

A National Approach to Reimbursement Decision-Making on Drugs for Rare Diseases in Canada? Insights from Across the Ponds

Démarche nationale quant aux décisions de
remboursement des médicaments pour maladies rares au
Canada? Pistes provenant d'outremer



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Abstract

Introduction: Regardless of the type of health system or payer, coverage decisions on drugs for rare diseases (DRDs) are challenging. While these drugs typically represent the only active treatment option for a progressive and/or life-threatening condition, evidence of clinical benefit is often limited because of small patient populations and the costs are high. Thus, decisions come with considerable uncertainty and risk. In Canada, interest in developing a pan-Canadian decision-making approach informed by international experiences exists.

Objective: To develop an inventory of existing policies and processes for making coverage decisions on DRDs around the world.

Methods: A systematic review of published and unpublished documents describing current policies and processes in the top 20 gross domestic product countries was conducted. Bibliographic databases, the Internet and government/health technology assessment organization websites in each country were searched. Two researchers independently extracted information and tabulated it to facilitate qualitative comparative analyses. Policy experts from each country were contacted and asked to review the information collected for accuracy and completeness.

Results: Almost all countries have multiple mechanisms through which coverage for a DRD may be sought. However, they typically begin with a review that follows the same process as drugs for more common conditions (i.e., the centralized review process), although specific submission requirements could differ (e.g., no need to submit a cost-effectiveness analysis). When drugs fail to receive a positive recommendation/decision, they are reconsidered by “safety net”-type programs. Eligibility criteria vary across countries, as do the decision options, which may be applied to individual patients or patient groups.

Conclusions: With few exceptions, countries have not created separate centralized review processes for DRDs. Instead, they have modified components of existing mechanisms and added safety nets.

Résumé

Introduction : Peu importe le type de système de santé ou le type de payeur, les décisions quant à la couverture des médicaments pour maladies rares (MMR) présentent tout un défi. Bien que ces médicaments constituent habituellement les seuls traitements pour certains états de santé évolutifs ou mettant en danger la vie, les données démontrant leurs avantages cliniques sont souvent limitées en raison de la petitesse des échantillons de patients et des coûts élevés. Ainsi, les décisions s'accompagnent d'incertitude et de risques. Au Canada, on montre un certain intérêt pour mettre au point une démarche de prise de décisions pancanadienne éclairée par l'expertise internationale.

Objectif : Développer un inventaire des politiques et processus touchant les décisions quant à la couverture des MMR dans le monde.

Méthode : Nous avons procédé à une revue systématique des documents publiés et non publiés

qui décrivent les politiques et procédures dans les 20 pays se classant en tête selon le produit intérieur brut. Les bases de données bibliographiques, l'Internet et les sites Web des gouvernements et des organismes d'évaluation des technologies de la santé de chaque pays ont été consultés. Deux chercheurs ont indépendamment recueilli les données et les ont tabulées pour permettre d'effectuer des analyses comparatives qualitatives. Nous avons demandé à des experts des politiques dans chacun des pays de réviser la précision et l'exhaustivité de l'information recueillie.

Résultats : Presque tous les pays sont dotés de multiples mécanismes par lesquels on peut obtenir une couverture pour les MMR. Cependant, cela commence habituellement par un examen qui suit les mêmes processus que dans le cas d'un médicament pour une maladie plus commune (c'est-à-dire un processus de révision centralisé), bien que les exigences pour soumettre un dossier peuvent être différentes (par exemple, il n'y a pas besoin de présenter une analyse du coût-efficacité). Si un médicament ne reçoit pas de recommandation ou décision positive, on l'aborde alors en fonction de programmes de type « filet de sécurité ». Les critères d'admissibilité varient d'un pays à l'autre, de même que les choix de décisions, lesquelles peuvent s'appliquer parfois à des patients individuels, parfois à des groupes de patients.

Conclusions : Sauf quelques exceptions, les pays n'ont pas créé de processus de révision distincts centralisés pour les MMR. Ils ont plutôt modifié les composantes des mécanismes déjà en place et ont ajouté des filets de sécurité.

Introduction

Most developed countries have instituted centralized review processes for making coverage/reimbursement recommendations or decisions around new therapies (Morgan et al. 2006, Stafinski et al. 2011). In Canada, they include the Common Drug Review (CDR) and the pan-Oncology Drug Review (pCODR), which make funding recommendations to a number of public drug programs (at federal, provincial and territorial levels). In general, these processes were designed for therapies that treat relatively common conditions. However, with the advent of promising drugs for rare diseases (DRDs), they are being challenged (Cote and Keating 2012; Simoens 2011; Stafinski et al. 2011), as such diseases affect small populations, and have limited clinical evidence, leading to considerable harm and benefit uncertainties. Additionally, treatment costs are often high, and while the budget impact for a single rare disease may be small, there are over 7,000 rare diseases (in the US) (National Institute of Health 2015), many with promising treatments on the horizon. Therefore, decision-makers need to balance access to treatments with health system sustainability. In an effort to achieve this, mechanisms for determining funding conditions for DRDs have been established in many countries. However, details of these, whether they are specific to DRDs and how they compare internationally, have not been systematically explored. This information is needed to inform the current policy debate around a possible national Canadian DRD formulary. Recently, concerns

from patients, providers and industry over the funding of some DRDs in Canada have heightened (Weeks 2014). This has resulted in a commitment from provincial and territorial health ministers to consider developing a national approach to managing access to DRDs (Alberta Public Affairs Bureau 2014; Goodman 2004).

Purpose and Objectives

The purpose of this paper is to determine the current landscape of reimbursement decision-making around DRDs, based on a review of processes in 20 OECD countries. Its objectives are:

1. To identify and systematically describe national-level reimbursement/coverage decision processes on DRDs in 20 OECD countries with socially insured healthcare systems.
2. To analyze and compare these processes across countries according to their scope, information requirements, decision criteria, stakeholder participation and decision options.

Methods

The top 20 OECD countries by gross domestic product per capita (in 2012) with socialized health insurance programs/universal healthcare were included. These countries were selected because they share similar competing healthcare demands and economic environments and provide coverage for some pharmaceuticals. They were: Australia (AUS), Austria (AUT), Belgium (BEL), Denmark (DEN), Finland (FIN), France (FRA), Germany (GER), Iceland (ICE), Ireland (IRE), Italy (ITA), Japan (JAP), Korea (KOR), Luxembourg (LUX), the Netherlands (NET), New Zealand (NZ), Norway (NOR), Spain (SPA), Swede (SWE), Switzerland (SWI) and the United Kingdom (UK), which includes England (ENG), Wales (WAL) and Scotland (SCO). The three UK jurisdictions were included, as they operate additional decision-making processes to those through the central UK National Health Service (NHS). To identify relevant published literature, bibliographic databases covering health and social science literature, including PubMed (MEDLINE), EMBASE and Web of Knowledge, were searched using a structured search strategy. The strategy combined controlled vocabulary terms, such as medical subject headings, with additional keywords and synonyms, such as “orphan drugs,” “rare diseases,” “decision-making” and “reimbursement” (see Appendix A at www.longwoods.com/content/24210 for the full strategy). To capture non-peer-reviewed, unpublished information, several grey literature sources were searched, including NHS Evidence, the Knowledge Utilization – Utilisation des Connaissances at Laval University, the New York Academy of Medicine Grey Literature Collection and the websites of rare diseases associations and ministries of health. Last, separate Google searches were conducted for each country using a set of standard keywords (“rare disease*” OR “rare disorder*” OR “orphan drug*” OR “ultra rare”) AND [decision* OR policy OR policies OR reimbursement OR economic* OR rationing OR access* OR fund* OR legislation OR catastrophic OR regular*]) combined with country name. For each search,

the first 300 “hits” were scanned. Please see “Appendix A1. Literature search strategy” at www.longwoods.com/content/24210.

A publication limit of 2004 or later was applied to increase the likelihood of identifying information reflecting current reimbursement processes. This period also included the points when reimbursement processes in many countries were first exposed to high-cost DRDs (United States Food and Drug Administration 2014). No language limits were placed. For non-English language information, translation software was used (Babylon® and GoogleTranslate®).

Information on each country was extracted independently by two researchers using a standard, pre-tested data extraction form, and included: country, reimbursement mechanisms and patient eligibility criteria, information and factors considered during the decision-making process, structure and membership of the decision-making committee and types of decision options available. To ensure the accuracy and comprehensiveness of the data collected, individuals from each country were contacted and asked to review their respective completed extraction forms. They were government policy makers or senior staff of agencies managing drug review processes in the country. The data were then summarized in tables to facilitate a qualitative comparative analysis. The qualitative analysis focused on 10 key policy elements (Table 1) identified by drug program decision-makers in Canada and abroad who are part of a Canadian Institutes of Health Research-funded team focusing on the development of policies around DRDs (University of Alberta, School of Public Health 2014). Drug plan managers from Canadian provinces were also consulted.

Results

Results, summarized in Tables B1 through B4, are presented by the policy element mentioned below (Please see Tables B1 through B4 at www.longwoods.com/content/24210).

TABLE 1. Summary of 10 key policy elements

Policy element	Description
Eligibility/scope	Characteristics of the disease or condition and the types of drugs that fall within the mandate of the review process
Patient population	Eligible patients and whether a process resulted in population or individual patient-level recommendations or decisions
Clinical evidence	Specific types of clinical evidence and study designs required by the review process
Cost data	Information on the cost implications of providing the drug
Cost-effectiveness	Requirements for economic evaluations
Patient input	Opportunities for patients and families to provide input into the review process
Review/decision-making participation	Review committee composition and terms of reference
Decision options	Range of reimbursement options available
Decision factors	Factors considered by the review committee
Transparency	Information on the review process and decisions available to the public

Eligibility and scope

Across the countries, two types of decision-making processes for DRDs were identified: (1) centralized drug reviews (CDRs), through which most new drugs considered for inclusion on the benefit list are reviewed, and (2) “safety net” programs, through which drugs unlicensed for the specific indication, failing to receive a positive CDR recommendation/decision or have yet to undergo CDR review are assessed (see Table B1 at www.longwoods.com/content/24210) (Garau et al. 2009; *Ministre des Affaires Sociale et de la santé* 2014; Ministry of Health, Welfare and Sport 2013; OrphaNews Europe 2009; Seoane-Vazquez et al. 2009). “Safety net” programs typically provide temporary reimbursement of a drug to individual patients. Drugs eligible for review through the CDR include all outpatient and, in some cases, in-patient drugs with market authorization/approval. “Safety net” programs exist in 13 countries (AUS, AUT, BEL, DEN, FRA, GER, IRE, ITA, NZ, NOR, SPA, SWI and the UK). However, except for the UK and BEL, these programs are not limited to DRDs, and eligible drugs typically also include those for “severe” conditions regardless of prevalence, which have no treatment alternatives (FRA, GER, SPA) or if alternatives have been insufficiently efficacious or have unacceptable side effects (NZ, NOR). “Severe” is commonly defined as “life-threatening” or “chronically debilitating” (AUS, JAP, KOR, NOR, SPA, SWE). In AUS and NZ, drugs must have already been reviewed by the CDR before they are eligible for consideration by a “safety net” program. There may also be further requirements. For coverage through AUS’s “safety net” program (“Life Saving Drugs Program” or LSDP), a drug must have failed to receive a positive recommendation based on unacceptable cost-effectiveness. In NZ, patients must first meet certain prerequisites before being considered for high-cost DRDs, through the Unusual Clinical Circumstances pathway. This pathway applies to patients with rare conditions, and requires that (i) the patient has reasonably tried and failed all alternative funded treatments, (ii) the patient is experiencing an indication or set of clinical circumstances that is so unusual that PHARMAC (the Pharmaceutical Agency in NZ that decides on behalf of District Health Boards which medicines will be subsidized) is unlikely to consider listing treatments for these on the Schedule and (iii) PHARMAC has not yet considered the treatment for the patient’s clinical circumstances, through the CDR (see Table B2 at www.longwoods.com/content/24210).

Seventeen of the countries have a formal national definition of DRDs. A majority (AUT, BEL, FIN, FRA, GER, IRE, ITA, LUX, the NET, SCO, SWI) use the European Union (EU) Regulation on Orphan Medicinal Products’ definition: “... intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating; the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; and no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition” (European Medicines

Agency 2014). Other countries have developed specific definitions, none of which are based solely on prevalence (AUS, JAP, KOR, NOR, SPA, SWE, the UK).

In a number of countries, “safety net programs” that include DRDs as well as other drugs involve reviews of requests for individual patients (AUT, DEN, FRA, ITA, SPA). By contrast, such programs in the UK and BEL are specific to DRDs only. The UK’s National Institute for Health and Care Excellence (NICE) has established the Highly Specialised Technology (HST) program, to which drugs are referred by the Secretary of State for Health, and must meet all of these criteria: “The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS; the target patient group is distinct for clinical reasons; the condition is chronic and severely disabling; the technology is expected to be used exclusively in the context of a highly specialized service; the technology is likely to have a high acquisition cost; the technology has the potential for life-long use; and the need for national commissioning of the technology is significant” (NICE 2013b). While “so small” is not explicitly defined, guidance around the criteria states that the number of patients affected in the UK should be fewer than 500. Decisions on drugs not selected for review through the HST program are left to the relevant budget holder (NHS England or one of the 211 local Clinical Commissioning Groups) (NICE 2013c).

Another exception is Belgium’s “Special Solidarity Fund” (SSF) comprising a “safety net” program exclusively for DRDs. Eligible DRDs are orphan drugs (as designated by the European Medicines Agency) that have yet to receive a positive recommendation from the Belgian CDR *and* meet at least one of the following criteria:

1. treat a rare disease requiring a specific physiopathological treatment,
2. treat a rare disease requiring a continuous and complex treatment,
3. treat chronically ill children,
4. involve innovative treatment techniques or
5. otherwise requires medical treatment abroad (Guillaume et al. 2010).

This program provides temporary funding. To obtain access to a drug through SSF, patients should have exhausted all other public or private reimbursement options at national, European or international levels. In several countries, existing CDR processes have been modified to accommodate DRDs and other high-cost drugs. ENG, SCO and WAL have each instituted “Patient Access Schemes,” which manufacturers or sponsors may propose as part of their CDR submission. These schemes facilitate patient access to expensive and typically innovative drugs that do not appear to offer significant benefits over existing treatments by improving their cost-effectiveness. This may be achieved through listing agreements or risk-sharing arrangements that incorporate outcomes guarantees realized within a defined period (Morel et al. 2013). Other countries have implemented “fast-track” mechanisms, where eligible drugs are prioritized by the CDR, bypassing the standard process in which drugs are reviewed

in the order received (e.g., FRA, the NET, SWI). In general, “fast-tracked” drugs are those that treat life-threatening conditions where no alternative treatment exists. Therefore, while eligibility may not include a prevalence condition, many DRDs meet these other criteria.

Patient population

In all countries, a DRD that receives a positive decision from the CDR is added to the list of publicly insured medicines. As with drugs for common diseases, the list specifies the groups of patients for whom the DRD will be provided. In contrast, decisions made within most “safety net” programs apply to an individual patient, whose prescribing physician has submitted a request for access on his/her behalf (AUT, BEL, DEN, FRA, GER, IRE, ITA, the NET, NOR, NZ, SPA) (see Table B1 at www.longwoods.com/content/24210). Some “safety net” programs also accept requests from other sources, including Centres of Excellence/Reference (virtual or real centres of a network of experts in research, treatment and care across the child-to-adult age spectrum) or patient organizations (FRA, ITA), manufacturers (AUS, GER, the NET, the UK), a pharmacist or pharmacy (FIN, the NET), the treating hospital (SPA) or a university (ITA) (see Table B1 at www.longwoods.com/content/24210). However, the decisions remain at the patient level. In the remaining countries (FRA, GER, ITA, SPA), “safety net” programs may provide access to groups of patients (see Table B1 at www.longwoods.com/content/24210).

EVIDENCE REQUIREMENTS

In all countries, funding requests for DRDs to the CDR must provide specific information that usually applies to all drugs. This includes: (1) indication and target population, (2) therapeutic claim, (3) net clinical benefit (safety, efficacy and effectiveness), (4) budget impact and (5) economic evaluation (usually a cost-effectiveness analysis) (see Table B3 at www.longwoods.com/content/24210). However, in NET, cost-effectiveness analyses are waived for DRDs (see Table B3 at www.longwoods.com/content/24210). All of the “safety net” programs require statements of medical justification and information on items (1), (2) and (3) above. In some programs, treatment protocols, e.g., treatment dose, duration or planned monitoring, must also be submitted (DEN, FRA, GER, SPA, the UK). Others require information demonstrating no appropriate alternative treatment (AUS, AUT, BEL, GER, the NET, NZ) or intent to submit an application for market authorization (FRA, GER).

Clinical evidence

In most countries, CDR submission guidelines indicate a *preference* for head-to-head randomized controlled trials (RCTs) for *all* drugs, with the drug being compared to current best practice or standard care based on hard clinical endpoints (as opposed to surrogate endpoints) (see Table B3 at www.longwoods.com/content/24210). However, no guideline specifies minimum evidentiary requirements/standards for determining clinical benefit. Moreover, most

indicate that all types and levels of evidence will be considered, including trials using surrogate endpoints, as well as unpublished and ongoing studies (AUS, AUT, BEL, the NET, NOR, SWE, the UK).

In contrast, all but two of the “safety net” programs have no formal clinical evidence requirements. ITA specifies data from Phase II/III clinical trials, and AUT requires at least one Phase III clinical trial to be in progress or completed.

Cost data

Most CDRs require budget impact analyses (BIAs) for all drugs, regardless of their indication (AUS, BEL, DEN, FIN, FRA, ICE, IRE, ITA, KOR, the NET, NOR, SPA) (see Table B3 at www.longwoods.com/content/24210). The BIAs must incorporate the prevalence and incidence of the disease and the potential number of patients, and comply with the CDR’s methodological guidelines. Almost all CDRs require information on both the cost and price of the treatment (AUS, FRA, IRE, ITA, LUX, the NET, NZ, SPA, SWE, SWI, WAL, the UK). In five of these, price information on comparable reimbursed drugs must be provided (AUT, ICE, ITA, LUX, SWI), and in three, price comparisons with other European jurisdictions must also be made (AUT, ITA, LUX). In countries where reimbursement decision-making and pricing may occur simultaneously, sales forecasts for the first year and usually three years after approval are required (AUS, FIN, ICE, NOR). In contrast, most “safety net” programs do not require cost information (AUT, DEN, FIN, FRA, GER, ITA, the NET, NOR, NZ, SCO, SPA, the UK, WAL). The exceptions are the LSDP (AUS) and SSF (BEL). Information demonstrating an unreasonable financial burden of treatment to the patient must be submitted.

Cost-effectiveness

In the majority of countries, *all* drugs considered by the CDR must provide an economic evaluation (AUS, AUT, FIN, ICE, IRE, JAP, NOR, NZ, SCO, SWE, SWI, the UK, WAL) (see Table A2 at www.longwoods.com/content/24210). Some state a preference for cost-utility analyses (AUS, IRE, NZ), others prefer cost-effectiveness analyses (ITA, SWI) and yet others accept either type (JAP, SCO, SWE). Most of these specify that it must be based on a comparison to available alternative treatments (AUS, AUT, FIN, ICE, SCO, SWE, the UK, WAL). In some countries, the perspective for the evaluation is also specified: societal (FIN, IRE, SWE), payer (AUS) or both (NOR). However, several countries do not require an economic evaluation for drugs with indications for which no alternative treatment exists (GER, ITA, KOR, the NET). Further, in the NET, CDRs waive economic evaluations specifically for DRDs. In GER, DRDs with annual sales below €50 million per year are exempted from cost-benefit assessments (Fulda 2011; Holtorf et al. 2009).

Patient input

Most CDR processes provide opportunities for input from patients/families; this applies to all drugs (including DRDs) (see Table B2 at www.longwoods.com/content/24210) (Danish Health and Medicines Authority 2012; Taruscio et al. 2011). This often consists of submissions in which patients or patient organizations provide prescribed information on their experiences with the condition/disease (AUS, FRA, GER, JAP, KOR, NZ, SCO, SWI, the UK, WAL). These are usually considered alongside the technical assessment of clinical and economic implications by the review/decision-making committee. In some countries (AUS, GER, JAP, KOR, SCO, WAL), that committee includes a patient representative (a further opportunity for patient input) (see Table B3 at www.longwoods.com/content/24210). Except for the Scottish Medicines Consortium (SMC) in Scotland, none of the CDR processes appear to have established separate opportunities for DRDs. The SMC's Patient and Clinician Engagement process was created solely for the review of end-of-life treatments and DRDs. It involves a meeting of patient representatives and healthcare professionals with relevant expertise to gather information on the benefits of a medicine, specifically around impact on patients' quality of life (Scottish Medicines Consortium 2014b). This information is subsequently presented to the review/decision-making committee during its meeting. Please see "Table B2. Information requirements of reimbursement review processes" at www.longwoods.com/content/24210.

Opportunities for patient input in "safety net" programs are limited. None have implemented patient submission processes comparable to those of CDRs. This may be, in part, because these are usually considered on a case-by-case basis (AUT, BEL, DEN, FRA, GER, IRE, ITA, the NET, NOR, NZ, SPA, the UK). Only two countries accept requests directly from patients or patient representatives (AUS, ITA).

Review/Decision-making participation

In all of the countries where DRDs are included in the CDR process, reimbursement recommendations or decisions are made by a review committee. These committees are appointed, range from 5 to 28 members, and represent multiple stakeholder groups (see Table B3 at www.longwoods.com/content/24210) (Nagae 2011; Office Federal de la Santé Publique 2013). All committees include physicians, healthcare providers or clinical experts. In some countries, members also include pharmacists/pharmacologists (AUS, BEL, FIN, ITA, JAP, LUX, the NET, SCO, SWI), social insurance representatives (AUT, BEL, ENG, FIN, GER, KOR, LUX, SWI), government representatives (AUT, BEL, FIN, FRA, LUX, the NET), health economists/economic experts (AUS, FRA, JAP, the NET, WAL), patient representatives (AUS, ENG, GER, KOR, SCO, SWI, WAL) or drug industry representatives (AUS, ENG, SCO, SWI, WAL). Please see "Table B3. Elements of processes through which reimbursement recommendations or decisions on DRDs are formulated" at www.longwoods.com/content/24210.

In “safety net” programs, adjudication may be by separate committees in the same organization as the CDR (AUS, DEN, FRA, ITA, NZ, the UK), or in a different organization (often the national pharmaceutical regulatory body) (FIN, GER, the NET, NOR, SPA), or a senior-level medical officer or group of physicians representing the payer (e.g., sickness funds) (AUT, BEL, respectively) (see Table B3 at www.longwoods.com/content/24210). In Belgium, the group of physicians consists of experts in rare diseases from the College of Medical Doctors for Orphan Drugs.

Decision options

In almost all of the countries, the CDRs consider, at a minimum, three options: “provide,” “do not provide” or “provide with conditions” (i.e., restrict to certain prescribing physicians, facilities or patients) (see Table B1 at www.longwoods.com/content/24210). In some countries (BEL, FRA, the UK), an option for interim provision of treatment with additional data collection to address existing evidence uncertainties to make a definitive recommendation or decision (“provide with data collection”) is available. In countries where all drugs receiving market authorization must be reimbursed (ITA, GER), the decision options comprise negotiations on price and patient sub-populations for whom the drug will be offered (see Table B1 at www.longwoods.com/content/24210). Therefore, all decisions are “provide with conditions”. For all “safety net” programs, decision options are limited to: “do not provide” or “provide with conditions”. “Conditions” include restrictions on prescribing to certain physicians, centres and/or patients who fulfill specific clinical criteria and enrolment in a registry to facilitate ongoing monitoring of patients receiving the drug (e.g., the UK). These decisions typically provide temporary funding only, and patients (through their physicians) must apply for renewal (BEL, DEN, FRA, GER, ITA, NZ, SPA, the UK). Renewal may require that a patient demonstrate improvement in certain pre-defined outcomes (FRA, the UK). In most countries, “provide with conditions” decisions are implemented through “managed access programs” or “patient access programs”.

Factors considered by review committees

Factors considered by at least two countries with CDRs that review DRDs are summarized in Table 2 (see Table 2 at www.longwoods.com/content/24210). They include, in decreasing order of frequency: clinical benefit or effectiveness (17 CDRs), value for money or cost-effectiveness (13 CDRs), affordability or budget impact (13 CDRs), disease severity or burden (12 CDRs), clinical need (12 CDRs), availability of alternative treatments (10 CDRs), safety or benefit-harm ratio (8 CDRs), therapeutic value (6 CDRs), price and level of reimbursement in other jurisdictions (6 CDRs), quality of and uncertainty in the evidence (5 CDRs), impact on public health (3 CDRs), innovativeness of the drug (4 CDRs), experience with the drug or extent of current use (2 CDRs) and the ethical principle of solidarity (2 CDRs). Some countries specify ethical principles used in their decision-making such as “rules-of-rescue” (AUS) or human value (SWE). In most countries, the CDRs have not defined a

threshold incremental cost-effectiveness ratio (ICER) (AUS, FIN, IRE, ITA, JAP, KOR, NZ, SWE, SWI, WAL). SCO and the UK are exceptions, with a formal ICER threshold of £30,000 per quality-adjusted life year gained (QALY). But this is waived for specific drugs, including those for ultra-rare diseases (with fewer than 500 patients in the UK). While few countries use fixed ICER thresholds, several identify informal thresholds (e.g., €45,000 per QALY [IRE] and NOK 500,000 per QALY [NOR]; Coughlan et al. 2009; Gothesen et al. 2013). Drugs with ICERs below thresholds would generally be considered cost-effective. In some countries, thresholds are either not applied (the NET) or are applied flexibly (KOR) for DRDs. Please see “Table 2. Factors/criteria most commonly used by centralized drug review committees considering DRDs” at www.longwoods.com/content/24210.

All “safety net” programs consider (see Table B3 at www.longwoods.com/content/24210): medical necessity or unmet clinical need arising from the lack of suitable alternative treatments (see Table B3 at www.longwoods.com/content/24210). In addition, most require some indication of clinical benefit (safety, efficacy and/or effectiveness) (AUS, BEL, DEN, FRA, ITA, NOR, NZ, the UK). Less common factors considered by programs include: patient’s financial burden (AUS, BEL, NOR), cost-effectiveness (although no ICER threshold is specified) (AUS, AUT, NOR, NZ, WAL), cost or budget impact (AUS, AUT, FRA, IRE, NZ, the UK), plans for additional studies (the UK), innovativeness (the UK), impact on existing services (AUT, FRA, the UK) and clinical plausibility and appropriateness (SCO, the UK, WAL). NZ is the only country that utilizes the same criteria for “safety net” decision-making as in the CDR.

Transparency

In 10 countries, key findings by the CDR, final recommendations/decisions and rationale for the recommendations/decisions are publicly available (AUS, DEN, FRA, GER, IRE, ITA, the NET, SCO, SWE, SWI, the UK), and are summarized and posted on the CDR’s website (see Table B4 at www.longwoods.com/content/24210) (Mossialos et al. 2008). In some countries, the full evaluation report and minutes of review committee meetings are also made public (AUS, FRA, the NET, SWE, SWI). Please see “Table B4. Public accountability and decision implementation considerations” at www.longwoods.com/content/24210.

In contrast, publicly available information on specific DRDs considered by “safety-net” programs is scarce. Rationale supporting a closed process includes the fact that most “safety-net” programs are offered at the individual patient level; if information is made public, patient confidentiality may be violated. Additional rationale relates to protecting commercial interests of the manufacturers/sponsors.

Interpretation

This paper presents a comparative analysis of national reimbursement processes for DRDs in 20 OECD countries on 10 key policy relevant elements. While in Canada, there are two CDR processes (the CDR for non-cancer drugs and the pan-Canadian Oncology Drug

Review for cancer drugs), their mandates are limited to the formulation of recommendations. Reimbursement decisions remain with provincial and territorial drug plans. Further, the review processes for DRDs are the same as those for other drugs. In general, DRDs reviewed through the CDR processes have fared poorly, and subsequent reimbursement decisions across the jurisdictions have varied (Menon et al. 2015).

Lessons that might be learned from other countries facing similar competing demands for health correlate to the overall process itself, the role of rarity (or prevalence), evidence uncertainties and costs. First, although all of these countries have established CDR processes for outpatient and, in some cases, in-patient drugs, none, except for the UK, have created a separate CDR process for DRDs. This may be explained by the explicit use of ICER threshold ranges by CDRs for non-DRDs in the UK that drugs for ultra-rare diseases would invariably fail to meet. Its separate process recognizes the need to assess “value” differently. In Canada, new drugs (including DRDs) being considered for reimbursement through the provincial and territorial drug benefit plans must first be assessed by the CDR (non-oncology drugs) or the pan-Canadian Oncology Drug Review (oncology drugs), both of which issue a funding recommendation. The absence of a separate centralized review process for DRDs may be attributable to the fact that decision-making still rests with the individual provincial and territorial drug plans. In four provinces (Alberta, British Columbia, New Brunswick and Ontario), “safety net” programs for some DRDs have been established.

Second, although many countries have adopted a definition of “rarity,” none have implemented DRD reimbursement eligibility criteria based on prevalence alone. Typically, the DRD must be indicated for a life-threatening or chronically debilitating condition for which there are no other treatment alternatives. Therefore, not all DRDs will meet these criteria. Internationally, healthcare systems have recognized that DRDs comprise treatments for complex, often severe, diseases with poor prognoses and limited treatment options. They do not represent salami-slicing, in which small sub-groups of patients within a more prevalent disease are identified and then classified as a DRD to gain access to special concessions, including pricing.

The third issue relates to evidence uncertainties, which are inherent in the area of rare diseases, and arise because of small patient number, heterogeneity of disease and, in many cases, limited understanding of the natural course of the disease (and, therefore, of relevant outcomes of an intervention). These uncertainties often challenge generally accepted methodological standards in health technology assessment and translate to increased risk in decision-making. It has been argued that the large uncertainties associated with DRDs have resulted in fewer positive funding decisions, when compared to non-DRDs. As demonstrated in this review, “safety net” programs have emerged as a means of providing coverage for DRDs that “fail” the standard CDR process. They may also include “managed access programs” (MAPs), whereby a DRD may be funded with the condition that an identified evidence gap

be filled through additional data collection. MAPs continue to generate significant interest from decision-makers in many countries and may be the way of the future for any new and innovative health technology which might appear very promising but requires definitive proof before widespread adoption.

Fourth, the per patient cost of most DRDs is extremely high. Numerous DRDs cost in excess of \$500,000 per patient per year, and there appears to be little indication that they will drop over time. Some governments have chosen to deal with “high-cost” technologies, regardless of their indication, as a specific class for review purposes. The argument often made is that as rare diseases affect small populations, the budget impact of a single DRD in a jurisdiction would be relatively small, despite the high individual price. However, it is anticipated that governments will soon need to contend with a long list of DRDs. Risk-sharing agreements with companies may be the only feasible alternative to ensure that there is appropriate control of DRDs when they are funded.

Conclusion

This review shows that DRDs are an issue for governments worldwide. Most continue to use pre-existing CDR processes, and when that fails, resort to “safety net” programs or modified decision criteria. When considering the experiences of other countries, it is important to keep in mind, differences in healthcare systems, which may limit their applicability to the Canadian context. However, international experience may yield some options in Canada for the development of a pan-Canadian approach to the funding of DRDs.

Limitations

This review relied on publicly available information. Therefore, it is possible that relevant information may have been missed. In addition, while the search for grey literature included non-English language documents, the search for published, peer-reviewed literature was limited to papers appearing in English. Translation software was used to convert non-English language articles to English. To the extent possible, policy experts from non-English-speaking countries were consulted to validate the information collected. However, it is possible that some information may have been missed.

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