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Priority setting for orphan drugs: An international comparison

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ABSTRACT

Objectives: To describe the process of priority setting for two orphan drugs – Cerezyme and Fabrazyme – in Canada, Australia and Israel, in order to understand and improve the process based on stakeholder perspectives.
Methods: We conducted qualitative case studies of how three independent drug advisory committees made decisions relating to the funding of Cerezyme and Fabrazyme. Interviews were conducted with 22 informants, including committee members, patient groups and industry representatives.
Results: (1) Description: Orphan drugs reimbursement recommendations by expert panels were based on clinical evidence, cost and cost-effectiveness analysis. (2) Evaluation: Committee members expressed an overall preference for the current drug review process used by their own committee, but were concerned with the fairness of the process particularly for orphan drugs. Other informants suggested the inclusion of other relevant values (e.g. lack of alternative treatments) in order to improve the priority setting process. Some patient groups suggested the use of an alternative funding mechanism for orphan drugs.
Conclusions: Priority setting for drugs is not solely a technical process (involving cost-effective analysis, evidence-based medicine, etc.). Understanding the process by which reimbursement decisions are made for orphan drugs may help improve the system for future orphan drugs.

1. Introduction

Drug expenditures in every health system are rapidly increasing and account for a large proportion of health spending. This increase is partially due to the fact that per patient costs of some new drugs are extremely high, particularly for orphan drugs used to treat rare diseases. There is no universal definition of what constitutes a rare disease. Rare diseases in the European Union (EU) are defined as affecting fewer than 5:10,000 people and in the US fewer than 200,000 people [1]. Currently, over 6000 rare disorders have been identified [2]. Some governments have recognized the need to support the development of orphan drugs. The US Orphan Drug Act was the first major initiative to provide incentive for pharmaceutical development to aid with rare disorders [3]. This initiative provides incentives to pharmaceutical companies for research and development of orphan drugs [4].

Priority setting for orphan drugs involves complex value-laden choices that are often ethically controversial. This controversy arises, in part, because it involves conflicting moral obligations (e.g., beneficence versus distributive justice) which result in different levels of funding and

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opposing interests of a number of involved stakeholders, including government officials, pharmaceutical companies, patients and the public (who are ultimately paying for the drugs). Expensive orphan drugs present a challenge to many drug recommendation committees because they seldom meet the cost-effectiveness and clinical evidence criteria commonly used to evaluate drugs under review for reimbursement. Notably, orphan drugs cannot undergo large clinical trials due to the small number of people affected by the disease. The scope of this issue is potentially universal because, as the science of genomics advances, medical treatments are becoming increasingly more personalized therefore more treatments may gain quasi-orphan status [5,6]. As science progresses it is likely that treatments will become even more targeted towards a smaller disease group. Today's policy decisions for a few orphan drugs may determine funding for future products.

Cerezyme, used in the treatment of Gaucher disease, and Fabrazyme used in the treatment of Fabry disease, are two examples of enzyme replacement therapies which are the most expensive type of orphan drugs. These drugs were chosen for the case studies because they are both innovative and extremely costly orphan drugs. The purpose of this study was to identify the values used by three national drug reimbursement recommendation committees in Canada where the committees makes non-binding funding recommendations to the provinces, as well as Australia and Israel where their committees make national funding decisions for their public healthcare systems regarding these two drugs. To date, there have been few studies describing priority setting in the context of orphan drug reimbursement decisions [7]. Describing and comparing the values involved in the process of drug reimbursement decisions within an international context may be an essential first step towards understanding and improving the process.

2. Methods

2.1. Design

We conducted qualitative case studies of priority setting of the drugs central to our case studies in three committees, across three countries. Tables 1 and 2 provide more specific details about each of the aforementioned drugs. Data collection involved semi-structured interviews with 22 committee members, patients, and manufacturers, and the review of several relevant documents.

2.2. Data collection

Data collection involved in-depth qualitative interviews, and the collection of relevant documents (please refer to Tables 3–5). We conducted face-to-face interviews or one-on-one telephone interviews with committee members, patient groups and industry representatives. Specifically, we conducted interviews with members of the Canadian Expert Drug Advisory Committee (CEDAC); Australia's Pharmaceutical Benefits Advisory Committee (PBAC); and Israel's Basket Committee (IBC). Additionally, interviews were conducted with patients who use the drugs central to our case studies and participants from Genzyme which manufactures the drugs central to our case studies. Interviews were 30–60 min in length. All interviews were recorded and transcribed. Interviews explored decision making in drug reimbursement of the two selected drugs [see Example of Interview Guide for Committee Members Appendix B].

Relevant documents related to reimbursement decisions were sampled and analyzed to explore reimbursement decisions surrounding both the drugs central to our case studies (please refer to Tables 3–5).

2.3. Setting

This research was conducted within both reimbursement recommendation committees and the drug manufacturer (i.e., Genzyme). These committees were selected because they all make recommendations about public funds and they provide guidance on drug funding to governments and other funders. The manufacturer of the drugs central to our case studies, Genzyme, was included because of their potential insight into the drug reimbursement process. Tables 3–5 below provide an overview of each of the committees based on information from their

Table 1
Cerezyme (*imiglucerase*).

Manufacturer	Genzyme, approved by US Food and Drug Administration in 1994
Use/symptoms	Reduces and in some cases reverse the chronic and debilitating symptoms of type 1 Gaucher's disease Affects 1 in 40,000–60,000 individuals in the general population Higher prevalence in Jewish Ashkenazi community Some patients have no symptoms, while others develop serious symptoms that can be life threatening Bone-related symptoms can be painful and debilitating, impairing a patient's mobility Life expectancy is mildly decreased [8,9]
Cost	$350,000 US per patient per year. However, in Israel the cost has been reduced due to lowering the dosing scheme [10]
Reimbursement recommendation	Prior to establishment of Canadian Expert Drug Advisory Committee (CEDAC) and Israeli Basket Committee (IBC); Pharmaceutical Benefits Advisory Committee (PBAC) recommended funding through the Life Saving Drug Program (LSDP)
Research studies	1. *Replacement therapy for inherited enzyme deficiency—macrophage-targeted glucocerebrosidase for Gaucher's disease* Clinical trial lasting 9-months of 12 patients with type 1 Gaucher's disease Safety and efficacy regarding improving haemoglobin levels and platelet counts and in reducing splenic and hepatic enlargement were demonstrated within 5 years [11] 2. Enzyme therapy in type 1 Gaucher disease: comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources Clinical trial comparing and demonstrating the safety and efficacy of imiglucerase with alglucerase [12] 3. Replacement therapy with imiglucerase for type 1 Gaucher's disease Clinical Trial comparing the frequency of administration of imiglucerase [13]

Table 2
Fabrazyme (*agalsidase beta*).

Manufacturer	Genzyme, approved by US Food and Drug Administration in April 2003
Use/symptoms	Treats Fabry disease, a potentially fatal lysosomal storage disorder Symptoms are widely varied resulting in diagnosis difficulty Childhood or adolescence onset Leads to life-threatening manifestations in adulthood involving the heart, kidneys, central and peripheral nervous system, and cerebrovascular system Average life expectancy (with transplantation) is 50 years [14]
Cost	$300,000 USD per patient per year
Reimbursement recommendation	CEDAC recommended against funding; IBC recommended funding; & PBAC recommended funding through the LSDP
Research studies	1. Safety and efficacy of recombinant human α-galactosidase a replacement therapy in Fabry's disease Randomized, placebocontrolled, double-blind study of 58 patients who were treated every 2 weeks [15] 2. Agalsidase-beta therapy for advanced Fabry disease Randomized, double blind, placebo controlled trial across 41 centres in 9 countries [16] 3. Long-term therapy with agalsidase alfa for Fabry disease: safety and effects on renal function in a home infusion setting Single centre, prospective open label treatment trial in 25 adult male Fabry patients [17] 4. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease 58 patients were enrolled in a Phase 3 doubleblind, randomized, and placebo-controlled trial [18] 5. Enzyme replacement therapy in Fabry disease: a randomized controlled trial Randomized control trial (double blinded) [19]

Table 3
General information about Canadian Expert Drug Advisory Committee (CEDAC).

Decision making criteria	Forms of publicity	Appeals process	Committee composition	Mandate	Documents reviewed
Safety	Internet	Available for manufacturers	Experts	To make drug listing recommendations to Drug Plans (based on submissions) [20]	Recommendation for agalsidase beta (i.e., Fabrazyme) 2005
Efficacy			Lay members		
Therapeutic advantage (relative to current treatments)					
Cost-effectiveness (related to other treatments)					

Table 4
General information about the Australian Pharmaceutical Benefits Advisory Committee (PBAC).

Decision making criteria	Forms of publicity	Appeals process	Committee composition	Mandate	Documents reviewed
Effectiveness (compared to alternative therapies)	Internet	Available for manufacturers	Experts	To make drug listing recommendations and give advice to the Minister [21]	Guidelines for the Treatment of Gaucher Disease
Cost (compared to alternative therapies)			Lay members		Guidelines for eligibility to receive treatment with agalsidase through the Lifesaving Drugs Program

Table 5
General information about Israeli Basket Committee (IBC).

Decision making criteria	Forms of publicity	Appeals process	Committee composition	Mandate	Documents reviewed
Clinical evidence	Internet	Re-submit in the new year	Experts, lay people, members of the ministry of finance, members of the health insurance	To make drug listing recommendations to the Cabinet [22]	Fabrazyme recommendation
Economic evidence	Radio				Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services
Social implications Ethical implications Legal implications	Newspaper				

website and/or literature (Information for IBC was based on literature). In addition to the committees, Genzyme, the company that manufactured both of the drugs central to our case studies, was included in this research.

2.4. Sampling

2.4.1. The case studies

The drugs central to our case studies were selected because they were expensive, orphan drugs. The first drug Cerezyme (*imiglucerase*), was developed using recombinant DNA from the enzyme glucosylceramidase, and is used to reduce, and, in some cases, reverse the chronic and debilitating symptoms of type 1 Gaucher's disease [23]. The second drug, Fabrazyme (*agalsidase beta*) was developed using recombinant human DNA from the enzyme α-galactosidase A to treat Fabry disease [24].

2.4.2. The participants

Interview participants for this study were key informants and were selected based on their experience with the drug decisions in question. This method is appropriate for in-depth studies of issues within their natural settings rather than in artificial isolation [25].

Twenty-two interviews were conducted with members of the advisory committees (CEDAC (4); PBAC (3) and IBC (4)), representatives of drug companies (4), and patient groups (7 respondents from Canada). Initial contact was made with individual informants either in-person, or by email or phone. If a response was not obtained, two more attempts were made. Snow ball sampling was also used, i.e., participants were asked to suggest other potential interviewees. Sampling continued until the analysis reached saturation, i.e., there was reiteration of the same ideas [26].

2.4.3. The documents

Five documents and three websites related to orphan drug reimbursement decisions were also analyzed. In general, documents were obtained in electronic format from committee and patient group websites. However, a number of documents were not publicly accessible (particularly in Israel) and were obtained through formal letters of request to the agency.

2.5. Data analysis

The interviews and documents were analyzed using a modified thematic analysis. First, the data were read to achieve a good working knowledge of the content – sometimes called 'immersion' [27]. Second, portions of data that related to similar concepts or ideas were identified and labeled, i.e., open coding [25]. For example, the ideas that related to accessibility, such as the ability of the public to review recommendations, were labeled as 'access.' Third, concepts were compared between and within transcripts and documents to ensure consistency and comprehensiveness. Inconsistencies were corrected through re-coding data portions into more appropriate codes or identified as areas of further analysis. Fourth, axial coding was used to identify and organize overarching themes. Fifth, primary themes were established and related to the other themes.

During each step, analytic memos were written on observations [28].

The issue of validity was addressed in three ways. First, different data sources were used, including literature, documents and interviews, which allowed for a triangulation of sources in developing emerging concepts [27]. Second, codes and themes were developed with other team members as a check on bias. Third, findings were introduced to an interdisciplinary group of scholars for feedback to help ensure reasonableness of findings. Specifically, three interim analysis meetings were held with a large interdisciplinary group of scholars, including faculty members, research fellows, and PhD students. These meeting provided an opportunity to discuss and explain the rationale behind the codes. While consensus was achieved for most of the codes, some concepts were coded under different themes as a result of the discussions during these sessions.

2.6. Research ethics

This project was approved by the University of Toronto's Human Subject Review Committee. The consent form, along with a description of the research, was sent via email to participants prior to the interview. The consent form was reviewed with each participant at the beginning of the interview and all questions and concerns were addressed. Consent forms were then signed and a copy was given to the participant. When interviews were conducted by telephone, the signed consent form was either faxed or sent electronically. All informants agreed to participate and written informed consent was obtained prior to every interview. All data is confidential and the anonymity of every participant was protected. Additionally, all raw data is protected and available only to the research team.

3. Results

In *Canada*, Cerezyme was not reviewed by CEDAC as Cerezyme was already marketed in 1994 [29], prior to the 2003 establishment of CEDAC [20]. Drug funding decisions for Cerezyme (and all other drugs not administered in the hospital setting) were and continue to be made provincially (see Appendix A). Obtaining reimbursement required much negotiation between healthcare professionals, government and public advocate appeals. For example, in Ontario, the Minister of Health initially rejected funding of Cerezyme because of the drug's inability to meet cost-effectiveness criteria [30]. This decision was publicly criticized by the National Gaucher Foundation of Canada in 1993, and the Minister of Health subsequently applied the 'rule of rescue' and approved a provincial program for reimbursement of enzyme replacement therapy (ERT) for Gaucher's disease [30].

In *Australia*, where drug funding decisions are made nationally through PBAC, Cerezyme was made available through the Life Saving Drug Program (LSDP). In order for a drug to be listed as part of the LSDP PBAC must determine (1) the drug to be clinically necessary and effective, (2) the drug's failure to meet the cost-effectiveness criteria required of all drugs listed as part of Pharmaceutical Benefits Scheme [31]. The Therapeutics Goods Administra-

Table 6
Values used in Cerezyme recommendations.

Values used	Canada's Ontario Ministry of Health	Israel's Federal Ministry of Health	PBAC
Evidence			
Cost-effectiveness	Failed	Initially failed	Failed
Effectiveness	N/A	Passed	Passed
Rule of Rescue	Passed	Passed	Passed
Equity	N/A	N/A	Passed
Final Funding Outcome	Funded	Funded	Funded

tion (TGA) has published "Guideline for the Treatment of Gaucher Disease" [32].

In *Israel*, the Ministry of Health rejected funding Cerezyme on the basis of its inability to meet the cost-effectiveness criteria. Israel has a high prevalence of this disease due to its large population of Ashkenazi Jews [8]. In 1995, the Ministry funded Cerezyme through the New Health Bill which allocated special funding to chronic diseases, including Gaucher's disease. This decision was based on a reduction in the cost of Cerezyme. Israeli researchers determined that a lowered dose (without negative effects) would reduce the cost to 25% when compared to the cost of the manufacturer's recommended dose [33,34]. The Israeli National Gaucher Committee (under the auspices of the Ministry of Health) determines patient eligibility for treatment with Cerezyme [8].

Fabrazyme was reviewed in *Canada* by CEDAC and their recommendation was against the funding of this drug. However, each province must make its own individual formulary decision (Please refer to Appendix A for Provincial decisions). In *Australia*, Fabrazyme was made available through the LSDP [31]. In *Israel*, Fabrazyme was recommended by the IBC for inclusion in the basket and has been part of the basket since 2002 [8].

Our main finding was that the participants from the three reimbursement committees, across the three different health systems, reported using essentially the same values when making reimbursement recommendations for the drugs central to our case studies. Those values were "*Evidence*" (as assessed through cost-effectiveness and effectiveness), "*Rule of Rescue*" and "*Equity*". Tables 6 and 7 below compare the values used by each committee and their evaluation of whether the drug passed or failed the particular value. Please note that in Table 6 below, both the CEDAC and IBC are omitted because these committees had not been established and did not review the drug Cerezyme. In Ontario Canada and in Israel, the decision to reimburse Cerezyme was made by the provincial Ministry of Health in the former and the Federal Ministry of Health in the latter (see table below for details). Moreover, despite the drugs' inability to meet all of the values applied by the three committees, all three jurisdictions have funded the drugs either through their general funding mechanism or through alternative mechanisms. Table 8 below indicates the mechanism by which each drug was funded in each country.

Table 7
Values used in Fabrazyme recommendations.

Values used	CEDAC	IBC	PBAC
Evidence			
Cost-effectiveness	Failed	Passed	Failed
Effectiveness	Failed	Passed	Passed
Rule of Rescue	N/A	Passed	Passed
Equity	Failed	N/A	Passed
Final Funding Outcome	Post market study	Funded	Funded

3.1. Evidence

All of the recommendation committees in this study placed a high value on clinical evidence. One concern a number of committee members raised, particularly as it related to orphan drugs, was the lack of good clinical evidence of the drug's cost-effectiveness. For example, one member commented,

> "A major issue, I think, internationally [is] not only the high cost of some of these agents but, the lack of data upon which to make a proper judgment of their cost effectiveness".

In Canada CEDAC's recommendation in 2004 against the funding of Fabrazyme was based on the lack of evidence regarding effectiveness: "This trial failed to show a clinical benefit of agalsidase beta on a range of tests" [35]. One CEDAC committee member explained the recommendation against the funding of Fabrazyme as related to effectiveness,

> "I mean, people just continued to progress on the medication, the disease progresses and this isn't a cure and it was hard to justify spending $300,000 dollars on a medication that is relatively effective at some end points but not effective at others"

Table 8
Availability of drug by country.

Country	Cerezyme	Fabrazyme
Australia	Life Saving Drug Program	Life Saving Drug Program
Canada	Varies by province (see Appendix A)	Post market study
Israel	Available since 1995 through New Health Bill for funding of chronic diseases	Included in the Health Basket since 2004

Similarly, Israel's Ministry of Health initially rejected Cerezyme for funding solely because of the drug's inability to meet cost-effectiveness criteria. However, the Israeli government was willing to provide the treatment once Israeli researchers determined in 1995 that lower doses without appreciable change in effectiveness (less than one quarter of the manufacturer's recommended dose) would reduce the cost significantly, saving $80,000,000 [33].

The application of cost-effectiveness criteria to orphan drugs was recognized as problematic by many committee members, as one PBAC member explained,

> "I don't regard those as being expensive drugs. I just regard those as being ridiculously expensive drugs. So they would never be cost-effective . . . in the paradigm."

Interestingly, a CEDAC committee member articulated that it was unclear on a policy level that orphan drugs should be prioritized differently from other types of drugs,

> "We didn't have a separate process for reviewing rare drugs and, you know, no one had told us that we needed to prioritize drugs for rare conditions differently than we prioritize all drugs."

Patients believed that the lack of clinical evidence should not be an insurmountable barrier in a committee's decision,

> "Some of these questions are typically asked or typically answered in large phase four studies. . .Things like clinical significance and statistical significance. . .these are very important factors, but not the only questions to ask. In particular, when trying to resolve issues around treatments for patients with rare disorders."

Industry recognized the high cost of the drugs, but thought that governments are re-framing the issues in terms of cost, as one representative noted:

> "I think they're good products . . .. But if you're spending 200 million dollars to treat heartburn, you can spend a couple of million dollars to provide a drug that potentially could save someone's life or prolong their life."

3.2. Rule of Rescue

The *Rule of Rescue* is a principle which values rescuing a specific endangered life when possible, regardless of cost [36]. The categorization of drugs as life saving is an application of the *Rule of Rescue*. A drug's ability to be a life saving treatment was a value considered by all of the committees, some more formally than others. Patients believed that a drug's ability to save a life should be a criterion in decision making.

Saving a life was a value used formally by the IBC. As one member of the IBC explained,

> "You have to implement other ethical values, legal, and decide - what are the priorities? . . ..It's our culture, Judaism. . .we are very concerned about life, about health."

Furthermore, the IBC prioritized life saving treatments. As one Israeli respondent commented

> "the life saving drugs . . . will get a higher rank . . . [and therefore] will be provided in the basket."

Life saving ability or the application of the rule of rescue was not clearly formulated as part of the CEDAC process. One CEDAC committee member explained,

> "I guess there's a distinction there that the life saving drugs could get a priority review and that would mean that they would be reviewed a little more quickly and brought to the committee a little more quickly. The actual type of information that is sought for each medication is similar . . .. there's other considerations that would go in as well, whether it's a specific drug for a condition that just improves quality of life or only improves life expectancy those types of things are considered but not in a formulaic approach or anything."

In Australia, PBAC recognized the inability for both Cerezyme and Fabrazyme to meet their cost-effective criteria. Consequently, these drugs are available through the Lifesaving Drug Program, which provides financial assistance for drugs that treat rare, inherited enzyme deficiencies. As one committee member explained,

> "We have a rule of rescue . . . so it's a condition for which there's no other therapy available and yet there's still demonstrable suffering from the disease and we may list the condition . . . I mean we still have . . . we need to inform the Minister of the consequences of that, the financial consequences, but we may not be able to apply as rigorously a cost effectiveness analysis to a small . . . to a group of patients with a rare disease."

Patients believe that a drug's life saving ability should be a consideration in reimbursement decisions. One patient respondent discussed the approach they would like to see used in such decisions,

> "It's sort of like the hospital . . .One doesn't come into a neonatal ward and say we're going to put the child on life support, but you know what, when his bill begins to go over a certain amount than we have to pull the plug . . .we leave the child on, until it becomes clear that the child's either going to survive or not going to be a benefit and if the child's not going to benefit then that's fine . . .I think that's the kind of approach we're trying to do here. In many cases these are life saving treatments we're talking about diseases for which no other treatment available, not even other types of interventions that one would make. So it is the case that we either have the drug or we have nothing."

3.3. Equity (of access)

Equity of access was a value used by some committees and discussed by a number of patient and industry respondents. Patients discussed their experience in accessing their particular drug and their use of advocacy to gain access to drugs. Also, patients discussed variations in access across and within countries. Patients also discussed access in terms of their ability or inability to access the reimbursement decision making process.

Access was not a criterion typically used by committees when making recommendations. Equity was cited by CEDAC in their rationale for their decision against reimbursement of Fabrazyme [35]. Additionally, a CEDAC committee member explained their conception of equity,

> "So, it was difficult to justify how we could say yes to that and no to, you know, medications for a more common condition. I mean, that has some equity issues as well, that you fund an expensive medication for a person with a rare disease who might get the same benefit as a less expensive for a common condition but you haven't funded that because it has much bigger budget implications."

One industry respondent, when asked about the Fabrazyme federal-provincial-territorial joint "research" protocol with industry in Canada, discussed the issue of equity in access,

> "I think, part of the chassis for the agreement had to do with recognition that the distribution of patients was not equal across the populations of the various provinces. So, that led to the idea that there needs to be some kind of national solution, because there was no way realistically to expect a small province like, Nova Scotia, to really be able to support the very high number of patients with that rare disease in relation to their population."

Patients also discussed variation in access of drugs across countries; for example,

> "It [Fabrazyme] was already made available to patients in 40 other countries, many of which are, you know, considered not developed countries . . .countries like Argentina and Turkey and Bulgaria. So we didn't think it would be a big issue but we found there were a number of obstacles to getting access."

3.4. Synthesis

Both industry and patient representatives believed (1) lack of evidence should not be an obstacle to accessing to treatment, (2) the rule of rescue should be a value used in reimbursement decision and (3) variations in drug access across and within provinces need to be addressed. There are a number of common values which emerged from the discussions with stakeholders, most notably evidence, rule of rescue and equity.

The participants' views regarding values were supported by the committees' assessment mandates. That is, all three values identified – evidence, life-saving ability and equity – were values stated on the committees' websites and/or related documents as decision making criteria. However, CEDAC's recommendation regarding Fabrazyme indicates (in addition to some other values) equity reasons as part of their rationale. Equity is not mentioned on CEDAC's website as a decision making criterion. Additionally, the IBC listed a number of decision making criteria which were not discussed by many respondents, particularly, legal considerations.

The inability of orphan drugs to meet the cost-effectiveness criterion was problematic for both the Canadian and Australian systems, which clearly weight this criterion heavily. Canada's drug priority setting system is predisposed against funding drugs which do not meet this criterion. In Australia, drugs which the PBAC considers clinically effective but fail to meet cost effectiveness standards are made available through a different route: the Lifesaving Drugs Program. Israel's Basket Committee weighted the value of life more heavily, and they occasionally make positive funding recommendations for drugs with an undesirable cost-effectiveness ratio.

4. Discussion

In this paper, we have described the values used by drug reimbursement recommendation committees in three countries pertaining to two expensive orphan drugs: Cerezyme and Fabrazyme. Our main finding was that participants from three different priority setting committees, working in three different health systems, from three very different cultures reported using essentially the same values when making reimbursement recommendations for the orphan drugs. Those values were evidence, rule of rescue, and equity.

The similarity in values used across the systems provides evidence about the global application of the economic approach to drug priority setting. During the 1990s, there was increasing interest in and use of economic assessments of new therapies and explicit rationing in decision making [37–40]. Even though countries continue to use economic assessments, problems remain [41]. Emphasis on meeting economic criteria such as cost-effectiveness places the value of efficacy above other values which are also important in decision making. Evidence-based medicine is another popular tool used to understand effectiveness. However, it does not weigh effectiveness against other values (i.e., benefits, costs, etc.). Limitations of the economic approach include, that it cannot objectively place a numeric value on a health outcome and it is dependant on the person conducting the evaluation [42]. Limitations of evidence-based medicine include the frequent lack of sufficient evidence to make decisions [43]. Some possible solutions to the challenge of insufficient evidence include: conditional listing, drug restrictions and risk sharing schemes. Conditional listing is the listing of a drug with the perceived potential for cost-effectiveness and/or effectiveness on the condition that it meets these two criteria. In the event that it fails to meet the criteria it becomes de-listed.

The use of drug restrictions i.e., limiting access of a drug to a particular indication or limiting prescribing ability to a select group of prescribers (i.e., specialists as opposed to general practitioners) was indicated as a cost containment measure by many committee members. Most drugs have restrictions, including usage, dosage, prescriber, etc. Restrictions were also used to combat misuse or abuse of a drug.

Risk sharing schemes are one way of approaching the funding of high cost treatments, with insufficient evidence regarding effectiveness. The payer must enter into

an agreement with the pharmaceutical company in which performance targets are negotiated based on predictable health gains for a particular expenditure. If the targets are not met, then the treatment costs are reduced to maintain an acceptable cost-effectiveness ratio. Likewise, 'no cure, no pay' initiatives have been implemented across Europe and the US. The health system is refunded its money in the event that the treatment does not cure, relieve, prevent symptoms, or results in severe, adverse events. These initiatives, to date, have been applied to common disease treatments [44].

Drug priority setting is not solely a technical process. At its core it involves adjudicating between and among a wide range of relevant values [45]. As Gallego et al., recently indicated, priority setting for high cost drugs is often based on other factors, in addition to effectiveness and cost [7]. The differences among committees with regards to their application of the *Rule of Rescue*, i.e., valuing a life-saving treatment, are fascinating.

The *Rule of Rescue* was used and applied by Canada, Australia and Israel. Both the Australian and Israeli committees considered the *Rule of Rescue* as part of their process. Australia considered three factors when considering whether to reimburse a drug through the LSDP: (1) whether an alternative exists, (2) whether the medical condition is severe, progressive and expected to lead to premature death, and (3) whether the medical condition affects only a very small number of patients. In Israel, the IBC, as part of their formulary listing process, considered the following: (1) life-saving technology with full improvement, (2) potential of technology to prevent mortality/morbidity, and (3) new technology for serious disease with no alternative treatment.

The tension between the *Rule of Rescue* and cost-effectiveness is best demonstrated through the Canadian example. Ontario's Ministry of Health applied the *Rule of Rescue*, recognizing that saving a life takes precedence over cost considerations after Cerezyme failed [30]. Alternatively, CEDAC did not consider the *Rule of Rescue* for Fabrazyme, and it was subsequently not recommended for funding as it did not meet cost-effectiveness criteria. CEDAC clearly considered issues of efficiency over those of saving a life. Recently, authors have suggested an alternative economic evaluation to ensure the availability of public funding for orphan drugs. Panju and Bell advice a system based on the *Rule of Rescue* [46]. The suggestion of an alternative funding mechanism may address this tension, however further investigation is required to determine the exact implication of such a mechanism, particularly for different arrangement health systems. Before an alternative process is established, a dialogue should occur regarding whether rarity is a sufficient value to warrant a different system of assessment. Moreover, discussion needs to occur regarding the cost limitations of the *Rule of Rescue.*

Despite orphan drugs' inability to meet the cost-effectiveness criteria and differences in the application of the *Rule of Rescue*, a number of countries are publicly funding these drugs through special drug access programs or by considering a fuller range of values (e.g. social and ethical impacts, etc.). This may be because committees recognize the value of saving a life over that of cost to the system.

Priority setting for orphan drugs involves deliberation about values, many of which conflict or are not quantifiable. Priority setting committees are very proficient at identifying quantifiable criteria, but struggle with other non-quantifiable values – such as the *Rule of Rescue.* Israel has tried to develop a more inclusive strategy for making decisions. In addition to cost, Israel considers life saving technology with full recovery and potential of the technology to prevent mortality/morbidity (for a more detailed account see Shani et al.) [22]. It is necessary to create a drug listing system which is able to formally assess these non-quantifiable values in order to establish consistency among drug reimbursement decisions within health systems. The countries in this study were able to afford funding (or had the ability to find resources to fund) these expensive drugs. Nevertheless, in order to fully understand values, future research could examine contexts with greater resource constraints. When committees are constrained by resources, discussions pertaining to values become more obvious and the identification of conflicting values will become more apparent. This type of research could be conducted in developing countries using non-expensive drugs/technologies as the cases (as these countries would not be able to afford the drugs included in this study) for instance, hemodialysis.

5. Conclusion

Drug funding decisions which provide some benefit to only some patients is highly contentious and morally controversial. It is clear that priority setting decisions will need to be made about which orphan drugs to reimburse, how to regulate them, and who will have access to them. Describing and evaluating decision making in specific contexts, such as in Canada, Australia, and Israel, and for two orphan drugs, Fabrazyme and Cerezyme, is the first step toward improving drug priority setting. This study has shown the importance of the *Rule of Rescue* to key stakeholders (i.e., industry and patients) in drug reimbursement, the advantages of establishing a mechanism for orphan drug reimbursement decisions (i.e., Australia), and the challenges in access associated with the absence of a national orphan drug system (i.e., Canada). The system established for orphan drugs will impact on future reimbursement decisions for personalized medical treatments. Therefore it is important to establish a system that can address the challenges of publicly reimbursing treatments that benefit only a few. This study has shown that an economic approach to reimbursement decisions is not always possible or even appropriate for all drugs. More research is necessary to determine the framework on which to base such decisions.

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Appendix A. Availability of Cerezyme and Fabrazyme in Canada

Formulary	Cerezyme		Fabrazyme	
	Listed on formulary	Other means of access	Listed on formulary	Other means of access
Alberta Health & Wellness	No	Special authorization process	No	Post market study
BC Pharmacare	No	No exception drug status	No	Under review
Manitoba Pharmacare	No	Exception drug status benefit	No	Post market study
New Brunswick Prescription Drug Program	No	Special authorization	No	Post market study
Newfoundland & Labrador Prescription Drug Program	No	Special authorization process may cover it	No	No exceptions yet
North West Territories Health Benefits Program	No	Exception drug coverage	No	Post market study
Nova Scotia Pharmacare	No	Exception drug status process	No	Exception Drug Status process
Nunavet Health Benefit Program	No	Exceptional circumstances	No	Exceptional circumstances
Ontario Drug Benefit Program	No	Special Drug Program	No	Post market study
PEI Drug Cost Assistance Program	No	High Cost Drug Program	No	High Cost Drug Program
Régie de l'assurance maladie du Québec	No	Can appeal with process lead by referring physician	No	Can appeal with process lead by referring physician
Saskatchewan Drug Plan	No	Not even by exception	No	Not even by exception
Yukon Pharmacare	No	Will only be reviewed on needs-basis	No	Reviewed on needs-basis

Appendix B. Interview Guide for Committee Members

Sample questions
Recommendation committees:

1. How are recommendations made regarding funding of expensive orphan drugs?
2. Is there a distinction made between drugs which are life saving, orphan, and/or QOL?
3. Who was involved in the decision-making process and what was the extent of their involvement? Specifically which stakeholders were involved?
4. What considerations do you feel are important in making the reimbursement recommendations for orphan drugs?
5. How were recommendations communicated/disseminated?
6. What happens if someone disagrees with a decision? Is there a formal process that people including the general public can challenge the decision?
7. Do you think it is a fair process?
8. What do you think could be done to improve this process?
9. How do you think the process affects innovation in the area of biotechnology?
10. Do you think priority setting affects innovation in the area of biotechnology? How?

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