature of assessing clinical and economic evidence about pharmaceuticals.

A final unresolved tension is the fit between the methods of drug assessment contained in both the Canadian guidelines and the CDR, and the nature of the pharmaceutical marketplace today. New drugs are becoming increasingly specialized, and as relevant patient populations become smaller, the generation of evidence about clinical efficacy (a key component of CDR assessments) becomes more difficult. This issue is mentioned in a variety

[32]Interview with an expert committee member.

[33]Interviews with an expert committee member, a former expert committee member and Torrance.

of studies that note limited clinical data is an important predictor of a "do not list" recommendation (Clement *et al.* 2009; Rocchi *et al.* 2012). When it was designed, the CDR addressed shortcomings in drug assessment under the Canadian guidelines regarding limited uptake and the need for greater transparency. Now, researchers and policymakers must ask whether drug assessment needs to change again to address shifting goals regarding harmonization and transparency, and different needs regarding pricing and evidence. The history of the Canadian Guidelines for the Economic Evaluation of Pharmaceuticals and the Common Drug Review demonstrates both the potential benefits of harmonized drug assessment and the barriers to achieving harmonization, but it does not prescribe the right balance between transparency to the public and bargaining power in price negotiations, or a solution to the different demands of assessing new drugs with limited clinical evidence. Resolving these questions about how to balance different goals and values in drug assessment will be a key component in the implementation of any national pharmacare program, and is of urgent importance to Canadians. Drug listing decisions have a crucial impact on the comprehensiveness, equity and sustainability of public drug programs, and through them, citizens' health.

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A APPENDIX

Interviews were conducted by the author with a total of nine individuals: three former or current members of expert committees to evaluate drugs, two former CCOHTA/CADTH employees, an academic and a former pharmaceutical industry representative who were closely involved in the guidelines' development, and one former and one current senior Health Canada official. Interviewees are cited by name or position according to their preference.

Interviewees were selected based on knowledge of and/or participation in pharmaceutical evaluation, purchasing, or reimbursement policy. Interviews were semi-structured, which allowed the author to ask a similar set of questions to each interviewee and provided an opportunity for interviewees to offer insights and reflections that were not well captured by the interview script. Interviews were transcribed (when interviewees gave permission for audio recording) or summarized based on notes taken during the interview. Transcripts and notes were hand-coded based on an initial set of themes regarding program goals, agenda-setting factors, implementation, and evaluation. Additional codes identified during this process were then added and transcripts and notes were reviewed on this basis.

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